Medtronic

Medtronic Clinical Investigation Plan	
Clinical Investigation Plan/Study Title	The Medtronic Harmony™ Transcatheter Pulmonary Valve Clinical Study
Clinical Investigation Plan Identifier	MDT16004CON001
Study Product Name	Harmony Transcatheter Pulmonary Valve and Delivery System
Sponsor/Local Sponsor	Global Sponsor: Medtronic Coronary and Structural Heart Clinical 8200 Coral Sea St NE, MVS 66 Mounds View, MN 55112 United States [redacted]
Document Version	6.0
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Lead Principal Investigator(s)	[redacted]

Confidentiality Statement

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1. Glossary

Term	*Definition*
ADE	Adverse Device Effect
AE	Adverse Event
AKI	Acute Kidney Injury
AOA®	Alpha-Amino Oleic Acid
CEC	Clinical Events Committee
CHD	Congenital Heart Disease
CIP	Clinical Investigation Plan
CMR	Cardiac Magnetic Resonance
CT	Computed Tomography
CV	Curriculum Vitae
DMC	Data Monitoring Committee
DTL	Delegated Task List
EC	Ethics Committee
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed Consent
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
LV	Left Ventricle
mTPV 25	Modified Transcatheter Pulmonary Valve 25
PA	Pulmonary Artery
PMDA	Pharmaceuticals and Medical Devices Agency
PVL	Paravalvular Leak
REB	Research Ethics Board

Term	*Definition*
RDC	Remote Data Capture
RV	Right Ventricle
RVEDVi	Right Ventricular End Diastolic Volume Index
RVOT	Right Ventricular Outflow Tract
RVOTO	Right Ventricular Outflow Tract Obstruction
SAE	Serious Adverse Event
SF-36	RAND 36-Item Short Form Survey
SOP	Standard Operating Procedure
SRDL	Substantial Radiation Dose Level
TOF	Tetralogy of Fallot
TPV	Transcatheter Pulmonary Valve
UADE	Unanticipated Adverse Device Effect

2. Synopsis

Title	The Medtronic Harmony Transcatheter Pulmonary Valve Clinical Study
Product Name	Harmony Transcatheter Pulmonary Valve (TPV) (Model NTPV0022) Harmony Transcatheter Pulmonary Valve (TPV) (Model HTPV254952) Harmony Transcatheter Pulmonary Valve (TPV) (Model HTPV254252) Harmony Delivery System (DS) (Model NTPVDS0022) Harmony Delivery System (DS) (Model HTPVDS0025)
Sponsor	Medtronic Coronary and Structural Heart Clinical 8200 Coral Sea St NE, MVS 66 Mounds View, MN 55112 United States
Local Sponsor(s)	[redacted]
Investigation Purpose	The purpose of this study is to evaluate the safety and effectiveness of the Harmony TPV system.
Primary Objective(s)	The primary objective of this study is to demonstrate the safety and effectiveness of the Harmony TPV system as measured by freedom from procedure or device-related mortality at 30 days and percentage of subjects with acceptable hemodynamic function at 6 months.
Primary Safety Endpoint	Freedom from procedure- or device-related mortality at 30 days.
Primary Effectiveness Endpoint	Percentage of subjects with acceptable hemodynamic function composite at 6 months as defined by: • Mean RVOT gradient as measured by continuous-wave Doppler echocardiography ≤40 mmHg ○ If a catheterization is performed for clinical purposes, the catheterization peak gradient measurement will supersede the continuous-wave Doppler echocardiography measurement and be used to support the primary endpoint. Acceptable hemodynamic function as measured by catheterization will be considered to be peak gradient ≤40 mmHg. -AND- • Pulmonary regurgitant fraction as measured by magnetic resonance imaging <20%

	○ If magnetic resonance imaging is contraindicated, a continuous-wave Doppler echocardiography measurement will be used to support the primary endpoint. Acceptable hemodynamic function as measured by continuous-wave Doppler echocardiography will be considered to be < moderate pulmonary regurgitation.
Additional Outcome Measures	• Technical success at exit from catheterization lab/operating room • Device success out to 5 years • Procedural success at 30 days • Freedom from TPV dysfunction out to 5 years • Assessment of safety • Characterize quality of life scores over time • Characterize right ventricle remodeling following TPV implant • Confirmation of the procedural feasibility, hemodynamic performance and safety profile of Harmony TPV 25 (roll-in cohort) • Confirmation of the procedural feasibility, hemodynamic performance and safety profile of the modified TPV 25 (10 US implants)
Study Design	Multi-center, prospective, non-randomized, interventional, investigational
Investigative Sites	Up to 15 investigational sites in the United States, Canada, and Japan
Sample Size	• Pivotal cohort: Primary analysis for up to 40 subjects implanted including the Harmony TPV 25 Roll-In cohort • Additional analysis for the Harmony modified TPV 25 (mTPV 25) cohort: ten subjects implanted in the United States, and up to five subjects implanted in Canada and/or Japan
Patient Population	Patients who have congenital heart disease and are clinically indicated for pulmonary valve replacement.
Inclusion Criteria	• Subject has pulmonary regurgitation as per one or more of the following criteria: ○ Severe pulmonary regurgitation as measured by continuous-wave Doppler echocardiography, or ○ Pulmonary regurgitant fraction ≥ 30% as measured by cardiac magnetic resonance imaging • Clinical indication for surgical placement of a RV-PA conduit or prosthetic pulmonary valve per one or more of the following criteria: ○ Subject is symptomatic secondary to pulmonary insufficiency (e.g. exercise intolerance, fluid overload) as classified by the investigator, or ○ Subject has right ventricular end diastolic volume index (RVEDVi) ≥ 150 ml/m², or ○ Subject has RVEDV: LVEDV Ratio ≥ 2.0 • Subject is willing to consent to participate in the study and will commit to completion of all follow-up requirements
Exclusion Criteria	• Anatomy unable to accommodate a 25 Fr delivery system • Obstruction of the central veins • Clinical or biological signs of infection including active endocarditis • Planned concomitant procedure at time of implant • Positive pregnancy test at baseline (prior to CT angiography and again prior to implant procedure) in female subjects of child bearing potential

	• Patients with right ventricular outflow tract obstruction (RVOTO) lesions surgically treated with an RV-PA conduit implant • A major or progressive non-cardiac disease (e.g. liver failure, renal failure, cancer) that results in a life expectancy of less than one year • Planned implantation of the Harmony TPV in the left heart • RVOT anatomy or morphology that is unfavorable for device anchoring • Known allergy to aspirin, heparin, or nickel • Echocardiographic evidence of intracardiac mass, thrombus, or vegetation • Pre-existing prosthetic heart valve or prosthetic ring in any position
Study Procedures and Assessments	• Clinical assessment at pre- and post-implant, 1 month, 6 months, 1 year, and annually through 5 years • Echocardiography at pre- and post-implant, 1 month, 6 months, 1 year, and annually through 5 years • Cardiac magnetic resonance (CMR) at pre-implant, 6 months, 2 years, and 5 years • CMR at 1 month for the mTPV25 cohort • CT Cardiac Angiography at pre-implant • CT Cardiac Angiography at post-implant for the mTPV 25 cohort and for TPV 25 subjects participating in the CT sub-study • Fluoroscopy at implant, 1 month, 6 months, 1 year, and 5 years • SF-36 at pre-implant, 1 month, 6 months, 1 year, and annually through 5 years
Professional Services	• Independent Echocardiography Core Laboratory • Independent CMR Core Laboratory • Independent Explant Pathology Core Laboratory • Patient Screening Committee • Independent Clinical Events Committee • Independent Data Monitoring Committee

3. Introduction

3.1. Background

[redacted]

[redacted]

[redacted]

3.2. Purpose

The purpose of this study is to evaluate the safety and effectiveness of the Harmony TPV system.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective(s)

The primary objective of this study is to demonstrate the safety and effectiveness of the Harmony TPV system as measured by freedom from procedure or device-related mortality at 30 days and percentage of subjects with acceptable hemodynamic function at 6 months.

4.2. Primary Endpoints

The following endpoints will be used to evaluate the primary study objective:

4.2.1. Primary Safety Endpoint

- Freedom from procedure- or device-related mortality at 30 days

4.2.2. Primary Effectiveness Endpoint

- Percentage of subjects with acceptable hemodynamic function composite at 6 months as defined by:

- Mean RVOT gradient as measured by continuous-wave Doppler echocardiography ≤40 mmHg
  - If a catheterization is performed for clinical purposes, the catheterization peak gradient measurement will supersede the continuous-wave Doppler echocardiography measurement and be used to support the primary endpoint. Acceptable hemodynamic function as measured by catheterization will be considered to be peak gradient ≤40 mmHg.

-AND-

- Pulmonary regurgitant fraction as measured by magnetic resonance imaging <20%
  - If magnetic resonance imaging is contraindicated, a continuous-wave Doppler echocardiography measurement will be used to support the primary endpoint. Acceptable hemodynamic function as measured by continuous-wave Doppler echocardiography will be considered to be < moderate pulmonary regurgitation.

4.3. Additional Outcome Measures

- Technical success at exit from catheterization lab/operating room (OR), as defined as:
  - No device- or procedural-related mortality, with
  - Successful access, delivery and retrieval of the delivery system, and
  - Deployment and correct positioning (including minor repositioning if needed) of the single intended device, and
  - No need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure

- Device success out to 5 years, as defined as:
  - No device- or procedural-related mortality, with
  - Original intended device in place, and
  - No additional surgical or interventional procedures related to access or the device since completion of the original procedure (i.e., exit from the catheterization lab), and
  - Intended performance of the device, as defined as:
    - Structural performance: No migration, embolization, detachment, major stent fracture, hemolysis, thrombosis, endocarditis, and
    - Hemodynamic performance: Relief of insufficiency (PR < moderate) without producing the opposite (mean RVOT gradient > 40 mmHg) as measured by continuous-wave Doppler echocardiography[1], and
  - Absence of para-device complications, as defined by:
    - PVL ≥ moderate, or
    - Erosion, or

[1] If a catheterization is performed for clinical purposes, the catheterization peak gradient measurement will supersede the continuous-wave Doppler echocardiography measurement and be used to support the outcome measure.

- RVOT or PA rupture

- Procedural success at 30 days, as defined as:
  - Device success at 30 days, and
  - None of the following device- or procedure-related serious adverse events:
    - Life-threatening major bleed
    - Major vascular or cardiac structural complications required unplanned reintervention or surgery
    - Stage 2 or 3 acute kidney injury (AKI) (includes new dialysis)
    - Pulmonary embolism
    - Severe heart failure (HF) or hypotension requiring IV inotrope, ultrafiltration, or mechanical circulatory support
    - Prolonged intubation >48 hours

- Freedom from TPV dysfunction out to 5 years.

- Assessment of safety, defined as assessment of:
  - All procedure-related serious adverse events
  - All device-related serious adverse events
  - Death (all-cause, procedural, and device-related)
  - Characterization of quality of life scores over time as assessed by the SF-36 at pre-implant, 1 month post-implant, 6 months post-implant, and annually post-implant out to 5 years
  - Characterization of right ventricle remodeling following TPV implant as assessed via CMR

4.4. Rationale for Selection of Study Endpoints

The basis for the selection of these endpoints includes the following considerations:

- They are clinically relevant and address important safety and effectiveness aspects of the Medtronic Harmony TPV system.
- They are objectively defined and measurable in the majority of subjects.
- They are consistent with current endpoints in TPV clinical studies.

5. Study Design

This is a prospective, non-randomized, multi-center study. Up to 40 subjects will be implanted at a total up to 15 centers in the United States, Canada, and Japan. It is anticipated that more than 40 subjects will be enrolled (i.e. consented) to meet the target of up to 40 implants as not all subjects will be anatomically suitable for implantation. No site shall implant more than 10 subjects in the pivotal cohort to avoid bias of the study results. Subjects who discontinue participation prematurely following implant will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of total study subjects implanted. All implanted subjects will receive the Harmony TPV. Each implanted subject will be followed for five years or until the subject's Harmony TPV is explanted.

The addition of the second device size (Harmony TPV 25) is intended to expand the number of patients anatomically suitable for implantation and will include a Roll-In cohort of Harmony TPV 25 subjects. The Roll-In phase is described in **Section 8.4. Harmony TPV 25 Roll-In Phase.** The addition of the larger sized valve completed the pivotal cohort of 40.

Following the completion of the 40 pivotal cohort of the TPV 22 and TPV 25, the TPV 25 was modified and is referred to as modified TPV 25 (mTPV 25). There will be an added cohort of up to 15 subjects implanted with the mTPV 25. This additional cohort will include 10 US implants and up to 5 OUS implants from Canada and/or Japan. The mTPV 25 cohort is described in **Section 8.5. Addition of mTPV 25 Cohort**. The study methods include the following measures to minimize potential sources of bias:

- A Screening Committee comprised of a subset of study investigators will confirm subject eligibility and anatomic suitability
- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and endpoint related adverse events. Safety endpoint results will be based on CEC adjudications.
- All sites will follow a standardized protocol for acquisition of echocardiographic endpoint data.
- An Echo Core Lab will evaluate all echocardiograms.
- A CMR Core Lab will evaluate all functional CMR results.
- Study endpoints, when appropriate, will be based on CEC or Core Lab assessments.
- Study sites will follow their institutional procedures for maintenance of echocardiography and imaging equipment used for assessing the study variables.

5.1. Duration

Subjects will be consented for participation in the study for follow-up through 5 years. The enrollment period for this study is estimated to be between 18 to 24 months; therefore, the estimated total duration of the study (first subject enrolled to last subject completing the last follow-up exam) is estimated to be 7 years.

When the Harmony TPV system receives marketing approval during the course of this clinical trial, the follow-up assessments will continue until all subjects have completed 5 years of follow-up.

5.2. Rationale

The clinical study design for this study aligns with other TPV studies, including the Medtronic Native Outflow Tract Transcatheter Pulmonary Valve Research Clinical Study. Results from the Medtronic Native Outflow Tract Transcatheter Pulmonary Valve Research Clinical Study support justification of further investigation of this device in humans and demonstrate these evaluations of clinical data are relevant to the proposed investigation.

6. Product Description

6.1. General

The Harmony TPV (Model NTPV0022) is comprised of a 22mm porcine pericardium valve, sewn to a polyester-covered asymmetrical hourglass nitinol frame. The Harmony TPV 25 and mTPV 25 (Model HTPV254952 and HTPV254252, respectively) is comprised of a 25mm porcine pericardium valve, sewn to a polyester covered asymmetrical hourglass nitinol frame with larger diameter inflow and outflow as well as shorter length compared to TPV 22. All TPV sizes are processed with an anti-mineralization treatment of alpha-amino oleic acid (AOA®), a compound derived from oleic acid, a naturally occurring long-chain fatty acid. The Harmony Delivery System (DS) for the TPV 22, TPV 25, and mTPV 25 (NTPVDS0022 and HTPVDS0025) are all 25 Fr delivery systems using a coil loading catheter. Refer to the Harmony TPV and DS Instructions for Use (IFU) documents for each device for full information regarding the product, which includes a description of the products being investigated, manufacturer information, packaging information, intended population description, and instructions for product use.

6.2. Packaging

Labeling of the Harmony TPV system will be provided in English and the local language, if needed according to local requirements. The labeling will indicate that the device is for investigational use only, and only to be used by qualified investigators, and consistent with the requirements of the geographies where the trial is conducted.

The IFU for the Harmony TPV system used in this trial will be provided as a separate document. If changes are made to the labeling, they will be provided under separate cover to the appropriate authorities per local requirements.

6.3. Product Training Requirements

Prior to first patient implant at an investigative site, Medtronic will provide product training to the implanting physician(s). Implanting physicians will receive didactic product training and hands-on device training. At a minimum, the first case at each investigative site for each valve size will be supported by an experienced Harmony TPV implanter. Additional implant support may be provided as needed.

6.4. Product Accountability

The Harmony TPV and DS are not approved for use in any geography, and therefore are considered investigational devices. The investigator shall maintain adequate records of the receipt and disposition of all investigational devices.

