Medtronic Clinical Investigation Plan	
Clinical Investigation Plan / Study Title	PERIGON Japan Study
Clinical Investigation Plan Identifier	MDT2-15-14
Study Product Name	Avalus aortic bioprosthesis 17mm
ClinicalTrials.gov Identifier	NCT02686814
Document Version / Date	Version 1.0 / 21-NOV-2019

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	PERIGON Japan Study
Clinical Investigation Plan Identifier	MDT2-15-14
Study Product Name	Avalus aortic valve bioprosthesis 17mm
Sponsor/Local Sponsor	Medtronic Japan, Co., Ltd. 1-2-70 Konan, Minato-ku, Tokyo 108-0075 Japan
Document Version / Date	Version 1.0 / 21-NOV-2019
Coordinating Investigator	Professor Yutaka Okita, MD Division of Cardiovascular Surgery, Takatsuki Hospital, Japan 1-3-13 Kosobe-cho, Takatsuki-shi, Osaka 659-1192 Japan

Confidentiality Statement

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2. Glossary

Term	*Definition*
AE	Adverse Event
ADE	Adverse Device Effect
AOA	Alpha-amino Oleic Acid
aPTT	Activated Partial Thromboplastin Time
AR	Aortic Regurgitation
AS	Aortic Stenosis
CA	Competent Authority
CE	Conformité Européenne (European Conformity)
CEC	Clinical Events Committee
CFR	U.S. Code of Federal Regulations
CIP	Clinical Investigational Plan
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
DTL	Delegated Task List
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOA	Effective Orifice Area
EOAI	Effective Orifice Area Index
EU	European Union
FDA	U.S. Food and Drug Administration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IFU	Instructions for use

Term	*Definition*
INR	International Normalized Ratio
EC	Institutional Review Board
ISO	International Organization for Standardization
LDH	Lactate Dehydrogenase
mm	Millimeters
MHLW	Ministry of Health, Labour and Welfare
NYHA	New York Heart Association
OPC	Objective Performance Criteria
PEEK	Polyetheretherketone
PERIGON	Medtronic PERIcardial SurGical AOritc Valve ReplacemeNt Study
PI	Principal Investigator
PI/ICF	Patient Information/ Informed Consent Form
PT	Prothrombin time
EC	Ethics Committee
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SAVR	Surgical Aortic Valve Replacement
SOP	Standard Operating Procedures
SVD	Structural Valve Deterioration
TTE	Transthoracic Echocardiography
US	United States
USADE	Unanticipated Serious Adverse Device Effect

3. Synopsis

Title	PERIGON Japan Study
Clinical Study Type	Prospective, nonrandomized, multicenter and observational study
Product Name	Avalus aortic valve bioprosthesis 17mm, 17 mm
Sponsor	Medtronic Japan, Co., Ltd.
Local Sponsor	Medtronic Japan, Co., Ltd. 1-2-70 Konan, Minato-ku, Tokyo 108-0075 Japan
Investigation Purpose	Evaluate long term safety and effectiveness of 17 mm size Avalus Aortic Valve (stented bovine aortic bioprosthesis valve) in patients undergone SAVR in MDT-2215 study
Product Status	Post approval
Study Design	Long term follow-up (3 to 5 years) for subjects undergone surgical aortic valvereplacement with Avalus bioprosthesis
Sample Size	10 subjects
Number of Sites	8 clinical sites
Inclusion/Exclusion Criteria	Inclusion Criteria: Enrolled and still being followed up in MDT-2215 study (Protocol identification No. MDT2-15-14) Exclusion Criteria: Research investigator determined it is difficult to continue being followed up because of medical reasons
Study Procedures and Assessments	Subjects will be evaluated at the research site at 3, 4 and 5 years (± 60 days) post-procedure. The following evaluations will be completed and data collected on the Follow-up eCRF: 1. NYHA classification 2. 12 lead ECG 3. Hematology/chemistry data 4. Echocardiography examination (TTE) 5. Relevant medications 6. SAE/Device related Adverse events/device deficiency
Safety and Effectiveness Assessments	1. Assessment of NYHA classification will be evaluated annually up to 5 years. 2. EOAI will be evaluated annually through 5 years. 3. Hemodynamic performance annually up to 5 years including: a. effective orifice area (EOA) b. peak pressure gradient c. mean pressure gradient d. valvular regurgitation e. performance index f. cardiac output

	g. cardiac index Safety endpoints: The following valve-related adverse events as defined by ISO5840:2009 will be evaluated in this study: 1. Thromboembolism 2. Thrombosis 3. Hemorrhage (all and major) 4. Paravalvular leak (PVL, all and major) 5. Endocarditis 6. Hemolysis 7. Structural valve deterioration 8. Non-structural dysfunction 9. Reintervention 10. Explant 11. Death
Statistics	Primary cohort is all the subjects meet all inclusion criteria and no exclusion criteria and also provide written informed consent. Statistical analysis will be performedin accordance with Statistical Analysis Plan (SAP).