Centers are required to maintain investigational device records that contain the following information:

- Investigational device name
- Device serial number (when applicable)
- Lot number (when applicable)
- Use by date
- Date of receipt of device
- Name of person receiving the device
- Name of person using the device (when applicable)
- Date of use (when applicable)
- ID number of subject receiving the device (when applicable)
- Disposition (unused, disposed of, implanted, or returned to Medtronic)

For devices that are returned to Medtronic or disposed of, centers are required to document the following additional information:

- The quantity and reason for the device being returned to Medtronic or disposed of
- Name of the person who disposed of each device
- Date of shipment back to Medtronic

At the completion of the study implant period, the investigator must return all unused devices and a copy of the completed device inventory to Medtronic. The investigator's copy of the device reconciliation records must document any unused devices that have been returned to Medtronic as well as all product usage including opened but non-implanted devices.

6.5. Product Storage

The Harmony TPV and DS are not approved for use in any geography, and therefore are considered investigational devices. As such, they should be stored as labeled and in a secure/locked storage area with access limited only to approved study staff. The method of storage should prevent the use of these investigational devices for applications other than described in this Clinical Investigation Plan (CIP). The investigator shall maintain adequate records of the receipt and disposition of all investigational devices.

6.6. Product Return

In the event of a device malfunction of the Harmony TPV system prior to implant, or in the event the Harmony TPV is explanted after implant (due to reintervention or autopsy), the Harmony TPV and/or affected components should be sent to Medtronic.

Additional details surrounding the device return process are contained within the Medtronic explant kit that will be provided upon notification of a device malfunction or explant. To obtain a product return kit, contact a Medtronic Representative. If a kit is not available, place the explanted valve in a container of glutaraldehyde or 10% buffered formalin immediately after excision.

Specific pathological studies of an explanted valve will be conducted under the direction of a consulting pathologist. A written summary of the findings will be returned to the physician. For specific instructions regarding explant, refer to **Appendix IX: EXPLANT PROTOCOL.**

7. Selection of Subjects

7.1. Study Population

The population includes patients who have congenital heart disease and are clinically indicated for pulmonary valve replacement.

7.2. Subject Enrollment

The process of subject enrollment is as follows:

1. Patients identified by or presented to the study site who have congenital heart disease and are clinically indicated for pulmonary valve replacement will be screened by the investigator or designee for the criteria described in **Section 7.3. Inclusion Criteria** and **Section 7.4. Exclusion Criteria**, using available medical records, including relevant imaging studies previously performed for diagnostic purposes.
2. If the patient is deemed a potential candidate for the study, the investigational status of the Harmony TPV and all aspects of the study will be explained to the patient. The patient will then be invited to participate in the study.
3. If the patient agrees to participate, written informed consent will be obtained. This will be considered the point of enrollment, and the subject will be assigned a subject ID number.

7.3. Inclusion Criteria

- Subject has pulmonary regurgitation as per one or more of the following criteria:
  - Severe pulmonary regurgitation as measured by continuous-wave Doppler echocardiography, or
  - Pulmonary regurgitant fraction ≥ 30% as measured by cardiac magnetic resonance imaging
- Clinical indication for surgical placement of a RV-PA conduit or prosthetic pulmonary valve per one or more of the following criteria:
  - Subject is symptomatic secondary to pulmonary insufficiency (e.g. exercise intolerance, fluid overload) as classified by the investigator, or
  - Subject has right ventricular end diastolic volume index (RVEDVi) ≥ 150 ml/m^2, or
  - Subject has RVEDV: LVEDV Ratio ≥ 2.0
- Subject is willing to consent to participate in the study and will commit to completion of all follow-up requirements

7.4. Exclusion Criteria

- Anatomy unable to accommodate a 25 Fr delivery system
- Obstruction of the central veins
- Clinical or biological signs of infection including active endocarditis
- Planned concomitant procedure at time of Harmony TPV implant
- Positive pregnancy test at baseline (prior to CT angiography and again prior to implant procedure) in female subjects of child bearing potential
- Patients with right ventricular outflow tract obstruction (RVOTO) lesions surgically treated with a RV- PA conduit implant
- A major or progressive non-cardiac disease (e.g. liver failure, renal failure, cancer) that results in a life expectancy of less than one year
- Planned implantation of the Harmony TPV in the left heart

- RVOT anatomy or morphology that is unfavorable for device anchoring
- Known allergy to aspirin, heparin, or nickel
- Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
- Pre-existing prosthetic heart valve or prosthetic ring in any position

8. Study Procedures

8.1. Schedule of Events

Evaluation / Visit	Pre-Implant	Implant[1]	Discharge	1 Month	6 Months	1 Year	Annual (2-5 Years)
Visit Window	Within 24 weeks prior to Implant procedure unless otherwise specified	Implant procedure date	Prior to hospital discharge, or at 30 days post-implant if subject remains hospitalized	Between 2 and 6 weeks after implant	Between 23 and 29 weeks after implant date	Between 44 and 60 weeks after implant date	Between ±8 weeks after the implant anniversary date
Informed Consent	X						
Screening Committee Review	X						
Clinical Assessment[2]	X		X	X	X	X	X
TPV Implant		X					
Echo	X[3]		X	X	X	X	X
Functional Cardiac Magnetic Resonance Imaging[4]	X[5]			X[6]	X		To be completed at 2 & 5 Year Follow-Up
CT Cardiac Angiography[7]	X[8]		X[9]				
Fluoroscopy		X		X	X	X	To be completed at 5 Year Follow-Up
Chest X-Ray			X				
SF-36[10]	X[11]			X	X	X	X
Assessment of Adverse Event/ Device Deficiency[12]	X	X	X	X	X	X	X

[1] Post-procedure care is carried out according to the standard care of the interventional cardiologist at his/her discretion.
[2] Clinical Assessment includes: at baseline – subject demographic, medical history, and medication assessment; at follow-up - medication assessment, review of adverse events, and device deficiencies.
[3] If an echo exam has been performed for routine diagnostic purposes prior to consenting, it can be used as the pre-implant echo exam, provided it was performed within 24 weeks prior to implant. The Principal Investigator must determine if the exam contains the protocol-required data and remains adequate for subject evaluation. If subject is screen failed, functional CMR imaging was used to satisfy the inclusion criteria, and pre-implant echo was not completed within window, a deviation is not required.
[4] If CMR imaging is contraindicated (e.g., subject has implantable cardiac rhythm device), no deviation will be required for MRI not performed.

[5] If a CMR functional exam has been performed for routine diagnostic purposes prior to consenting, it can be used as the pre-implant CMR functional exam, provided it was performed within 52 weeks prior to implant. The Principal Investigator must determine if the exam contains the protocol-required data and remains adequate for subject evaluation.
[6] Functional CMR at the 1 month visit will be required for subjects implanted with mTPV 25.
[7] CT post implant will be required for subjects implanted with TPV 25 who are participating in the Post Implant CT sub-study following **Appendix XII**.
[8] If a CT cardiac angiography exam has previously been performed prior to consenting, it can be used as the pre-implant CT exam, provided it was performed within 2 years prior to implant. The Principal Investigator must determine if the exam contains the protocol-required data and remains adequate for subject evaluation (e.g. subject has not undergone significant growth in the interim). Pre-implant CT angiography will follow Appendix VII.
[9] CT at discharge will be required for subjects implanted with the mTPV 25 who are participating in the Post Implant CT sub-study following **Appendix XII**.
[10] SF-36 is suitable for self-administration or administration by an interviewer in person or by telephone.
[11] The pre-implant SF-36 can be administered after a subject has been evaluated by the screening committee but prior to implant.
[12] Investigators are required to evaluate and document in the subject's medical records all adverse events and device deficiencies observed in study subjects from the time they are enrolled (consented) until they are exited from the study.

8.2. Subject Consent

Prior to enrolling in the study, patients should be fully informed of the details of study participation as required by applicable regulations, the site's IRB/EC and by Medtronic. Informed consent must be obtained from each patient or legally authorized representative prior to conducting any protocol-induced activities beyond standard of care, by using the informed consent form (ICF) approved by that site's IRB/EC and by Medtronic. The ICF must be signed and dated by the patient or legal representative. Any additional persons required by the site's IRB/EC to sign the informed consent form must also comply. In Japan, the relationship between the patient and legal representative must be documented in the ICF and IC process if a legal representative signed the ICF.

This study has the potential to include individuals that may be considered vulnerable. The Investigator should consider the definition of vulnerable per ISO 14155, which defines vulnerable patients as: "those patients that could be unduly influenced by the expectation or benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. For example, this could include Individuals with loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects could include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention." Any additional requirements by the site's IRB/EC or local regulations regarding the informed consent process requirements relating to vulnerable populations must be followed.

Informed assent should be considered depending on the age and understanding of the subject per IRB/EC requirement and local regulations or when the investigator feels that a minor cannot understand the content of the ICF sufficiently before a minor will be enrolled in the study. When required, informed assent must be obtained using the IRB/EC approved form.

Prior to the patient or legal representative signing the ICF, the investigator or authorized designee will fully explain to the patient or legal representative the nature of the research, study procedures, anticipated benefits, and potential risks of participation in the study. The investigator or designee will allow adequate time for the patient or legal representative to read the consent form and to ask questions. Signing the ICF serves to document the written and verbal information that the investigator or designee provided to the patient or legal representative, the patient or legal representative's understanding of the information, and their agreement to participate. The case history for each patient shall document the entire informed consent process including who participated in the consent discussions and that informed consent was obtained prior to participation in the study. The original signed consent form will be retained in the patient's study records and a copy of the informed consent will be provided to the patient or legal representative.

The point at which the ICF (and informed assent as applicable) is executed by all parties will be considered the point of enrollment for this study, and the subject will be assigned a subject ID number.

The ICF will be revised whenever important new information becomes available, or there is an amendment to the protocol which necessitates a change to the ICF. All revisions to the consent form must be approved in advance by the IRB/EC and local regulatory body, as appropriate. The subject should be re-consented according to IRB/EC requirements following the process as described above. If required, the investigator or designee should re-consent the subject in a timely manner.

8.3. Subject Screening

All consented subjects will be assigned a subject ID and will be considered enrolled into the study. All consented subjects who exit the study prior to study completion will have the reason for exit documented on the Study Exit case report form as well as in the medical record.

After obtaining informed consent, the following process for patient screening will be followed:

1. The study site will assign a unique subject ID number to all enrolled (consented) subjects.
2. The subject will have transthoracic echocardiography[2] (TTE) and cardiac magnetic resonance (CMR) exams[3] to assess pulmonary regurgitation and RV size and function, if not already performed per requirements given in [redacted]
3. Subjects that do not meet echocardiographic and/or CMR criteria will be exited from the study. Subjects that meet the echocardiographic and CMR criteria will undergo baseline cardiac

[redacted]

computed tomography (CT) angiography per [redacted]

4. Anatomic measurements will be performed by Medtronic from the CT images and evaluated per device sizing guidelines given in [redacted]
5. It is possible that subjects deemed eligible for implant may not meet all sizing guidelines due to variation in RVOT anatomy. The investigator can use the criteria described in [redacted] as a guideline to assess the subject's candidacy for TPV implantation
6. Medtronic will provide the sizing evaluation (perimeter plot) to the investigator. If the Investigator considers the subject anatomically suitable for implantation of the Harmony TPV, the following clinical information from the subject will be submitted to the Screening Committee:
    a. Clinical assessments and medical history
    b. Echocardiographic, CMR, and CT data on anatomical suitability
7. The Screening Committee will review the screening data and provide a recommendation to the investigator, including valve size, who will make the final determination of implantation suitability. If it is determined the subject's anatomy is not suitable for implantation, the subject will be exited from the study. Subjects originally screened for TPV 22 who were exited due to screen failure may be re-screened for TPV 25 or mTPV 25 after being re-consented. For those subjects re-screened, a unique subject ID will be assigned.
8. Subjects who are determined to be device candidates by the investigator are eligible for cardiac catheterization and Harmony TPV implantation. Implant attempt is considered the point at which the investigational product is introduced into the subject's body. Implantation procedures are described in the IFU document.

8.4. Harmony TPV 25 Roll-In Phase

Prior to any implant of the Harmony TPV 25, there will be a Roll-In phase to include a cohort of subjects for the implant of the TPV 25.

Roll-in Objectives:

The objective of the Harmony TPV 25 Roll-In Phase is to confirm the procedural feasibility, hemodynamic performance and safety profile of the Harmony TPV 25 prior to the Harmony TPV 25 becoming available for implant at all sites. Also, the Roll-In phase is intended provide Study Proctors familiarity and added expertise in the implant technique for Harmony TPV 25 prior to proctoring all sites in implanting the Harmony TPV 25.

Roll-in Methodology:

Subjects enrolled in the Roll-in phase will follow all methods and procedures according to the CIP. This section will provide information on methods and requirements specific to the Roll-in phase of the study.

Roll-in Phase Design:

The Roll-in phase is specific to the initial implants of the Harmony TPV 25, to confirm the procedural feasibility, hemodynamic performance and safety profile of the device before all sites can implant the Harmony TPV 25. This phase of initial Harmony TPV implants will be limited to the investigative sites with experienced implanters (Study Proctors).

Investigative Sites:

The Roll-in subjects will be implanted at up to four investigative sites where the implanting physician is an experienced implanter and is currently proctoring other sites on the Harmony TPV implantation procedure (Study Proctor).

Number of Subjects:

A minimum of five and up to eight qualifying subjects will be implanted with the Harmony TPV 25 at up to four Study Proctor sites. Each Study Proctor site can implant up to three subjects.

Subject Selection Criteria

Prospective subjects for the Roll-in phase must meet all subject selection criteria for enrollment in the Medtronic Harmony TPV Clinical Study (see **Section 7. Selection of Subjects**).

Informed Consent:

Prior to enrolling in the study, patients will be fully informed of the details of study participation in the Roll-In Phase as required by applicable regulations, the site's IRB/EC and by Medtronic.

Screening and Enrollment:

See **Section 7. Selection of Subjects** for screening and enrollment information.

Roll-in Cohort Analysis:

The procedural feasibility, and hemodynamic performance and safety profile at hospital discharge following Harmony TPV 25 implantation of the Roll-In cohort will be analyzed. The outcome measures are defined as:

Procedural Feasibility:

- No device- or procedural-related mortality, with
- successful access, delivery and removal of the delivery system, and
- deployment and correct positioning (including minor repositioning if needed) of the device.

Hemodynamic Performance:

- Mean RVOT gradient ≤ 40mmHg as measured by echocardiography

Safety Profile:

None of the following device- or procedure-related serious adverse events:

- Life-threatening major bleed
- Major vascular or cardiac structural complications required unplanned reintervention or surgery
- Pulmonary embolism

Roll-in cohort subjects will be followed per the CIP. Roll-in data for the follow-up phase will be included in the 40-subject pivotal cohort as approved by FDA.

If Roll-in phase outcome measures are met and no concerns are raised by the DMC, Steering Committee or Medtronic, the Harmony TPV 25 will be made available to all participating Harmony TPV study sites. Harmony TPV 25 subjects implanted following the Roll-in phase will also be included in the 40-subject pivotal cohort.

8.5. Addition of mTPV 25 Cohort

Following the completion of the 40 pivotal cohort of TPV 22 and TPV 25, the TPV 25 was modified. There will be an added cohort of up to 15 subjects implanted with the mTPV 25. This additional cohort will include 10 US implants and up to 5 OUS implants from Canada and/or Japan.

mTPV 25 Cohort Objectives:

The objective of the mTPV 25 addition is to confirm the procedural feasibility, hemodynamic performance, and safety profile of the mTPV 25.

mTPV 25 Methodology:

Subjects enrolled in the mTPV 25 cohort will follow all methods and procedures according to the CIP. This section will provide information on methods and requirements specific to the mTPV 25 cohort addition into the study.

mTPV 25 Study Design:

The addition of the mTPV 25 cohort into the study will follow the same study design of the study described in **Section 5. Selection of Subjects.**

Investigative Sites:

The study sites include 9 US sites, 2 Canada sites, and 1 Japan site.

Number of Subjects:

There will be 10 US implants and up to 5 OUS implants from Canada and/or Japan.

Subject Selection Criteria

Prospective subjects for the mTPV 25 cohort must meet all subject selection criteria for enrollment in the Medtronic Harmony TPV Clinical Study (see **Section 7. Selection of Subjects).**

Informed Consent:

Prior to enrolling in the study, patients will be fully informed of the details of study participation in the mTPV 25 cohort as required by applicable regulations, the site's IRB/EC and by Medtronic.

Screening and Enrollment:

See **Section 7. Selection of Subjects** for screening and enrollment information.

mTPV 25 Cohort Analysis:

The procedural feasibility, hemodynamic performance, and safety profile of mTPV 25 at 1 month following mTPV 25 implantation will be analyzed. The outcome measures are defined as:

Procedural Feasibility:

- No device- or procedural-related mortality, with
- successful access, delivery and removal of the delivery system, and
- deployment and correct positioning (including minor repositioning if needed) of the device.

Hemodynamic Performance:

- Mean RVOT gradient ≤ 40mmHg as measured by echocardiography

Safety Profile:

None of the following device- or procedure-related serious adverse events:

- Life-threatening major bleed
- Major vascular or cardiac structural complications required unplanned reintervention or surgery
- Pulmonary embolism

mTPV 25 subjects will be followed per the CIP. A supplemental analysis for the mTPV 25 subjects for outcomes of procedural feasibility, hemodynamic performance and safety profile will be performed separately when mTPV 25 subjects have been followed for 1 month.

8.6. Implant Catherization Procedure

Cardiac catheterization is performed according to the standard procedures of the interventional cardiologist. Detailed outline of the catheterization procedure recommendations is provided in the IFUs for Harmony TPV 22, Harmony TPV 25, and Harmony mTPV 25.

The Principal Investigator is anticipated to be the primary operator for the implant procedure must stay consistent throughout the duration of the study for all implanted patients at each site, unless prior

approval is received from Medtronic. Sub-investigators with appropriate training and experience may assist in the implant procedure at the discretion of the Principal Investigator.

8.6.1. Post-Procedure Care

Post-procedure care is carried out according to the standard post-procedure care of the interventional cardiologist at his or her discretion. It is recommended investigators comply with the AHA/ACC guidelines for bioprosthetic tissue valves and prescribe lifelong Aspirin therapy and prophylactic antibiotic therapy prior to dental procedures.[35] For any imaging performed (i.e. intracardiac echocardiography, transesophageal echocardiography, or other imaging) post procedure, before leaving the catheterization lab, per standard of care at the investigational site, a copy of the imaging may be requested by Medtronic for review.

8.6.2. Discharge Criteria

Following completion of Discharge procedures described in **Section 8.1. Scheduled of Events**, hospital discharge will occur at the discretion of the investigator.

8.6.3. Device Explant

In the event of a medically indicated explant of the Harmony TPV, the explanting physician will follow standard local explant procedures. Subjects will be followed through discharge of the explant hospitalization or until study closure, whichever occurs first. Study sites should attempt to obtain copies of autopsy reports and the death certificate in the event of a subject's death. Requirements specific to explantation at reoperation or autopsy are described in **Appendix IX: EXPLANT PROTOCOL**. The explanted Harmony TPV should be returned to Medtronic as outlined in **Section 6.6. Product Return**.

8.7. Subject Evaluations

Subjects in whom the Harmony TPV was implanted will be evaluated at hospital discharge, one month, six months, one year, and annually thereafter through five years or until the Harmony TPV is explanted. Protocol-required evaluations should be performed at the study site when possible. Evaluations to be performed are summarized in **Section 8.1. Schedule of Events**. If the subject is seen at a clinic not associated with the study site, all efforts should be made to obtain copies of medical records from that visit. Data obtained from these outside medical records can be used to support data entry for that visit.

8.7.1. Unplanned Visits

Unplanned subject visits that are not detailed in **Section 8.1. Schedule of Events** and are deemed necessary in order to evaluate the Harmony TPV are considered unplanned visits for the purposes of the protocol and do not need to take place at the study site. Additionally, only data that can be obtained by the study sites are required to be reported. Potential relevant unplanned procedures include:

- Clinical assessment
- Echocardiography
- CMR
- CT cardiac angiography
- Radiography

8.7.2. Missed Visits

Every effort should be made to ensure subjects return to the study site for all protocol required follow-up visits. If the subject is unable to return for an in-person clinic visit, the investigator, or designee, should document in the subject record the reason the subject was unable to complete the visit and, if applicable, follow the requirements for deviation reporting outlined in **Section 8.10. Deviation Handling**.

In the case that the subject will not be seen for a protocol required follow-up visit, the investigator should make every effort to contact the subject or subject's legal representative within the visit window to collect the subject's vital status as well as information related to potential adverse events, safety data, and hospitalizations.

8.8. Substantial Radiation Dose Level

A Substantial Radiation Dose Level (SRDL) is an appropriately selected reference value used to trigger additional dose management actions during a procedure and medical follow-up for a radiation level that might produce a clinically relevant injury in an average patient. There is no implication that radiation levels above the SRDL will always cause an injury or that radiation levels below the SRDL will never cause an injury. The established SRDL for this study is a kerma-area product of 500 Gy*cm^2.

When the SRDL has been exceeded, the Substantial Radiation Dose Level electronic case report form (eCRF) should be completed and clinical follow-up is required. The subject should be advised of the possibility of a skin injury due to a tissue reaction and instructed to examine the beam entrance site for 2-4 weeks post-procedure. The subject should report any skin changes. In the event the subject does not contact the site within 30 days after the procedure, the site should follow-up with the subject to assess if a potential skin injury has taken place.

If a skin injury is suspected, the subject should be seen at a clinic visit and appropriate follow-up care should be determined. In the event a skin injury occurs, an Adverse Event eCRF must be completed to document the injury.

8.9. Assessment of Safety

Methods and timing for assessing, recording, and analyzing safety parameters are explained in **Section 10. Adverse Events and Device Deficiencies.**

An external, independent clinical events committee (CEC) will review and adjudicate all endpoint related AEs and subject deaths.

An external, independent data monitoring committee (DMC) will assess interim study data and provide recommendations to Medtronic regarding study conduct, should they identify any issues that may affect the safety of the study subjects.

8.10. Recording Data

Study sites will assign a unique subject ID number to each enrolled (consented) subject. Records of the subject/subject ID relationship will be maintained by the study site. Individual subject medical information obtained as a result of this study will be considered confidential.

This study will utilize Oracle Clinical Remote Data Capture (RDC) system that is the property of Medtronic. Required data will be recorded on eCRFs by authorized site personnel as indicated on the Delegation Task List (DTL). Study personnel delegated for eCRF completion and/or approval will be trained on the use of the RDC system and thereafter provided with a unique username and password to access the system. The eCRFs must be completed and/or updated to reflect the latest observations on subjects participating in the study. The Principal Investigator (or appropriately delegated sub-investigator) will electronically sign (i.e. approve) each eCRF attesting to the accuracy of the data provided. The RDC system will maintain an audit trail of eCRF data entries and corrections. If site personnel make corrections to a previously approved eCRF, an appropriately delegated investigator shall re-approve this eCRF. Data from the core lab will be entered into the RDC system by core lab personnel per their procedures established for the study.

All study-related documents must be retained until notified by Medtronic that retention is no longer required. Medtronic will inform the investigator/institution when these documents are no longer required to be retained.

No study document or image should be destroyed without prior written agreement between Medtronic and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

8.11. Deviation Handling

A protocol deviation is defined as an occurrence where the study was not conducted according to the protocol or the Investigator Agreement. Examples of protocol deviations include but are not limited to:

- Failure to obtain informed consent prior to study participation
- Incorrect version of the informed consent form used
- Failure to obtain IRB/EC approval before the start of the study

- Enrolled subject did not meet inclusion/exclusion criteria[4]
- Required testing and/or measurements not done or incorrectly done
- Follow-up visit missed or completed outside window
- Unauthorized use of investigational devices
- Adverse events not reported in the required time frame as defined by regulation or the CIP
- Control of study devices not maintained
- Source data permanently lost
- Enrollment of patients during lapse of IRB/EC approval

Every attempt should be made to avoid protocol deviations. Investigators should obtain prior approval from Medtronic before initiating any change or deviation from the CIP, except where necessary to protect the rights, safety or wellbeing of a subject in an emergency situation. Such approval shall be documented in writing and maintained in the Investigator Site File. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control (e.g., subject did not attend scheduled follow-up visit).

Deviations will be reported to Medtronic regardless of whether the occurrence was medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Study deviations should be reported to Medtronic via the Study Deviation eCRF.[5]

Investigators should report the following deviations to Medtronic and their reviewing IRB/EC (if required by local regulation) within 5 working days of the occurrence of the deviations:

- Failure to obtain written informed consent
- Deviations to protect the life or physical well-being of a subject in an emergency

In addition, investigators are required to adhere to local IRB/EC procedures for reporting deviations.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any corrective and/or preventive actions that may be warranted. Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan, which may include suspension of enrollment or termination of the investigator or site's participation in the study.

[4] Subjects must meet all inclusion/exclusion criteria to be eligible for implantation. However, it will not be considered a protocol deviation if new study related testing (e.g., echo, CT cardiac angiography, or Screening Committee assessment) of a consented subject identifies implantation eligibility criteria that are not met.

[5] In the case of a missed study visit or an out of window visit (e.g., follow-up visit), one eCRF is required. A deviation eCRF is not required for each assessment missed at one visit.

8.12. Subject Withdrawal or Discontinuation

All implanted subjects will be encouraged to remain in the study through the final follow-up visit at 5 years. Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of total study subjects. The reason for premature discontinuation should be documented in the subject file and via the Study Exit eCRF.

The study site will make every effort to have implanted subjects complete the follow-up visit schedule. A subject will not be considered lost to follow-up unless all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include at minimum 3 attempts to make contact via telephone or e-mail. If these contact attempts are not successful, a traceable letter from the investigator should be sent to the subject's last known address and the subject's primary physician contacted. Subjects will then be deemed lost to follow up. All contact efforts to obtain follow-up must be documented in the subject's medical records.

If a subject discontinues the study prematurely, is withdrawn from the study by the investigator, or completes all protocol required follow-up, they should continue to be followed by the implanting site according to their routine clinical practice for pulmonary valve patients. If, for any reason, this is not possible, or if subject needs to change his/her follow-up site at any time point after conclusion of the study, investigators should refer subjects to a local site with appropriate training and experience in managing patients with implanted pulmonary valves.

9. Risks and Benefits

9.1. Potential Risks

All materials used in the Harmony TPV have been used previously in implantable medical devices with long-standing clinical experience. The frame is constructed from nitinol, which has been used in coronary and peripheral arterial stenting applications as well as in transcatheter aortic valves with clinically acceptable performance. Glutaraldahyde-fixed porcine tissue with AOA® has been used in commercially available bioprosthetic heart valves since 1992. Therefore, the materials used in the Harmony TPV do not represent unreasonable risks to patients.

No cardiac catheterization procedure can be considered entirely without risks, discomfort, distress, or inconvenience. As with any cardiac catheterization procedure, certain complications may occur through participation in the clinical study. There may be risks that we do not know yet. There may be risks that we do not know how often will happen or how severe they will be when they happen. This is because the study is in the early phase and we do not have much experience with this device. Although CT tests are becoming the standard method of assessment for transcatheter valve implantation, there is an additional risk of increased radiation exposure from the required CT test for this clinical study.

If the subject is a female of childbearing potential, a pregnancy test will take place before the CT test and again before the implant procedure to make sure the subject is not pregnant as there may be risks to the embryo or fetus that are currently unknown.

Please refer to the Harmony TPV IFU document for a full listing of risks and further information on the risks of the Harmony TPV.

9.2. Potential Benefits

The primary potential benefit of the Harmony TPV to patients is restoration of hemodynamic function of his or her pulmonary valve without the need for invasive cardiac surgery. Specifically, the Harmony TPV is intended to restore and maintain pulmonary valve competence for patients with pulmonary regurgitation. Reduction in regurgitant volume could result in improved or preservation of right ventricular function, a decrease in the incidence of arrhythmias, and an improvement in effort tolerance. These potential benefits could delay the next surgical intervention, ideally reducing the number of cardiac surgeries a patient requires over his or her lifetime. Additionally, data gained from this study may benefit others in the future. Due to the relatively small experience with this device, these benefits are possibilities and not known for certain.

9.3. Risk-Benefit Rationale

The Harmony TPV early feasibility study demonstrated that Harmony TPV implantation may be a safe and effective treatment option for patients with repaired congenital heart disease with pulmonary regurgitation.

Although there are risks associated with implantation of the Harmony TPV as outlined in **Section 9.1. Potential Risks**, they are not anticipated to be worse than the risks associated with current interventions for dysfunctional pulmonary valves, namely surgical replacement. The potential benefits of the study as outlined in **Section 9.2. Potential Benefits** outweigh the potential risks; therefore, the investigation is justified.

The following measures will be implemented to minimize risks to the study subjects:

- All subjects will be acceptable surgical candidates
- Implanting physicians will have considerable experience in interventional congenital cardiology procedures
- Study sites will have comprehensive congenital cardiology and surgery programs with established capacity for emergency catheterization and cardiac surgery, if necessary
- Patients being considered for the study will be rigorously screened
- Subjects will undergo thorough assessments during their pre-implant workup

- Subjects will be rigorously followed over the course of the study. The follow-up protocol includes frequent contact with the investigative clinicians, echocardiography, magnetic resonance imaging and radiography. Collectively, the follow-up protocol will enable detection of deterioration in TPV function should it occur, and allow appropriate intervention, as adjudicated by the implanting physician.
- Radiation dosages will be monitored and documented for the implant procedure and for each radiography and CT angiography procedure. If the Substantial Radiation Dose Level (SRDL) of 500 Gy*cm2 is met for any given procedure, the subject will be educated about examining the tissue site for a possible skin reaction within 30 days and clinical follow-up will berequired.
- Any unanticipated or unforeseen complications will be reported to the IRB/EC, the appropriate regulatory agencies, and to Medtronic
- An independent DMC will review adverse events and interim results in order to advise Medtronic regarding study conduct, should safety concerns be identified

10. Adverse Events and Device Deficiencies

10.1. Definitions/Classifications

The definitions to be applied for the purposes of reporting adverse events are provided in Table 1: Adverse event definitions for reporting requirements.

Table 1: Adverse event definitions for reporting requirements

Event Type	Definition
Adverse Event (AE) (ISO14155:2011 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other parties, whether or not related to the investigational medical device.[36] *NOTE 1: This definition includes events related to the investigational medical device or the comparator.* *NOTE 2: This definition includes events related to the procedures involved.* *NOTE 3: For users or other parties, this definition is restricted to events related to investigational medical devices.*
Serious Adverse Event (SAE) (ISO14155:2011 3.37)	Adverse event that a) led to death, b) led to a serious deterioration in the health of the subject, resulting in 1) a life-threatening illness or injury, or

Event Type	Definition
	2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect.[36,37] *NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.*
Adverse Device Effect (ADE) or Device Related Adverse Event (ISO14155:2011 3.1)	Adverse event related to the use of an investigational medical device. *NOTE 1: 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.*[36] *NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.*
Serious Adverse Device Effect (SADE) (ISO 14155:2011 3.36)	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Unanticipated Adverse Device Effect (UADE) (21 CFR 812.3)	Any serious adverse effect on health or safety of a patient, or any life-threatening problem or death caused by or associated with the device, if the effect, problem, or death has not been previously identified in nature, severity, or degree of incidence in the investigational plan 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.[38]
Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155:2011 3.42)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects. *NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.*

Event Type	Definition
Device Deficiency (ISO 14155:2011 3.15)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.[36] *NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.*
Mandatory Problem Reporting Incident (SOR/98-282 59-61.1(2))	An incident that (a) is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or in the directions for use, and (b) has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur. *NOTE: This definition and reporting requirement pertains to events that occur within Canada only.*

10.2. Evaluations and Documentation of Adverse Events and Device Deficiencies

Investigators are required to evaluate and document in the subject's medical records all adverse events (AE) and device deficiencies (per the definitions in **Table 1: Adverse event definitions for reporting requirements**) observed in study subjects from the time they are enrolled (consented) until they are exited from the study. If an AE or device deficiency is ongoing at the time of study exit, efforts should be made to report the final outcome of that event to Medtronic and the IRB/EC (if required) should the final outcome of that event be known prior to study closure.

10.2.1. Reporting of Adverse Events by Investigator

Investigators should assess observed AEs and report the appropriate information on the AE eCRF including updates to AE information after initial reporting. Definitions of select adverse events can be found in **Appendix II: ADVERSE EVENT DEFINITIONS**. The investigator should refer to **Appendix III: Adverse Event Code List** and assign the appropriate AE code on all AE eCRFs.

Unavoidable effects that are expected for patients undergoing catheterization procedures such as pain at the puncture site, anesthesia-related nausea and/or vomiting, minor hematomas (not requiring surgical treatment), transient low-grade fever (<39.0°C), headache, etc. do not need to be documented or reported.