4. Introduction

4.1. Background

Bovine pericardial aortic heart valves have good left ventricular mass regression (remodeling), freedom from structural valve deterioration (SVD), and a high rate of survival, which may offer better early hemodynamics (low transvalvular pressure gradients and increased effective orifice area) and ease of use (low stent profiles). [1-4] For these reasons, bovine pericardial heart valves hold the majority of the stented aortic heart valve market.

The market leader in the bovine pericardial stented aortic heart valve market is the Carpentier-Edwards Perimount series of heart valves (Perimount, Perimount Magna, and Perimount Magna Ease). The original Perimount aortic heart valve has long-term results out to 18 years demonstrating freedom from explant due to SVD of 68±12% and survival of 22±4%.[5] The original Perimount valve has undergone minor modifications/upgrades in the last several years and the name has been modified to reflect these changes. The Perimount Magna uses the original Perimount valve, which was modified to be a true supra-annular design for optimal hemodynamics and increased flow characteristics.[6] The Magna Ease uses the Magna design, with a lower profile and contoured sewing ring to enhance implantability.[7] The Perimount valves utilize anti-calcification treatments to inhibit the binding of calcium to the prosthetic leaflets.

Medtronic has developed the MDT-2215 aortic valve bioprosthesis, a stented bovine pericardial tissue valve. This valve has been designed to incorporate the proven attributes of the leading bovine pericardial heart valves along with the use of the anti-calcification agent, alpha amino oleic acid (AOA™), which has been shown to mitigate leaflet calcification in animal studies.[8-9]

The purpose of this study is to evaluate the safety and effectiveness of the Medtronic 17mm Avalus aortic valve bioprosthesis [herein referred to as MDT-2215 valve] in a patient population undergone SAVR. Regulatory approval was granted before 5-year subject follow-up period is over. The rest of the follow-up period will be conducted under Ethical Guidelines for Medical and Health Research Involving Human Subjects.

4.2. Purpose

The purpose of this research is to confirm the long term (3-5 years) safety and effectiveness for subjects undergone SAVR with Avalus bioprosthesis valve 17 mm.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The purpose of this study is to evaluate the safety and effectiveness of the Medtronic 17mm Avalus aortic valve bioprosthesis in a patient population undergone SAVR in the preceded MDT-2215 trial. Regulatory approval was granted before 5-year subject follow-up period is over. The follow-up period after regulatory approval is granted will be conducted under Ethical Guidelines for Medical and Health Research Involving Human Subjects.

5.1.1.1 Primary Endpoint

The primary endpoints are as follows:

Efficacy - Functional and Anatomical;

Changes in New York Heart Association (NYHA) Class and effective orifice area (EOA) from baseline to 1 year.

The primary endponts were achieved with preceded trial. The primary endpoints are not applicable to PERIGON Japan research, which is a long term follow-up study.

5.1.1.2 Secondary Endpoint

The Secondary Endpoints are as follows:

1. Assessment of NYHA classification will be evaluated annually up to 5 years.
2. EOAI will be evaluated annually through 5 years.
3. Hemodynamic performance annually up to 5 years including:
   a. effective orifice area (EOA)
   b. peak pressure gradient
   c. mean pressure gradient
   d. valvular regurgitation

e. performance index
f. cardiac output
g. cardiac index

Safety endpoints: The following valve-related adverse events as defined by ISO5840:2009 will be evaluated in this study:

1. Thromboembolism
2. Thrombosis
3. Hemorrhage (all and major)
4. Paravalvular leak (PVL, all and major)
5. Endocarditis
6. Hemolysis
7. Structural valve deterioration
8. Non-structural dysfunction
9. Reintervention
10. Explant
11. Death

Safety of the valve will be evaluated by the incidence of valve-related adverse events, reintervention, explant, and death. The endpoints will be summarized and the number of events as well as number and proportion of subjects experiencing an event will be reported. The endpoint is descriptive and no statistical hypothesis test will be performed.

6. Study Design

Long term follow-up (3 to 5 years) will be conducted for subjects undergone surgical aortic valvereplacement with Avalus bioprosthesis at 3, 4 and 5 years after implant in preceded MDT-2215 study (Investigation Plan identifier: MDT2-15-14). This is an observational study which is not physically or mentally invasive to subjects. This study will be conducted within the regular practice. No new subject will be enrolled in this study.