For AEs that require immediate reporting (

Table 2 and Table 3), initial reporting may be done by phone, fax, e-mail, or on the eCRF, completing as much information as is available. The fully completed eCRF must be submitted to Medtronic as soon as possible.

Table 2: Adverse Event and Device Deficiency Reporting Requirements to Sponsor for US and Canada

Event Type	Timeframe for Reporting
Unanticipated Adverse Device Effect (UADE)	Immediately but no later than 10 working days after the investigator first learns of the effect *(21 CFR 812.150(a)(1))*
Mandatory Problem Reporting Incident *This reporting requirement pertains to events that occur within Canada only.*	Immediately but no later than 72 hours after it comes to the attention of the qualified investigator *(SOR/98-282 59-61.1(2)).*
All other Adverse Events (AEs), Serious AEs (SAEs), and Device Deficiencies (DDs)	As soon as possible but no later than 10 working days after the investigator first learns of the event/deficiency

Table 3: Adverse Event and Device Deficiency Reporting Requirements to Sponsor for Japan

Event Type	Submit to	Description/Constraints
Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE) and Unanticipated Adverse Device Effects (UADE)	Sponsor	Immediately, but no later than 72 hours of the investigator's/site's first knowledge of the event.
	Head of Medical Institution	Report to Head of Medical Institution immediately. Head of Medical Institution of each site request the IRB to deliberate them.
Serious Adverse Events (SAE)	Sponsor	Immediately, but no later than 72 hours of the investigator's/site's first knowledge of the event.
	Head of Medical Institution	Report within the time frame as per local IRB requirement.
Adverse Device Effects (ADE)	Sponsor	As soon as possible as per local reporting requirement, but no later than 10 working days after the investigator first learns of the event.
All other AEs	Sponsor	As soon as possible as per local reporting requirement, but no later than 10 working days after the investigator first learns of the event.
Device Deficiency with SADE potential	Sponsor	Immediately, but no later than 72 hours of the investigator's/site's first knowledge of the event
	Head of Medical Institution	Report within the time frame as per local IRB requirement.
All other Device Deficiencies	Sponsor	As soon as possible as per local reporting requirement, but no later than 10 working days after the investigator first learns of the event.

10.2.2. Reporting of Adverse Events by Sponsor

Table 4: Adverse Event and Device Deficiency Reporting Requirements by Sponsor for Japan

Event Type	Submit to	Description/Constraints
Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE) and Unanticipated Adverse Device Effects (UADE)	Pharmaceuticals and Medical Devices Agency (PMDA)	Report within the time frame as per local requirement *(Pharmaceutical and Medical Device Act Enforcement Regulations, Article 274, paragraph 2).*
	Head of Medical Institution and PI	Report to Head of Medical Institution and PI immediately. Head of Medical Institution of each site request the IRB to deliberate them. As for periodic report, report to Head of Medical Institution and PI annually. Head of Medical Institution of each site request the IRB to deliberate them. Or, report to Head of Medical Institution, PI and IRB chairman annually if needed.
Serious Adverse Events (SAE)	PMDA	Report within the time frame as per local requirement *(Pharmaceutical and Medical Device Act Enforcement Regulations, Article 274, paragraph 2).*
	Head of Medical Institution and PI	As for individual report, report to Head of Medical Institution and PI immediately. Head of Medical Institution of each site request the IRB to deliberate them. As for periodic report, report to Head of Medical Institution and PI annually. Head of Medical Institution of each site request the IRB to deliberate them.
Device Deficiency with SADE potential	PMDA	Report within the time frame as per local requirement *(Pharmaceutical and Medical Device Act Enforcement Regulations, Article 274, paragraph 2).*
	Head of Medical Institution and PI	As for individual report, report to Head of Medical Institution and PI immediately. Head of Medical Institution of each site request the IRB to deliberate them. As for periodic report, report to Head of Medical Institution and PI annually. Head of Medical Institution of each site request the IRB to deliberate them.

10.2.3. Classification of Serious Adverse Events

Any event that meets the SAE criteria provided in **Table 1: Adverse event definitions for reporting requirements** is to be classified as a serious adverse event (SAE).

10.2.4. Classification of Causal Relationships

For each observed AE, the causal relationship between the AE and the TPV, the AE and the DS, and the AE and the implant procedure will be categorized as: causal relationship, probable relationship, possible relationship, unlikely relationship, and not related, according to the definitions provided below.[37] It should be assumed there is a causal or probable relationship to the TPV, DS, or implant procedure unless another cause is identified as a possibility.

Causal Relationship

The event is associated with the TPV, DS, or implant procedure when:

- the event is a known side effect of the product category the TPV or DS belongs to or of similar devices and procedures;
- the event has a temporal relationship with TPV or DS use/application or implant procedure;
- the event involves a body-site or organ that
  - the TPV, DS, or implant procedure are applied to;
  - the TPV, DS, or implant procedure have an effect on;
- the event follows a known response pattern to the TPV, DS, or implant procedure (if the response pattern is previously known);
- the discontinuation of TPV or DS application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) has an impact on the event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use.

Note: In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of investigational device/implant procedure and the event.

Probable Relationship

The relationship with the use of the TPV, DS, or implant procedure seems relevant and/or the event cannot be explained by another cause, but additional information may be obtained.

Possible Relationship

The relationship with the use of the TPV, DS, or implant procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment).

Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Unlikely Relationship The relationship with the use of the TPV, DS, or implant procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Not related Relationship to the TPV, DS, or implant procedure can be excluded when:

- the event is not a known[6] side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

10.2.5. Reporting of Device Deficiencies

Device deficiency information will be collected throughout the study and reported to Medtronic. Device deficiencies that led to an AE are reported on the AE eCRF. Device deficiencies that did not lead to an AE should be reported on a Device Deficiency eCRF (one for each device deficiency).

[6] When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, it generally is considered "not related". Yet, the unexpected effect shall not be excluded from evaluation and reporting.

10.3. Anticipated Adverse Events

Anticipated AEs for subjects participating in the study are outlined in **Section 9.1. Potential Risks.** Further information is provided in the Investigator's Brochure and IFU.

10.4. Emergency Contact Details for Reporting SAE, UADE, and Device Deficiencies

Investigators should contact the Medtronic study manager or site manager if they have any questions regarding reportable AEs. Medtronic will maintain a listing of current study contact details and provide to each site

11. Data Review Committees

11.1. Screening Committee

- A Screening Committee will be used to ensure patient selection is appropriate and consistent among trial sites. The role of the Screening Committee will include the following: Confirmation that subjects meet inclusion / exclusion criteria
- Confirmation that subjects are anatomically suitable for Harmony TPV implant

The Screening Committee will be comprised of a subset of study investigators with expertise including:

- Congenital Heart Disease
- Interventional Cardiology
- Cardiac Surgery
- Cardiac Imaging

11.2. Clinical Events Committee

A Clinical Events Committee (CEC) will provide independent medical review and adjudication of adverse event data used in the safety assessment of the investigational device. The CEC will adjudicate, at a minimum, all deaths and endpoint related adverse events, as outlined in the CEC charter. Any related source documentation provided to the Sponsor for CEC review and adjudication will be de-identified. All efforts should be made by the PI to provide source documentation for review as requested by the CEC. In the event source documentation cannot be obtained, a summary of the event and related clinical findings may be provided by the PI.

The analysis of the study safety data will be based on CEC adjudications. The CEC members will be free from bias towards the study and will be independent from the study investigators and Medtronic. The committee will consist of at least 3 independent experts (non-Medtronic employed physicians) with expertise relevant to the study. This may include experience in the areas of:

- Congenital Heart Disease
- Interventional Cardiology
- Cardiac Surgery

11.3. Data Monitoring Committee

A Data Monitoring Committee (DMC) will assess interim study data and provide recommendations to Medtronic regarding study conduct, should they identify any issues that may affect the safety of the study subjects. DMC members will be free from bias towards the study and will be independent from the study investigators, and Medtronic. The DMC will consist of a minimum of 3 members who may have experience in the areas of:

- Congenital Heart Disease
- Interventional Cardiology
- Cardiac Surgery

The DMC will meet (via teleconference or in person) to establish procedures for safety data review, chair appointment, and guidelines for study recommendations. The DMC will meet on a periodic basis to perform a comprehensive data review, including at a minimum, all SAEs and deaths, and will meet more frequently when needed. Safety-related endpoints may also be reviewed at these meetings. DMC meetings may consist of both open and closed sessions. Medtronic personnel may facilitate the DMC meeting but will not have voting privileges.

Following each meeting, the DMC will report to Medtronic in writing and may recommend changes in the conduct of the study. The DMC recommendations may include recommendations on study status such as continuing the study without modifications, continuing the study with modifications, stopping or suspending enrollment, or recommendations regarding study conduct including recommendations around enrollment or protocol deviations.

In the case of UADEs, if Medtronic and the DMC determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical study within 5 working days after making that determination and no later than 15 working days after Medtronic first receives notice of the effect. All study sites will be notified of this action.

The DMC may call additional meetings if, at any time, there is concern about any aspect of the study. All data presented at the meetings will be considered confidential.

12. Statistical Design and Methods

The primary analysis for safety and effectiveness will be performed when the first 40 implanted subjects have completed their 6-month follow-up.[7] A supplemental analysis will be performed when the 10 US implants of mTPV 25 cohort have completed their 1-month follow-up. Both cohorts will be pooled for additional analysis out to 5 years after the previously mentioned analyses are completed.

12.1. Analysis Sets

The analysis subsets are defined as follows:

Enrolled Cohort

The enrolled cohort consists of all enrolled subjects. Subjects are considered enrolled at the point of signing the Informed Consent Form.

Catheterized Cohort

The catheterized cohort consists of all subjects who undergo catheterization for possible implantation of the Harmony TPV.

Attempted Implant Cohort

The attempted implant cohort consists of all subjects who undergo catheterization and a Harmony TPV implantation was attempted (Harmony TPV is introduced into the subject's body).

Implanted Cohort

The implanted cohort consists of all subjects who undergo catheterization and a Harmony TPV was implanted.

Implanted > 24 hours Cohort

The implanted >24 hours cohort consists of all subjects who have a Harmony TPV implanted which remains implanted for greater than 24 hours.

12.2. Primary Objectives

The primary objectives are descriptive, and no statistical hypothesis test will be performed. There is no sample size calculation for the primary objectives. The analysis population will include data from this study in combination with the data from the Native Outflow Tract Transcatheter Pulmonary Valve Research Clinical Study (IDE #G120175).

[7] While the primary safety endpoint is measured at 30 days, primary objective analysis will be completed upon completion of the primary efficacy endpoint, which is measured at 6 months.

The analysis for primary objectives will be performed when all subjects have reached their 6-month endpoint.[8]

12.2.1. Primary Safety Endpoint

The primary safety endpoint is freedom from procedure or device-related mortality.

CEC adjudicated data will be used to assess the safety endpoint.

The analysis cohort will be the catheterized cohort. The endpoint will be described by Kaplan-Meier statistics. The loglog transformed two-sided 95% confidence interval using the Peto standard error at 30 days will be presented. The primary safety objective will be met if the point estimate of the freedom from procedure or device-related mortality rate at 30 days post-procedure is equal to or greater than the performance target of 95%.

12.2.2. Primary Efficacy Endpoint

The primary efficacy endpoint is percentage of subjects with acceptable hemodynamic function composite at 6 months as defined by:

- Mean RVOT gradient as measured by continuous-wave Doppler echocardiography ≤40 mmHg
  - If a catheterization is performed for clinical purposes, the catheterization peak gradient measurement will supersede the continuous-wave Doppler echocardiography measurement and be used to support the primary endpoint. Acceptable hemodynamic function as measured by catheterization will be considered to be peak gradient ≤40 mmHg.

-AND-

- Pulmonary regurgitant fraction as measured by magnetic resonance imaging <20%
  - If magnetic resonance imaging is contraindicated, a continuous-wave Doppler echocardiography measurement will be used to support the primary endpoint. Acceptable hemodynamic function as measured by continuous-wave Doppler echocardiography will be considered to be < moderate pulmonary regurgitation.

Core lab data will be used to assess the efficacy endpoint, with an exception in the case that a catheterization is performed to measure mean RVOT gradient, in which site reported data will be utilized.

[8] While the primary safety endpoint is measured at 30 days, primary objective analysis will be completed upon completion of the primary efficacy endpoint, which is measured at 6 months.

The analysis cohort for the primary efficacy endpoint will be the implanted > 24 hours cohort. The percentage of subjects with acceptable hemodynamic function at 6 months and a two-sided 95% Clopper-Pearson interval will be provided. The primary efficacy objective will be met if the point estimate is equal to or greater than the performance target of 75%.

12.3. Additional Outcome Measures

Technical success at exit from catheterization lab/operating room (OR)

Technical success is defined as:

- No device- or procedural-related mortality, with
- Successful access, delivery and retrieval of the delivery system, and
- Deployment and correct positioning (including minor repositioning if needed) of the single intended device, and
- No need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure

The analysis cohort for technical success will be the attempted implant cohort. The percentage of subjects with technical success will be presented. If an element of the composite is missing and available elements meet the success criteria, the subject will be excluded from the analysis.

Device success out to 5 years

Device success is defined as:

- No device- or procedural-related mortality, with
- Original intended device in place, and
- No additional surgical or interventional procedures related to access or the device since completion of the original procedure (i.e., exit from the catheterization lab), and
- Intended performance of the device, as defined as:
  - Structural performance: No migration, embolization, detachment, major stent fracture, hemolysis, thrombosis, endocarditis, and
  - Hemodynamic performance: Relief of insufficiency (PR < moderate) without producing the opposite (mean RVOT gradient > 40 mmHg) as measured by continuous-wave Doppler echocardiography[9], and
- Absence of para-device complications, as defined by:
  - PVL ≥ moderate, or
  - Erosion, or
  - RVOT or PA rupture

[9] If a catheterization is performed for clinical purposes, the catheterization peak gradient measurement will supersede the continuous-wave Doppler echocardiography measurement and be used to support the outcome measure.

The analysis cohort for procedural success will be the attempted implant cohort. The endpoint will be described by Kaplan-Meier statistics. The loglog transformed two-sided 95% confidence interval using the Peto standard error at 6 months (183 days), 1 year (365 days), 2 years (730 days), 3 years (1095 days), 4 years (1460 days) and 5 years (1825 days) will be presented.

Procedural success at 30 days

Procedural success is defined as:

- Device success at 30 days, and
- None of the following device- or procedure-related serious adverse events:
  - Life-threatening major bleed
  - Major vascular or cardiac structural complications required unplanned reintervention or surgery
  - Stage 2 or 3 acute kidney injury (AKI) (includes new dialysis)
  - Pulmonary embolism
  - Severe heart failure (HF) or hypotension requiring IV inotrope, ultrafiltration, or mechanical circulatory support
  - Prolonged intubation >48 hours

The analysis cohort for procedural success will be the attempted implant cohort. The percentage of subjects with procedural success will be presented. If an element of the composite is missing and available elements meet the success criteria, the subject will be excluded from the analysis.

Freedom from TPV dysfunction out to 5 years

TPV dysfunction is defined as any one of the following:

- RVOT reoperation for device-related reasons
- Catheter re-intervention of TPV
- Hemodynamic dysfunction of the TPV (moderate or greater pulmonary regurgitation, and/or a mean RVOT gradient >40 mmHg)

The analysis cohort will be the implanted longer than 24 hours cohort. The endpoint will be described by Kaplan-Meier statistics. The loglog transformed two-sided 95% confidence interval using the Peto standard error at 6 months (183 days), 1 year (365 days), 2 years (730 days), 3 years (1095 days), 4 years (1460 days) and 5 years (1825 days) will be presented.

Assessment of safety

Assessment of safety is defined as assessment of:

- All procedure-related serious adverse events
- All device-related serious adverse events
- Death (all-cause, procedural, and device-related)

For assessment of safety, the CEC data will be used for analysis. The analysis cohorts are:

- All procedure-related adverse events: Catheterized cohort
- All device-related adverse events: Attempted Implant cohort
- Death (all-cause, procedural, and device-related): Catheterized cohort

Adverse events will be analyzed either via survival analysis using the Kaplan-Meier method or summarized by count and percent as appropriate.

Characterization of quality of life scores over time

Quality of life score over time will be assessed by the SF-36 at pre-implant, 1 month post-implant, 6 months post-implant, and annually post-implant out to 5 years. The analysis cohort will be the implanted > 24 hours cohort.

Summary statistics such as mean, standard deviation, minimum, median, and maximum will be provided for quality of life scores over time as assessed by the SF-36 at pre-implant, 1 month post-implant, 6 months post-implant, and annually post-implant out to 5 years.

Characterization of right ventricle remodeling following TPV implant as assessed via CMR

Right ventricle remodeling will be assessed via CMR at pre-implant, 6 months post-implant, 2 years post-implant, and 5 years post-implant. The analysis cohort will be implanted longer than 24 hours cohort. Summary statistics such as mean, standard deviation, minimum, median, and maximum will be provided for continuous variables and count and percentage will be provided for categorical variables.

Final Analysis

Final analysis on the additional outcome measures will be performed when the implanted subjects have reached their 5 year endpoints, with the exception of the following endpoints, which will be analyzed in conjunction with the primary objective analysis (when all implanted subjects have reached their 6-month visit):

- Technical success at exit from catheterization lab/operating room (OR)
- Procedural success at 30 days

13. Ethics

13.1. Statement(s) of Compliance

This study was designed to reflect the Good Clinical Practice (GCP) principles outlined in ISO 14155:2011. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted, including data protection laws, the Clinical Study Agreement and the CIP. The study will also be conducted in

accordance with the Declaration of Helsinki. The principles of the Declaration of Helsinki are implemented in this study by means of the Patient Informed Consent (IC) process, IRB/EC approval, study training, clinical study registration, pre-clinical testing, risk benefit assessment, and publication policy.

In the United States, the study will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56 and 812. In Canada, the study will be conducted under an Investigational Testing Authorization in compliance with SOR/98-282 Section 79-88. In Japan, the study will be conducted in accordance with the Japan GCP Ordinance and the Pharmaceutical and Medical Device Act. In addition, the study will be conducted in compliance with 21 CFR Parts 11 and 54 in all participating geographies.

Regulatory authority notification/approval to conduct the study is required. Investigational sites will not be activated, nor begin enrolling subjects, until the required approval from the regulatory agency and IRB/EC has been obtained. Additionally, any requirements imposed by a local regulatory agency or IRB/EC shall be followed, as appropriate.

This study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, Section 810(a)).

13.2. Institutional Review Board/Ethics Committee

The study will be conducted in accordance with the requirements of each investigational site's IRB/EC. The responsible IRB/EC must approve the CIP and Informed Consent form prior to implementation. Study activities will not commence prior to receipt of documentation of IRB/EC approval by the site and Medtronic. The investigator and study staff must comply with the requirements of their IRB/EC.

Prior to enrolling subjects, each study site's IRB/EC will be required to approve the current CIP, the Informed Consent form, and any other written information to be provided to the subjects. Study sites in the United States must also utilize IRB approved Health Insurance Portability and Accountability Act (HIPAA) Authorization.

IRB/EC approval of the study must be received in the form of a letter and provided to Medtronic before commencement of the study at an investigational site. The approval letter must contain enough information to identify the version or date of the documents approved. In addition to the approval letter, an IRB/EC roster or letter of compliance must be submitted to Medtronic to allow verification that the investigator, other center study staff, and/or Medtronic personnel are not members of the IRB/EC. If they are members of the IRB/EC, written documentation is required stating that he/she did not participate in the approval process. Investigators must inform Medtronic of any change in status of

IRB/EC approval once the investigation site has started enrollment. If any action is taken by an IRB/EC with respect to the study, that information must be forwarded to Medtronic.

13.3. Regulatory Submissions

Each study site must fulfill all local regulatory requirements prior to enrolling subjects. Each study site must have written documentation of site/investigator readiness, including but not limited to IRB/EC approval of the current version of the CIP, ICF, a signed Investigator's Agreement, current investigator curriculum vitae (CV), and documentation of training. The principal investigators and their institutions shall agree to this CIP and any amendments and indicate their approval by signing and dating the Clinical Study Agreement.

In the United States and Canada, each study site is required to have a copy of the approval letter from the respective geography's regulatory agency prior to their first subject enrollment. Medtronic will obtain a copy of the approval letter from the regulatory agencies.

Other documents referred to in this CIP are listed as follows and will be made available upon request:

- Monitoring Plan
- Data Management Plan
- Statistical Analysis Plan
- Clinical Safety Management and Potential Complaints Plan
- Electronic Case Report Forms (eCRFs)

If a regulatory agency imposes any additional requirements (e.g. safety reports, progress reports, etc.), Medtronic will prepare the required documents and send them to the applicable regulatory agency. Any revisions or amendments to the CIP, Reports of Prior Investigations, or Informed Consent template documents will be submitted to the regulatory agencies. A final report will be submitted to the regulatory agencies, if requested, upon study closure.

13.4. Ethical Conduct of the Study

The study will be conducted in accordance with the design and specific provisions of this protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP, local laws and the applicable regulatory requirements. The study will begin in each geography only when all the requirements of the appropriate regulatory authority have been fulfilled. The principles of the Declaration of Helsinki have all been implemented by means of the patient Informed Consent process, IRB/EC approval, study training, clinical study registration, preclinical testing, risk benefit assessment, and publication policy.

14. Study Administration

14.1. Site Activation

All local and regional regulation requirements will be fulfilled prior to site activation and enrollment of subjects into the study. Each investigational site must have written in documentation of site readiness, including but not limited to:

- IRB approval letter
- Fully executed Clinical Trial Agreement (CTA)
- Financial Disclosure for Investigators
- Delegated Task List
- Training documentation

14.2. Monitoring

Investigational sites will be monitored to ensure compliance with the study protocol, adherence to applicable regulations, and accuracy of study data. A monitoring visit will be conducted primarily to ensure the safety and well-being of the subjects is preserved. Monitoring visits will also be used to verify that study data submitted on case report forms are complete and accurate with respect to the subject clinical records and to verify device accountability. Site personnel will complete eCRFs following each subject visit. Study data submitted will be reviewed against subject charts and other sources containing original records of subject data. Source document verification will occur in accordance to the Monitoring Plan. The investigator and/or institution shall permit Medtronic monitoring representatives direct access to source data and documents. All monitoring activities shall be documented per the monitoring plan. In Japan, the monitor will confirm periodic testing, calibration and maintenance of equipment used for study assessments according to local standard of practice.

It is recommended for all medical records to be clearly marked to indicate that the subject is enrolled in this study.

The progress of the study will be monitored by:

- On-site review, and/or remote data clarification and verification, as deemed appropriate by Medtronic
- Telephone communications between the site personnel (e.g., investigator, study coordinator) and study monitors
- Review of eCRFs and the associated clinical records
- Review of regulatory documents

Monitoring and monitoring oversight will be provided by Medtronic. Representatives of Medtronic (i.e. contractors and designees) may also act as study monitors.

14.2.1. Pre-Study Visits

Prior to enrollment, Medtronic personnel will visit the study site(s) to verify the investigator and facilities are prepared for the study and that requirements for study initiation were completed or in progress at the time of the visit.

14.2.2. Interim Monitoring

The study will be monitored throughout its course. Frequency of monitoring visits will be determined on a case-by-case basis. The monitor may verify the following during monitoring visits:

- The study is being conducted according to the protocol and applicable regulations
- Changes to the protocol requiring IRB/EC review have been approved
- Accurate, complete, and current records are being maintained
- Approved informed consent forms are being completed correctly (including documentation that the subject was given ample time to review the consent, that a copy of the consent was given to each subject, and that no study procedures occurred prior to consent)
- The consent process is being documented correctly
- Timely reports (annual reports, adverse events, protocol deviations) are being made to the sponsor and IRB/EC as required

In addition, the following activities may occur during monitoring visits:

- Case report form review
- Informed consent review
- Investigational product accountability review
- Review of device storage location

14.2.3. Study Close-Out

A final visit to the center may be made at study conclusion or at the end of the site's participation.

The following items may be verified during the closeout process:

- Investigator/study administration files are complete and accurate
- Final receipt of eCRFs confirmed; missing data or clarification issues closed
- Annual and interim reports (if any) are up to date
- Reported deficiencies for the site have been resolved or closed
- Investigational product accountability (e.g. disposition logs) balance and are current

- Schedule determined for final study report submission by investigator to the respective IRB/EC
- Record retention requirements discussed and agreed to by the investigator

After the study has been completed, medical care will be provided to the subjects upon the discretion of the treating physician.

14.3. Auditing

Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independent of the personnel directly involved in the study. Regulatory bodies, such as the Food and Drug Administration, Health Canada or PMDA may also perform inspections at participating sites. The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents.

14.4. Source Data/Documents

Source data/documentation is defined as the first time the data appear and may include all clinical records, hospital records, procedural reports, autopsy reports, and any other material that contains original information used for study data collection or adverse event reporting. Data entered into the study database must be traceable to source documents.

The eCRFs may not serve as source documents. Source documentation for data elements not routinely captured in medical records (eg, echocardiography variables, investigator assessment of adverse events, reason for study exit, reason for study deviations) may vary from center to center. For example, the site may use technical worksheets if they are clearly identified as source documents and signed and dated by the person completing the worksheet and a study investigator.

Source documents are required to be maintained following the record retention policies outlined in **Section 15.3. Record Retention**. Source documents must be made available for monitoring or auditing by the sponsor's representative or representatives of applicable regulatory agencies or the IRB/EC.

The investigator must ensure the availability of all source documents from which data on the eCRFs were derived. Where printouts of electronic medical records (EMR) are provided as source documents, or where copies of medical records are retained as source documents, they must be identified as certified copies that follow a documented certification process attributing to their accuracy and completeness.

In addition, the medical records of study subjects should be marked in such a way to indicate their participation in the study.

14.5. Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique subject identification number (ID) to each subject. Records of the subject/ID relationship will be maintained by the study site. The ID is to be recorded on all study documents to link them to the subject's medical records at the site. To maintain confidentiality, the subject's name or any other personal identifiers should not be recorded on any study document other than the informed consent form. In the event a subject's name is included for any reason, it will be masked as applicable. In the event of inability to mask the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel.

Study information and data may be shared with the following for reasons including, but not limited to, monitoring or auditing purposes:

- With the study sponsor, Medtronic and its agents and contractors (together "Medtronic");
- With other researchers in the study to support study conduct or processes (e.g., patient screening);
- With government organizations and review boards required to watch over the safety and effectiveness of medical products and therapies and the conduct of research; and
- With other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research.

The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

Investigational sites will protect the personal information of subjects in accordance with applicable laws, regulations and IRB/EC requirements.

14.6. Data Management

Medtronic will be responsible for the processing and quality control of the data. Data review, database cleaning and issuing and resolving data queries will be done according to Medtronic internal standard operating procedures (SOPs) and the Data Management Plan for this study. The study database will employ validation programs (e.g. range and logic checks) on certain entered data to identify possible data entry errors and to facilitate data validation. Required images for Medtronic or Core Lab evaluation will be de-identified and electronically transferred using a secure file transfer or other secure methods as appropriate. All study imaging including protocol required assessments, implant angiography, and any unscheduled imaging performed to assess the Harmony TPV should be sent to Medtronic.

14.7. Liability

Subject compensation, indemnification and liability insurance coverage are included In the Clinical Study Agreement for each participating center.

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and customs concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB/Head of Medical Institution.

14.8. CIP Amendments

The investigator may propose any appropriate modification(s) of the CIP or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the CIP, including a justification for the amendment, to the applicable regulatory agency(ies) and to the investigators to obtain approval from their IRB/EC. The investigator will only implement the amendment after receiving approval from the IRB/EC, applicable regulatory agencies and Medtronic. Administrative amendments to the CIP will be submitted to the IRB/EC for notification.

14.9. Publication and Use of Information

Medtronic is committed to the widespread dissemination of all primary and additional endpoint results. A Publication Plan will be implemented and followed. At the conclusion of the study, a multisite abstract reporting the primary results will be prepared by the Principal Investigator (in collaboration with others) for subsequent presentation at an annual scientific meeting. A multisite publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single site experience within the study is not allowed until both the preparation and publication of the multisite results, and then only with written permission from Medtronic.

Following analysis and presentation of the endpoint results, active participation of all participating investigators, CEC committee members, DMC members, and core laboratory personnel will be solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications from the study requires approval by the steering committee and publication committee.

A separate Publication Plan will provide detailed information about the publication committee, authorship, publication proposals, and requests for data.

14.10. Suspension or Early Termination of the Study

Medtronic may decide to suspend or prematurely terminate the study. If the study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators and regulatory authorities of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB/EC. Medtronic will, as soon as possible, provide a written statement to the investigators to enable prompt notification of the IRB/EC. If study enrollment is terminated early, follow-up visits will continue for all enrolled subjects.

14.11. Suspension or Early Termination of a Study Site

Medtronic may decide to suspend or prematurely terminate a study site (e.g. in case of expiring approval of the reviewing IRB/EC, non-compliance to the CIP, or lack of enrollment). If a study site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB/EC.

15. Record Retention and Reporting Responsibilities

15.1. Responsibilities of the Investigator

The investigator is responsible for the preparation, review, and signature (as applicable), and retention of the following records:

- All essential correspondence that pertains to the investigation
- Device use/disposition records
- Records of each subject's case history and exposure to the device. Case histories include the eCRFs and supporting data (source documentation), including, for example:
- Signed and dated consent forms
- Medical records, including, for example, progress notes of the physicians, the subject's hospital chart(s) and the nurses' notes
- All adverse event/device deficiency information
- A record of the exposure of each subject to the investigational device (e.g., date of implant procedure and follow-up assessment dates)
- Documentation of any deviation from the CIP, including the date and the rationale for such deviation
- Signed Investigator Agreement, signed and dated curriculum vitae of the PI, sub-investigator(s) and key members, signed Delegated Task List
- In Canada, Investigator's Agreement in accordance with Subsection 81(k) of the Medical Devices Regulations

- The approved CIP, Patient Information/Informed Consent Form, Investigator Brochure or Report of Prior Investigations, and any amendments
- Insurance certificate, where applicable
- IRB/EC Approval documentation and voting list
- Regulatory authority notification and approval documentation
- List of sponsor and monitoring contacts
- Training records
- Disclosure of conflict of interest of the PI and sub-investigator(s)

The investigator may withdraw from responsibility to maintain records by transferring custody to another person, who will accept responsibility for record and report maintenance. The Investigator is responsible for the preparation, review, signature, and submission of the reports listed in Table 5, Table 6, and Table 7 as applicable to the respective geography. These are also subject to inspection by government agencies and must be retained. Reports will be submitted to regulatory authorities per local reporting requirements/regulations.

Table 5: Investigator records and reporting responsibilities applicable to the United States

Report	Submit To	Description/Constraints
Withdrawal of IRB approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. *(21 CFR 812.150(a)(2)).*
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (3)).*
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. *(21 CFR 812.150(a)(4))*
Failure to obtain IC prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final investigator report	Sponsor, IRB s and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

Table 6: Investigator records and reporting responsibilities applicable to Canada

Report	Submit To	Description/Constraints
Withdrawal of REB approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing REB of the investigator's part of the investigation within 5 working days of the date of withdrawal. (Medtronic Requirement)
Study Deviations	Sponsor and REB as applicable	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. (Medtronic Requirement)
Final Report	REB, Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. (Medtronic Requirement)
Adverse Device Effect Reporting (Mandatory Problem reporting)	Health Canada	DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the Regulator within 72 hours after it comes to the attention of the qualified investigator.

Table 7: Investigator records and reporting responsibilities applicable to Japan

Report	Submit to	Description/Constraints
Co-investigator/Clinical Research Coordinators List	Head of Medical Institution	When the principal investigator assigns important parts of the clinical trial duties to co-investigators and/or clinical research coordinators, he or she shall prepare a list of the assigned duties and the individual performing the assigned duties, submit the list to the Head of Medical Institution on the list, and receive the understanding of such individuals. *(MHLW Ordinance 36, 2005 Article 63)*
Study Deviations	Sponsor and Head of Medical Institution	The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/EC approval. In this case, the investigator shall immediately submit to the sponsor, the Head of Medical Institution, and to the IRB/EC via the Head of Medical Institution, the description and reason for the deviation and the proposed revision to the protocol, if one is necessary, to receive agreement.

		All deviations, regardless of the reason, shall be submitted to the sponsor. *(MHLW Ordinance 36, 2005 Article 66)*
Summary of the Clinical Study Status	Head of Medical Institution	The principal investigator shall submit a summary of the clinical study status to the Head of Medical Institution in writing once a year, or more frequently if requested by the IRB/EC, to receive the continuation review by the IRB/EC. *(MHLW Ordinance 36, 2005 Article 68)*
Premature Termination or Suspension of the Clinical Investigation	Head of Medical Institution	When the principal investigator discontinues or suspends the clinical study, he or she shall promptly notify the Head of Medical Institution thereof in writing, and explain in detail in writing the discontinuation or suspension. *(MHLW Ordinance 36, 2005 Article 69)*
Completion of the Clinical Investigation	Head of Medical Institution	When the clinical study is completed, the principal investigator shall notify the Head of Medical Institution thereof in writing and report on a summary of the clinical study results in writing. *(MHLW Ordinance 36, 2005 Article 69)*

15.2. Responsibilities of the Sponsor

The Sponsor will maintain the following records, including but not limited to:

- All essential correspondence related to the clinical study
- Signed Investigator Agreement
- Signed and dated current curriculum vitae for each investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event and device deficiency information
- All data forms, prepared and signed by the investigators, and received source documentation and core lab reports
- CIP, investigator brochure or report of prior investigations and subsequent amendments
- Site monitoring reports
- Financial disclosure information
- Study training records for site participants and internal study staff members
- Contact lists of all participating investigators/investigative sites, study monitors and Sponsor staff members; Sponsor will maintain these lists and provide updates to the necessary parties
- Sample of device labeling attached to investigational device
- Insurance certificates
- Ethics Board approval documentation and voting list

- Regulatory authority notification and approval documentation
- Lab certificates /Lab normal ranges
- Statistical analyses
- Clinical study report

The Sponsor is responsible for the preparation of, the accuracy of the data contained in, the review of and the submission of the reports listed in Table 8, Table 9, and Table 10 as applicable to the respective geography.

Table 8: Sponsor records and reporting responsibilities applicable to the United States

Report	Submit To	Description/Constraints
Unanticipated Adverse Device Effect	Investigators, IRB, FDA, and relevant authorities	Notification within ten working days after the sponsor first receives notice of the effect. *(21 CFR 812.150(b)(1))*
Withdrawal of IRB approval	Investigators, IRB, FDA, and relevant authorities	Notification within five working days after receipt of the withdrawal of approval. *(21 CFR 812.150(b)(2))*
Withdrawal of FDA approval	Investigators, IRB, and relevant authorities	Notification within five working days after receipt of notice of the withdrawal of approval. *(21 CFR 812.150(b)(3))*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	IRB and FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(4)(5), 812.36(f)*
Recall and device disposition	Investigators, IRB, relevant authorities and FDA	Notification within 30 working days after the request is made and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain IC	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final Report	Investigators, IRB, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*

Table 9: Sponsor records and reporting responsibilities applicable to the Canada

Report	Submit To	Description/Constraints
Unanticipated Serious Adverse Device Effects (USADE)	REB, Investigators, Health Canada	Medtronic will notify investigators and Ethics Boards in all geographies as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. Preliminary and final reporting to the Canadian Ministry of Health of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Canada Medical Device Regulations, SOR/98-282; Mandatory Problem Reporting 59(1), 59(2), 60 (1))
Serious Adverse Device Effects (SADE)	REB as applicable, Health Canada	Submit to Ethics Boards per local requirement. (ISO 14155) Preliminary and final reporting to the Canadian Ministry of Health of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective

		action. (Canada Medical Device Regulations, SOR/98-282; Mandatory Problem Reporting 59(1), 59(2), 60 (1))
Device Deficiency that might have led to an SADE	REB as applicable, Investigators, Health Canada	Submit to Ethics Board per local requirement. Submit to regulatory authority as per local requirement.
Premature termination or suspension of the clinical investigation	Investigators, REB, Health Canada	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2011)
Recall and device disposition	Investigators, REB, Health Canada	Notification within 30 working days of the request and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. (Medical Devices Regulation Mandatory Problem Reporting 63 – 65.1)
Final Report	Investigators, REB, and Health Canada if applicable	The investigator shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). The principal clinical investigator in each center shall sign the report. (ISO 14155:2011)
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators quarterly. (ISO 14155:2011)
Significant new information	Ethics Board and Health Canada	Ensure that the Ethics Boards and Regulatory Authorities are informed of significant new information about the clinical investigation. (ISO 14155:2011)

Table 10: Sponsor records and reporting responsibilities applicable to Japan

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Head of Medical Institution Pharmaceuticals and Medical Devices Agency (PMDA)	When the sponsor suspends or discontinues the clinical trial, he or she shall promptly notify the heads of all the medical institutions and regulatory authorities thereof and the detailed reason therefor in writing. (*MHLW Ordinance 36, 2005 Article 32*)
Termination of development of investigational device	Head of Medical Institution PMDA	When the sponsor decides not to attach the documents concerning clinical trial records collected in the clinical trial to the authorization application, he or she shall promptly notify the

		heads of all the medical institutions other facilities engaged in the clinical trial thereof and the detailed reason therefor in writing. (*MHLW Ordinance 36, 2005 Article 32*)
Investigator List	Head of Medical Institution PMDA	The sponsor shall beforehand submit the list of investigators to PMDA and Head of Medical Institution. *(MHLW Ordinance 36, 2005 Article 10, Pharmaceutical and Medical Device Act Enforcement Regulations, Article 269, 275)* The sponsor shall submit the list of investigators to PMDA and Head of Medical Institution when making any changes in the list. *(MHLW Ordinance 36, 2005 Article 51, Pharmaceutical and Medical Device Act Enforcement Regulations, Article 270, 275)*
Important information concerning the quality, efficacy, and safety of the investigational device	Principal Investigator Head of Medical Institution PMDA	When new, important information is obtained, the sponsor shall revise the investigator's brochure. In addition, prior to revising the investigator's brochure, the sponsor shall report the information to the principal investigator, Head of Medical Institution, and regulatory authorities. *(MHLW Ordinance 36, 2005 Article 28)*
Clinical Trial Report	PMDA upon request	The sponsor shall prepare, according to the procedure, a clinical study report that summarizes the results, etc., of a clinical study when it is completed or discontinued. *(MHLW Ordinance 36, Article 33)*
Study deviation	Principal Investigator Head of Medical Institution as necessary	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. *(ISO 14155:2011)* When the monitor confirms deviation as a result of monitoring, the monitor shall notify the principal investigator and, as necessary, the Head of Medical Institution thereof. The monitor shall also request for appropriate measures to be taken to prevent such deviation in the future. *(MHLW Ordinance 36, 2005 Article 30)*

15.3. Record Retention

The investigator must retain the Investigator Site File, source documents, and the records listed in **Section** 15.1. **Responsibilities of the Investigator**, until informed by Medtronic they no longer need to be retained. At a minimum, the investigator must retain records for at least 3 years (or longer if required by local law) after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 3 years have elapsed since the formal discontinuation of the clinical study or clinical development of the investigational devices. The investigator should take measures to prevent accidental or early destruction of the study related materials.

Medtronic will maintain study records under its responsibility in accordance with federal laws and regulations, J-GCP and Medtronic policy.

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17. Appendices

Appendix I: Informed Consent Template

Appendix II: Adverse Event Definitions

Appendix III: Adverse Event Code List
Appendix IV: Echocardiography Protocol
Appendix V: Radiography Protocol
Appendix VI: Cardiac Magnetic Resonance Imaging Protocol – Functional Parameters
Appendix VII: Computed Tomographic Angiography (CT) Imaging Protocol
Appendix VIII: Anatomic Measurements and Device Screening Guidelines
Appendix IX: Explant Protocol
Appendix X: Instructions for Use Document
Appendix XI: SF-36 Questionnaire
Appendix XII: Post-Implant CT Sub-Study

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Initial Release *Note: Version 1.0 of this document may not align to the version of the document determined in the Medtronic Trial Master File (RAD)*	[redacted]
2.0	• Additional outcome measures added (technical success, device success) • Modification of additional outcome measure (procedural success) • Addition of implant maximum of 10 subjects per site • Modification of event causality terms/definitions • Minor administrative changes throughout *Note: Version 2.0 of this document may not align to the version of the document determined in the Medtronic Trial Master File (RAD)*	[redacted]
3.0	• Addition of Canada as a planned geography • Expanded scope of document to include Canadian regulatory requirements • Clarified Primary Effectiveness Endpoint to include Echocardiography assessment should CMR not be available • Minor administrative changes throughout *Note: Version 3.0 of this document may not align to the version of the document determined in the Medtronic Trial Master File (RAD)*	[redacted]

4.0	• Addition of Japan geography • Expanded scope of document to include Japan regulatory requirements • Adjustment of pre-implant window for imaging requirements • Addition of post-care lifelong Aspirin and prophylactic antibiotic therapy recommendation • Addition of section regarding role & membership of screening committee • Revised Appendix VII Anatomic Cardiac Magnetic Resonance Imaging Protocol to become a Sub-study including subsequent requirements • Removed requirement for sites to perform anatomic measurements on CT and MRI images • Minor administrative changes throughout *Note: Version 4.0 of this document may not align to the version of the document determined in the Medtronic Trial Master File (RAD)*	[redacted]
5.0	• Added information describing additional size Harmony TPV device • Addition of section describing a subset of subjects for initial implant of the Harmony TPV 25 • Addition of a post-implant CT sub-study Appendix XIII • Adjustment of pre-implant window for imaging requirements • Minor administrative changes throughout	[redacted]
6.0	• Added information describing additional modified TPV25 size Harmony TPV device • Removed language allowing deferring subjects • Added discharge CT and one month post-implant functional CMR for mTPV 25 implants • Removed screening log requirements • Updated Appendix XII for Post Implant CT Sub-study • Minor administrative changes throughout	[redacted]

Appendix I: INFORMED CONSENT TEMPLATE

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Appendix II: ADVERSE EVENT DEFINITIONS

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Appendix III: ADVERSE EVENT CODE LIST

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Appendix IV: ECHOCARDIOGRAPHY PROTOCOL

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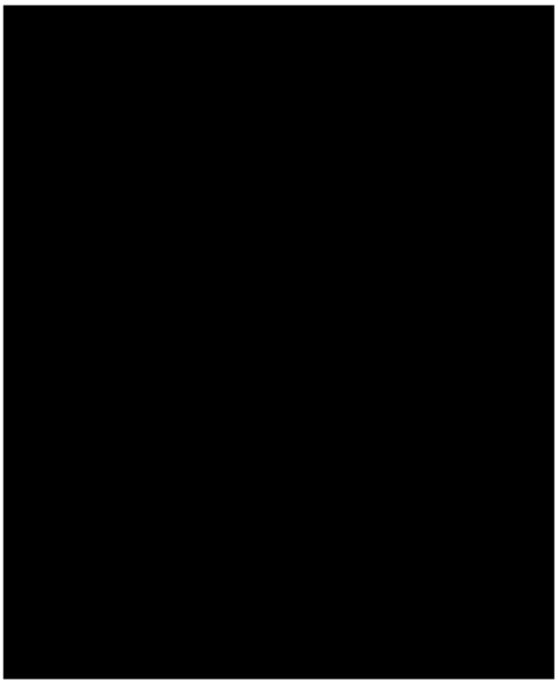

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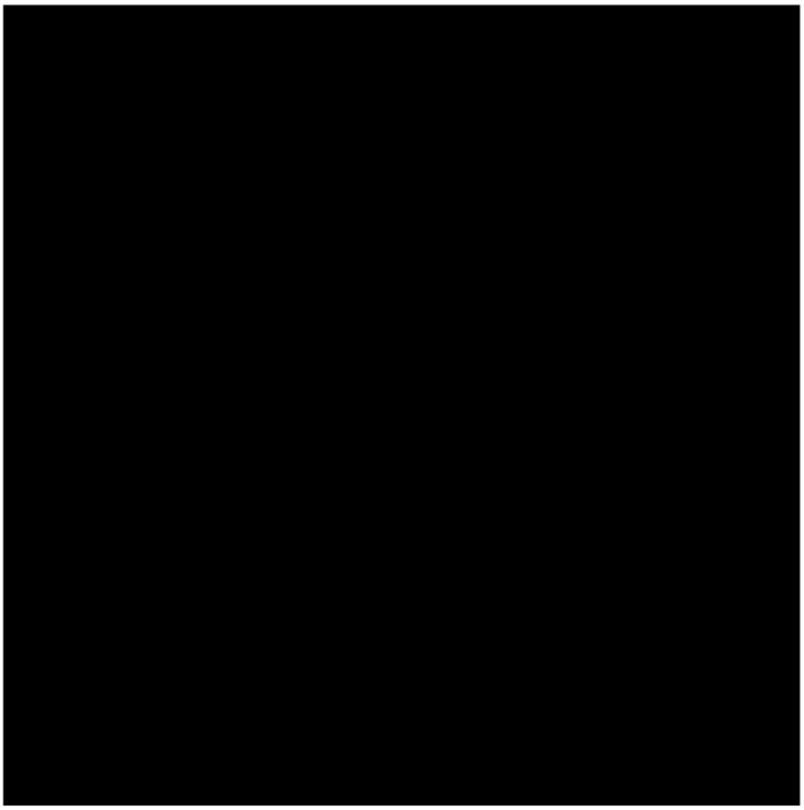

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Appendix V: RADIOGRAPHY PROTOCOL

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Appendix VI: CARDIAC MAGNETIC RESONANCE IMAGING PROTOCOL-FUNCTIONAL PARAMETERS

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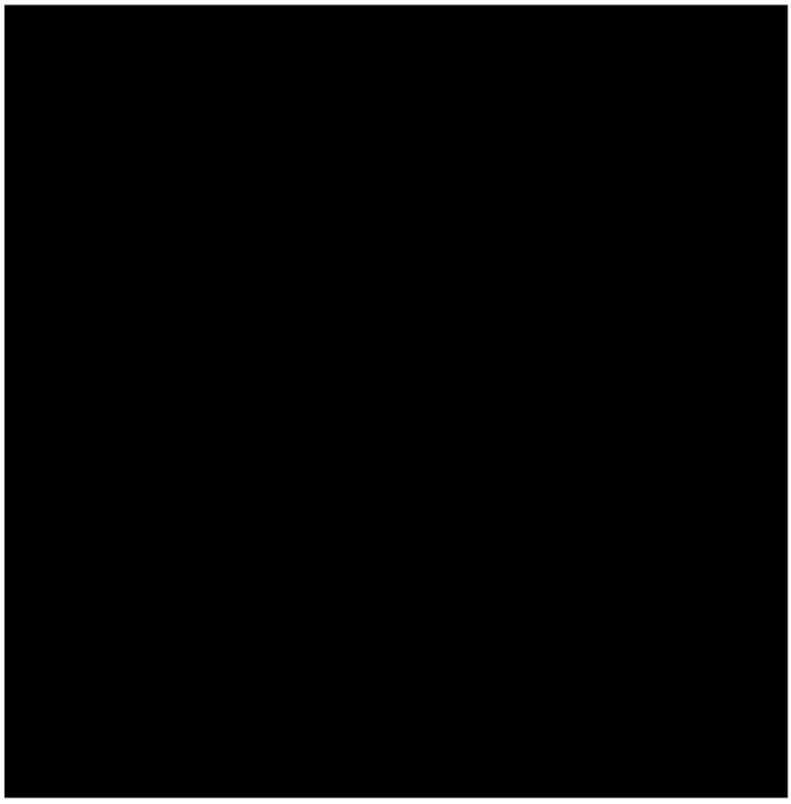

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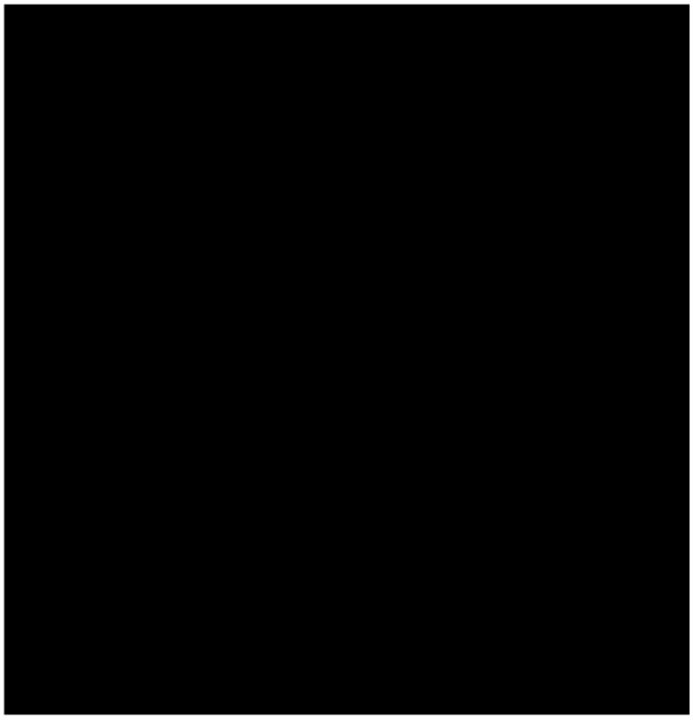

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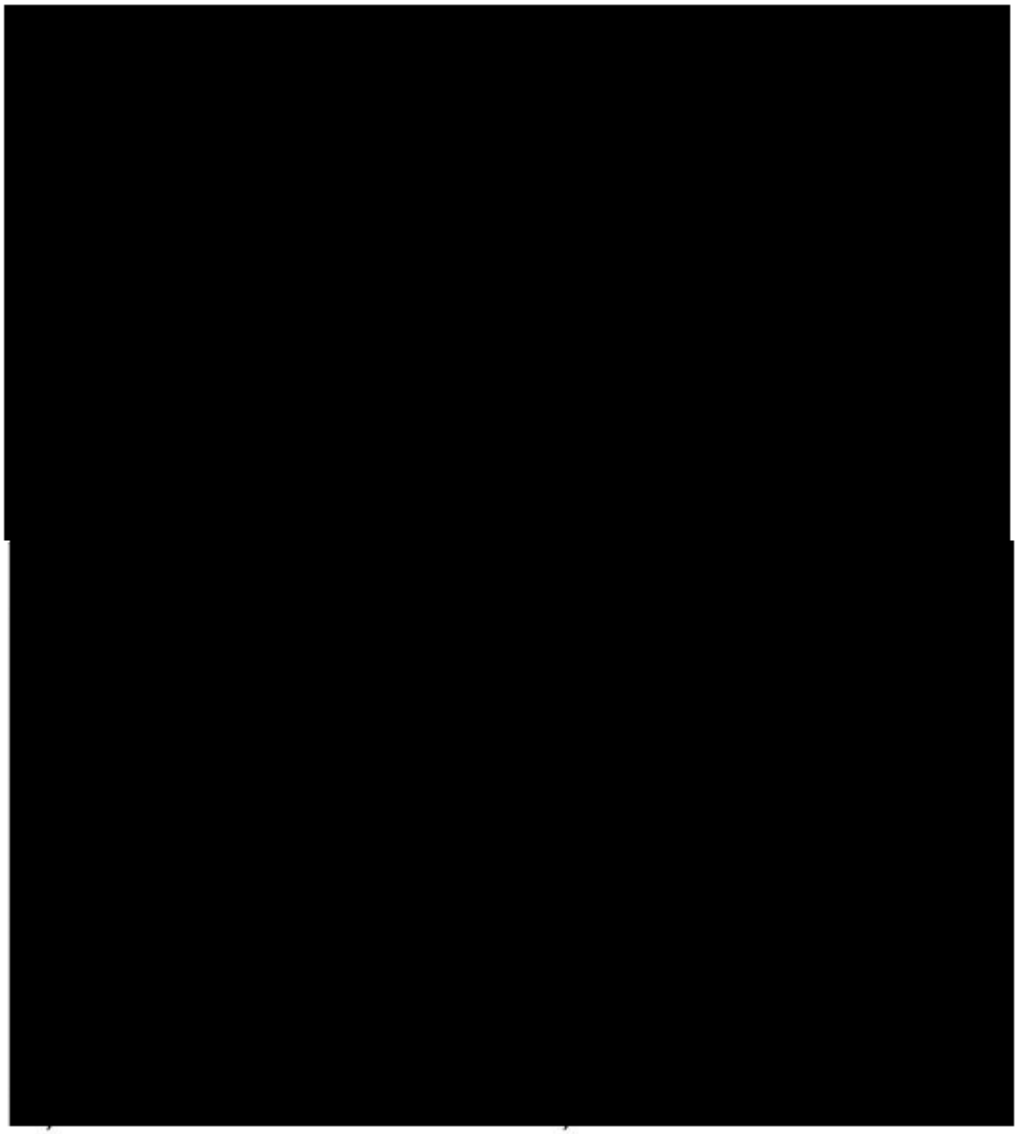

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Appendix VII: COMPUTED TOMOGRAPHIC ANGIOGRAPHY (CT) IMAGING PROTOCOL

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Appendix VIII: ANATOMIC MEASUREMENTS AND DEVICE SIZING GUIDELINES

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Appendix IX: EXPLANT PROTOCOL

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Appendix X: INSTRUCTIONS FOR USE DOCUMENT

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Appendix XI: SF-36 QUESTIONNAIRE

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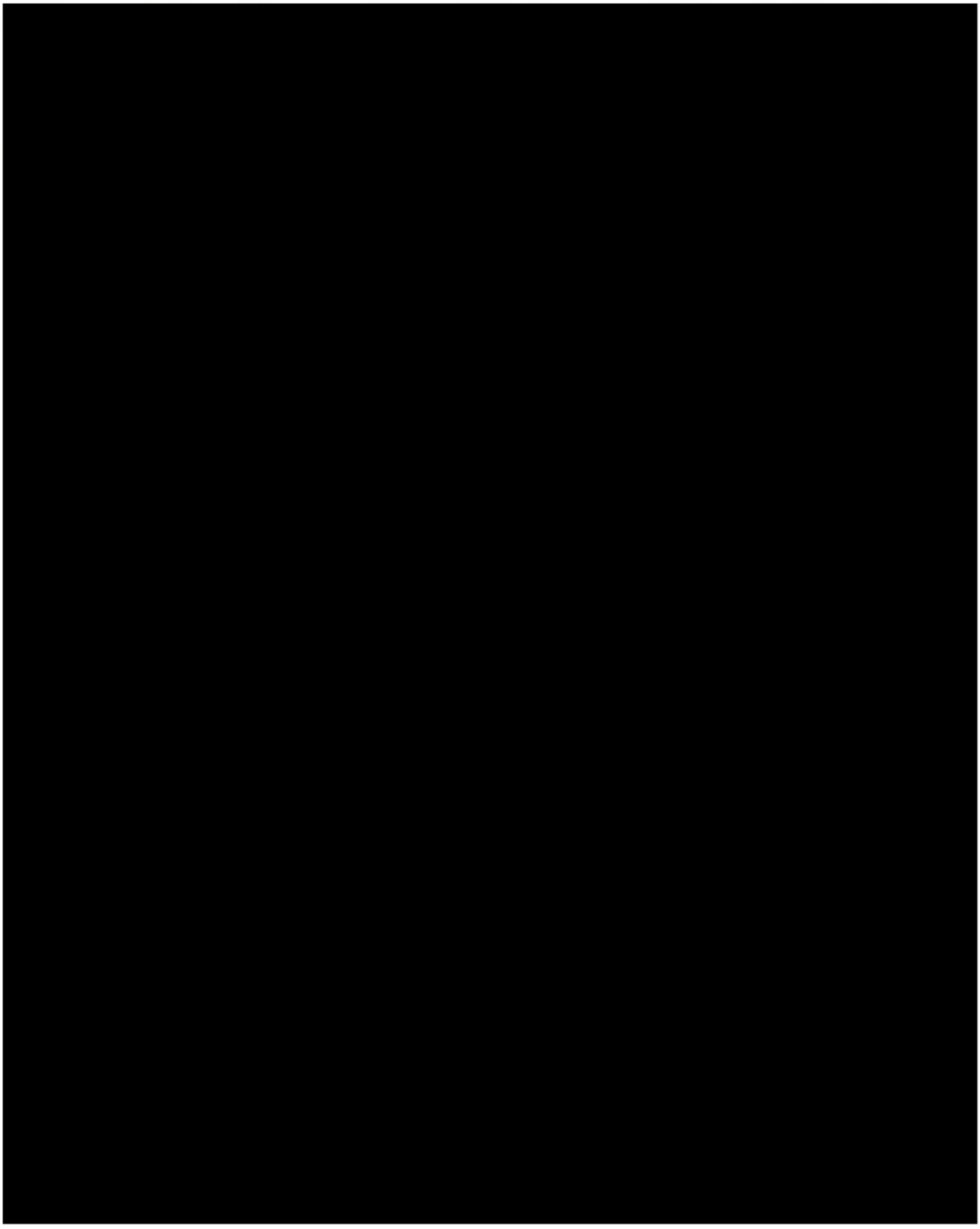

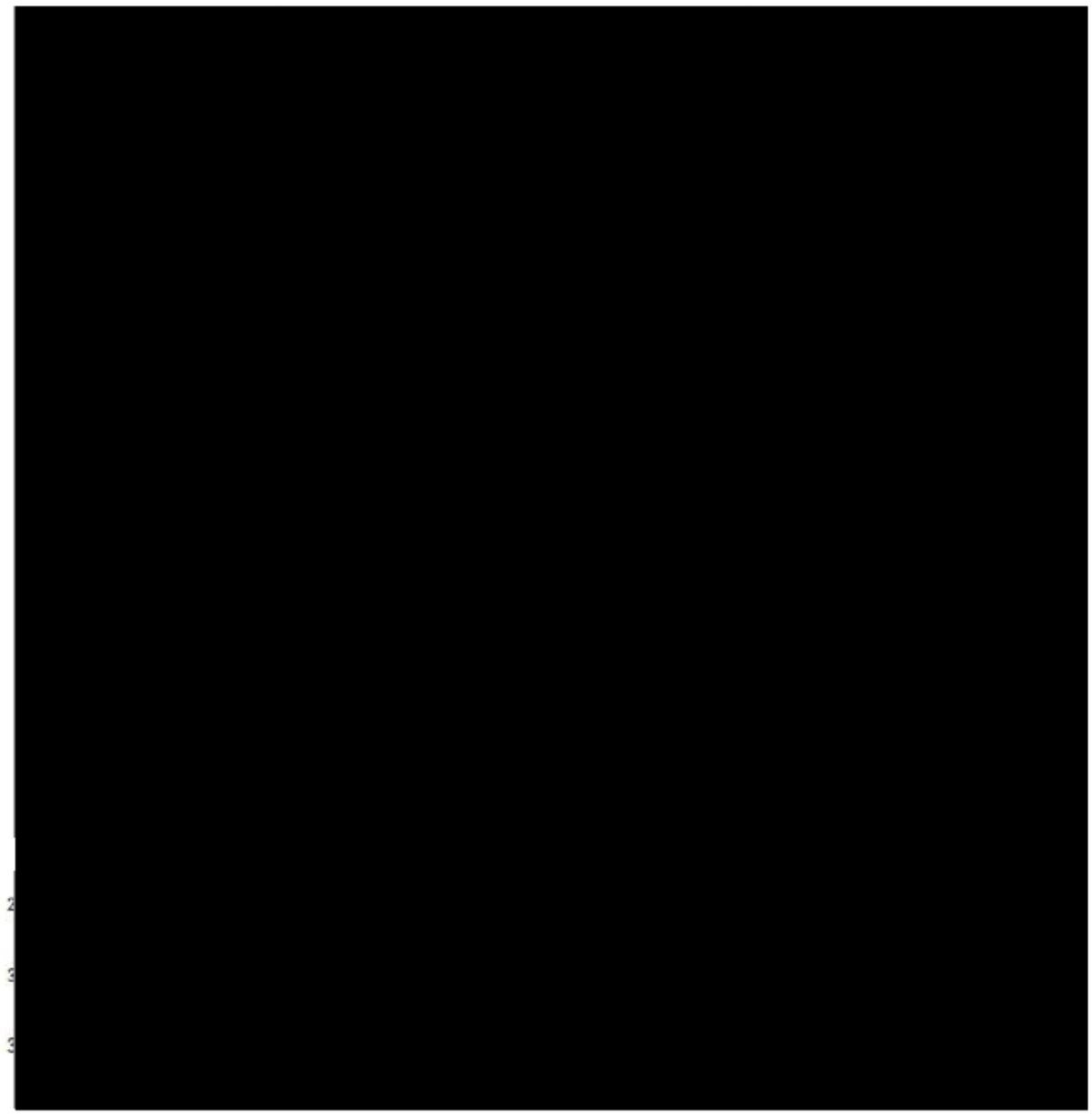

Appendix XII: POST-IMPLANT COMPUTED TOMOGRAPHIC ANGIOGRAPHY (CTA) IMAGING SUB-STUDY PROTOCOL

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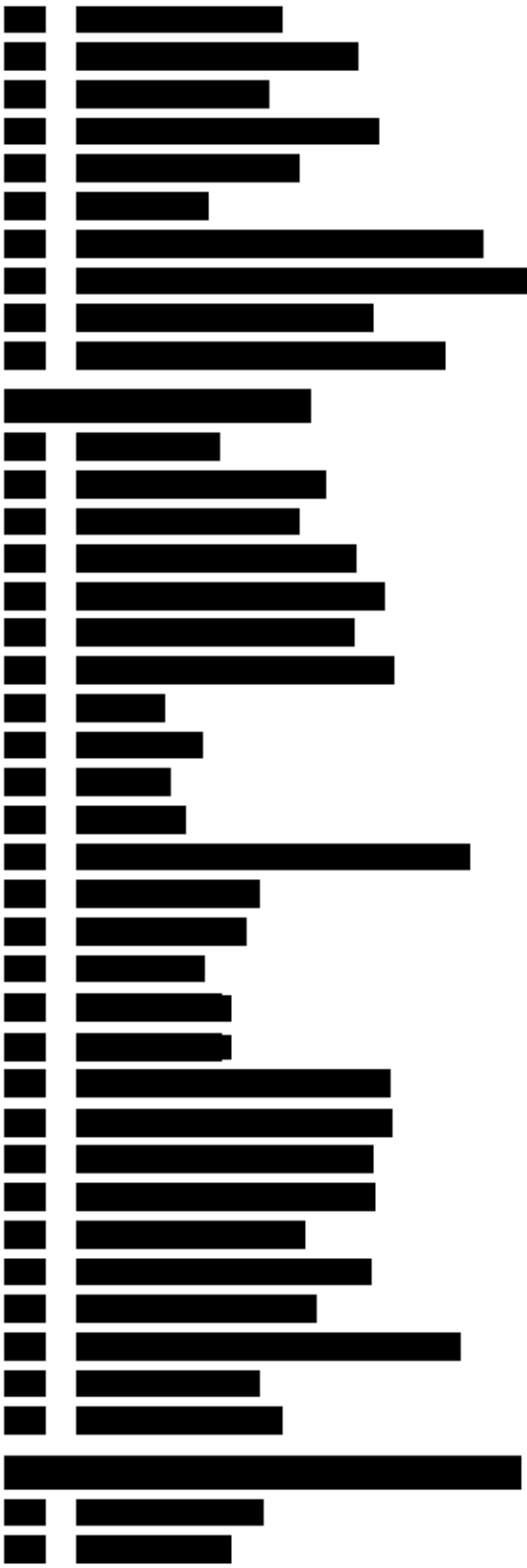
Appendix III: ADVERSE EVENT CODE LIST



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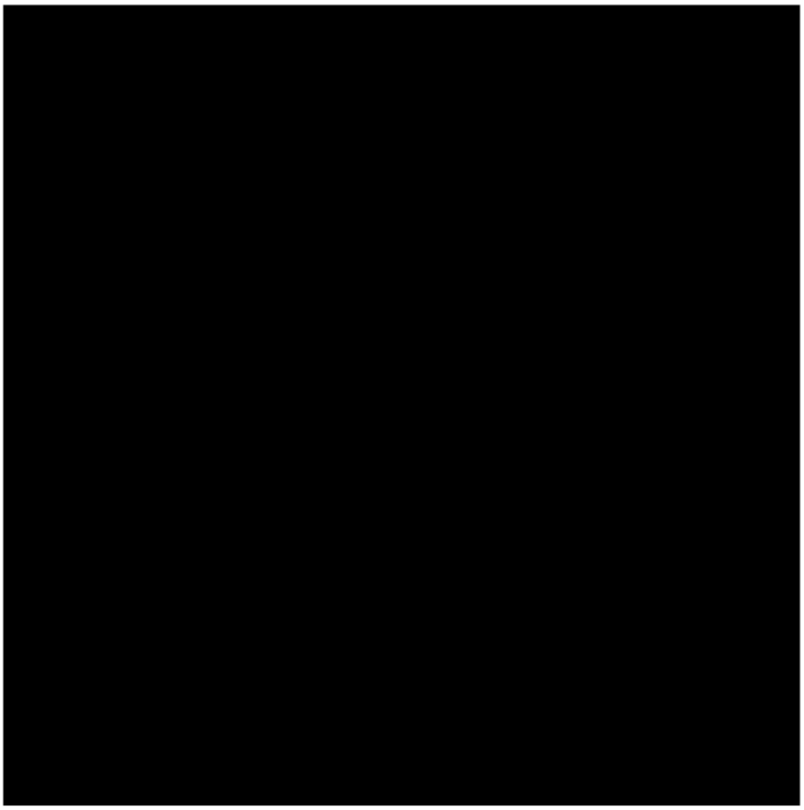

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Appendix VI: CARDIAC MAGNETIC RESONANCE IMAGING PROTOCOL-FUNCTIONAL PARAMETERS

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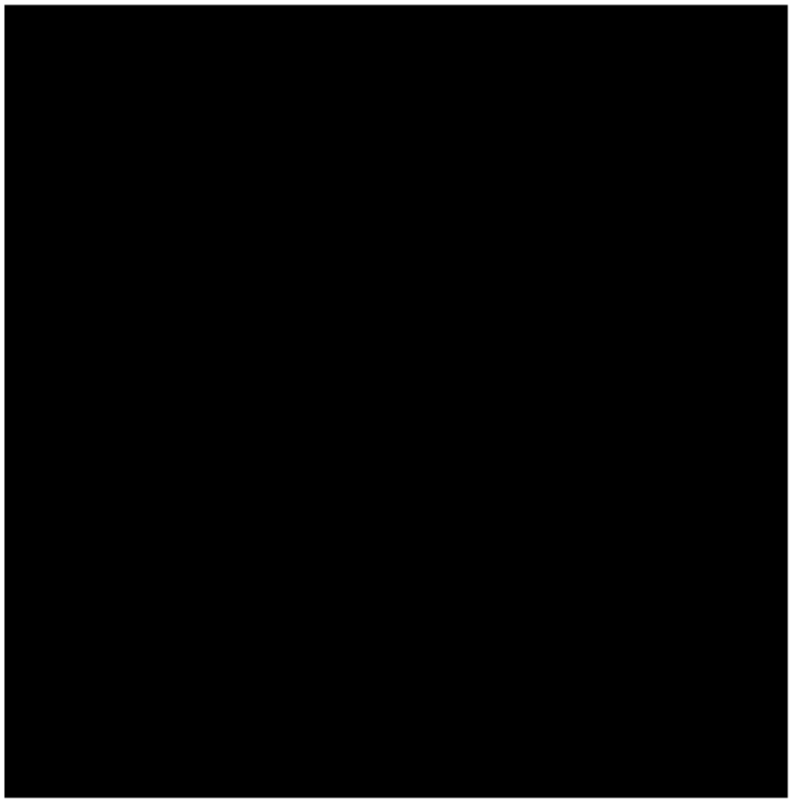

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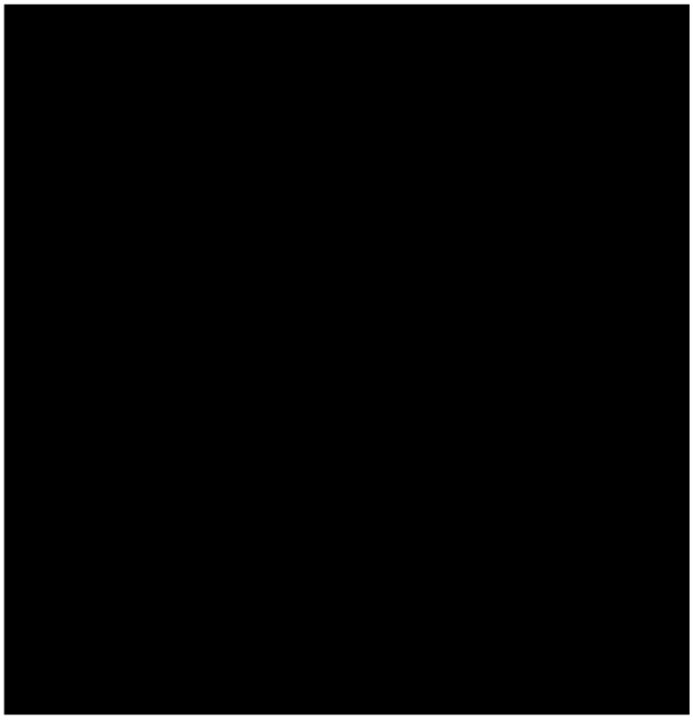

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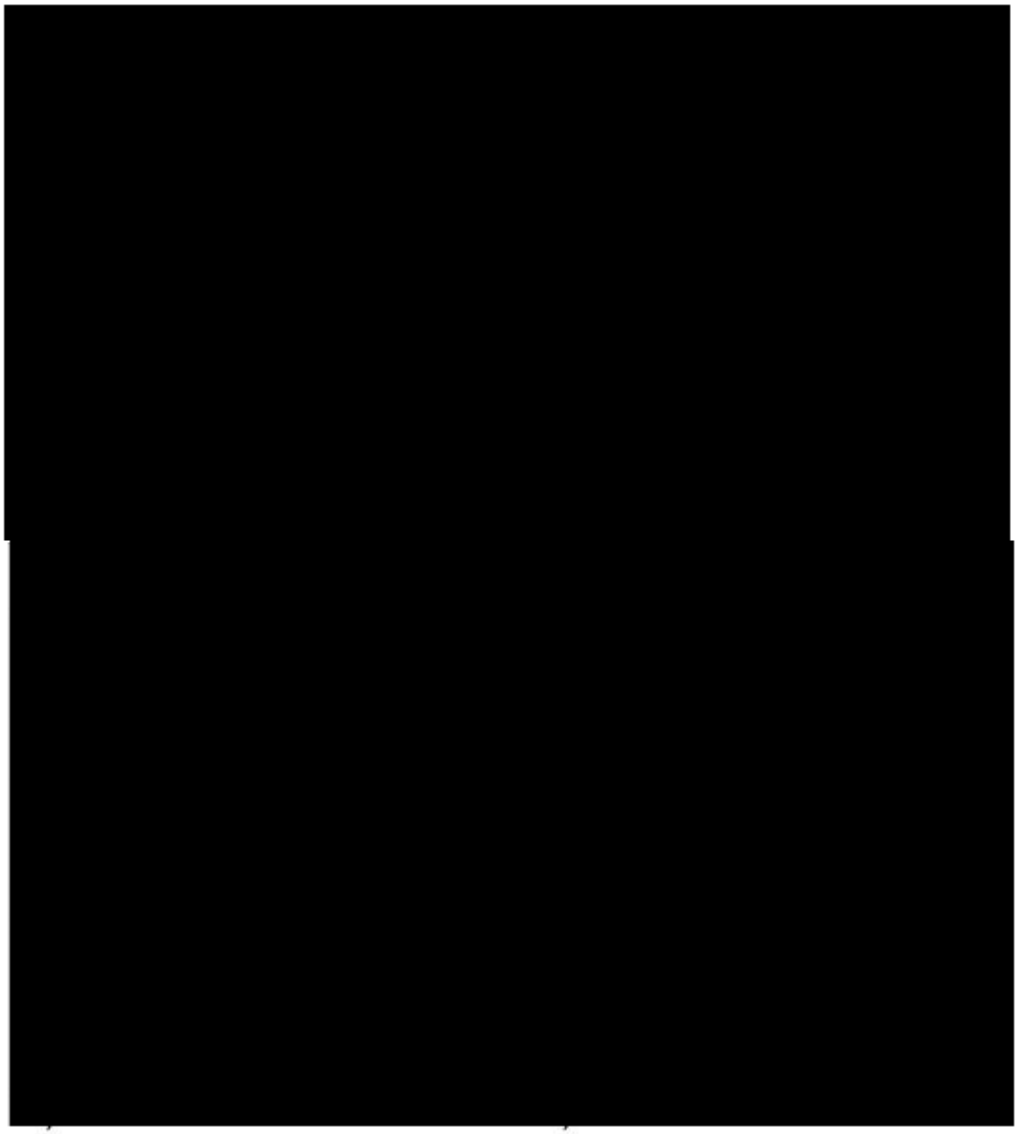

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Appendix VII: COMPUTED TOMOGRAPHIC ANGIOGRAPHY (CT) IMAGING PROTOCOL

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Appendix VIII: ANATOMIC MEASUREMENTS AND DEVICE SIZING GUIDELINES

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Appendix IX: EXPLANT PROTOCOL

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Appendix X: INSTRUCTIONS FOR USE DOCUMENT

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Appendix XI: SF-36 QUESTIONNAIRE

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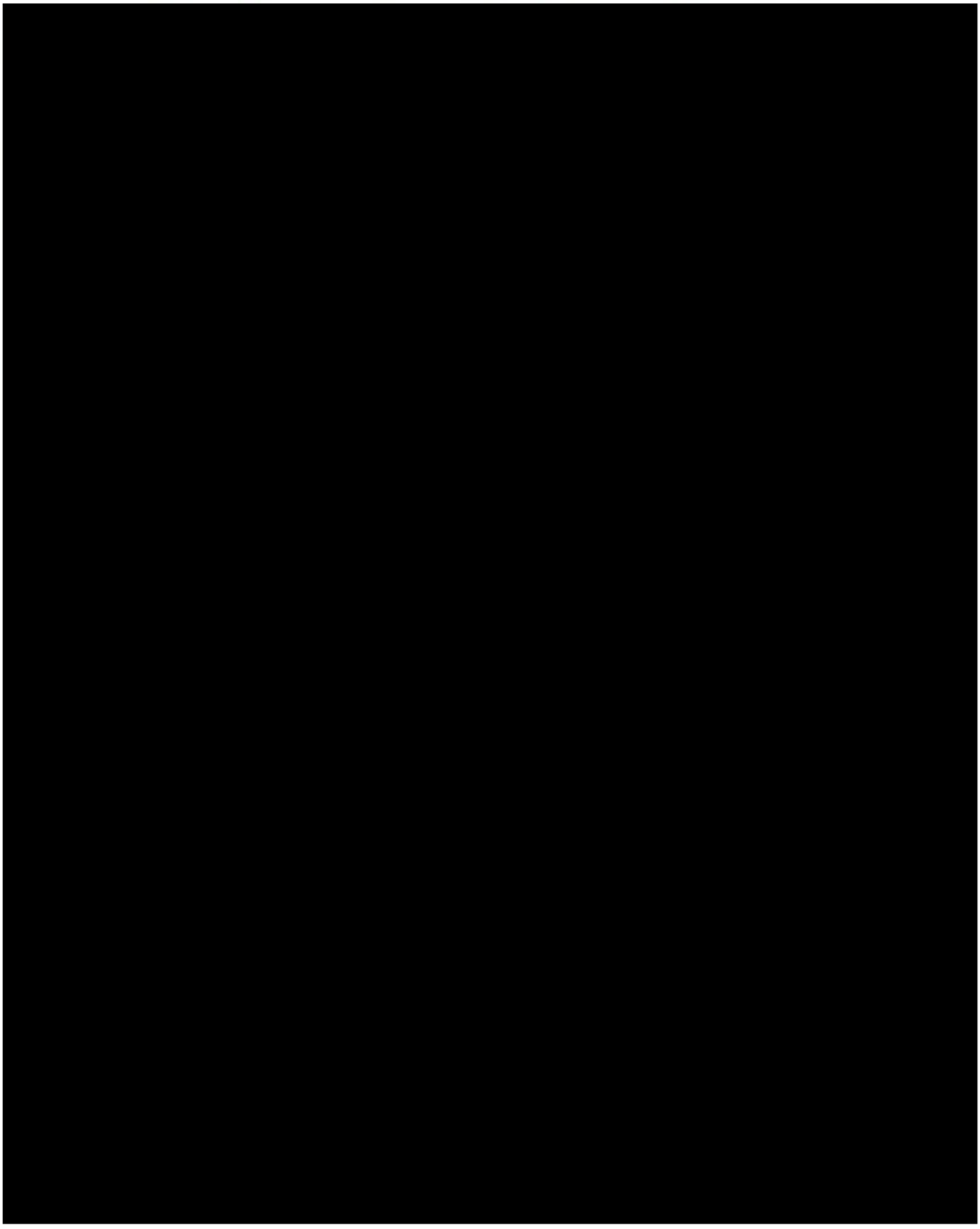

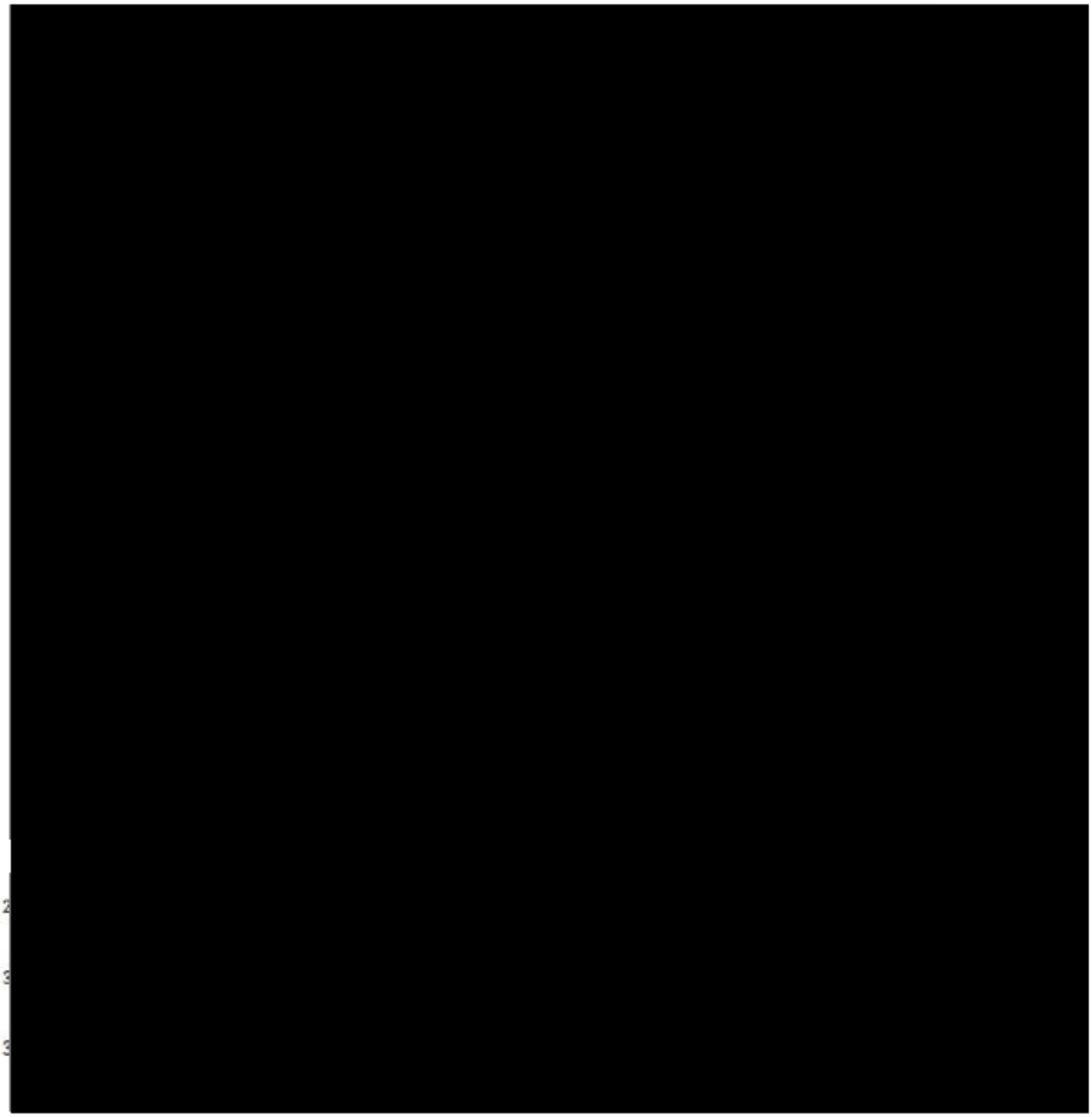

Appendix XII: POST-IMPLANT COMPUTED TOMOGRAPHIC ANGIOGRAPHY (CTA) IMAGING SUB-STUDY PROTOCOL

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