MDT-2215 study was a prospective, interventional, non-randomized, multi-center trial, with each site following a common protocol. The design of the trial was based on the recommendations by the FDA Heart Valve guidance (2010) and EN ISO 5840:2009 standard for cardiac valve prostheses.

6.1. Duration

Planned start date of the study is November 2019 and the subject follow-up will be completed in July 2023. Clinical Study Report will be completed in December 2023.

6.2. Rationale

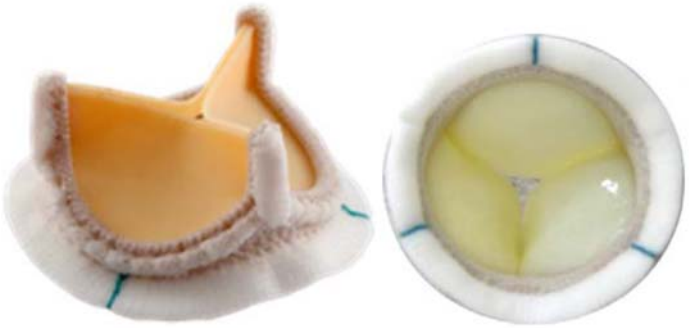
Refer to Section 4.1 Background and Rationale.

7. Product Description

Avalus aortic valve bioprosthesis (17 mm size) is indicated for the replacement of a diseased, damaged, or malfunctioning native or prosthetic aortic valve.

Avalus aortic valve bioprosthesis (17 mm size) shown in Figure 1 consists of a polyester covered base frame and tri-leaflet support frame, which are injection molded using Polyetheretherketone (PEEK) material. The base frame PEEK material is impregnated with barium sulphate to allow for radiographic visualization.

Figure 1: Avalus bioprosthetic aortic valve



The valve leaflets are laser cut from bovine tissue that has been cross-linked in buffered glutaraldehyde. The leaflets are inserted between the cloth covered tri-leaflet support frame and base frame, and then all components are securely sutured together. Avalus aortic valve bioprosthesis (17 mm size) is treated with an alpha amino oleic acid (AOA™) anti-mineralization process that has been shown to mitigate calcification of bioprosthetic valves in animal studies.

A sewing ring, fabricated from polyester cloth, is integrated into the inflow base frame cover to allow for suturing and seating of the valve in the supra-annular position. Sewing markers are located on the sewing ring in the mid sinus area of each cusp to provide guidance for even spacing of implant sutures.

8. Selection of Subjects

8.1. Study Population

Subjects who had aortic valve replacement (AVR) in preceded MDT-2215 study may be considered for this study if they meet all of the inclusion and none of the exclusion criteria. Written consent should be provided.

8.2. Subject Enrollment

The point of enrollment for this study is once the EC-approved patient informed consent form has been signed and dated by all of the required parties.

8.3. Inclusion Criteria

Subject enrolled in the MDT-2215 study and being followed up continuously.

8.4. Exclusion Criteria

Subjects will be excluded if study investigator considers it is difficult for the subject to participate in the study because of medical reasons.

9. Study Procedures

Subjects implanted with Avalus prosthetic valve will be evaluated at research site at 3, 4 and 5 years (± 60 days) post-procedure.

9.1. Subject follow-up schedule

The following table indicates the parameters expected to be routinely evaluated by physicians participating in the study.

Table 1: Schedule of assessments

Data Collection Requirement	**Assessment Intervals**				
	3-year	4-year	5-year	Unscheduled Visits	Exit
Visit Window	± 60 days	± 60 days	± 60 days	As necessary	Date of Exit
Physical Examination				×*	
NYHA Classification	×	×	×	×*	
12-Lead ECG	×	×	×	×*	
Blood Labs	×	×	×	×*	
Transthoracic Echo (TTE)	×	×	×	×*	
Adverse Event/Device Deficiency	×**	×**	×**	×**	×**
Relevant Medications	×	×	×	×*	×*

Vital Status					×

*Any assessments for unscheduled visits are done at the discretion of the Investigator.

**Only SAE/device related adverse events/device deficiencies will be collected

Subjects will be evaluated at the research site at 3, 4 and 5 years (± 60 days) post-procedure. The following evaluations will be completed and data collected on the Follow-up eCRF:

1. NYHA classification
2. 12 lead ECG
3. Hematology/chemistry data
4. Echocardiography examination (TTE)
5. Relevant medications
6. SAE/Device related Adverse events/device deficiency

9.1.1. Unscheduled Follow-up Visits

If a subject returns to the institution for an unplanned visit between the protocol-required follow-up visits specifically for a problem related to their Avalus valve (17mm), the visit will be treated as an unscheduled visit. The assessments completed at this visit will be done at the discretion of the investigator. The reason for the unscheduled visit, as well as any assessment data will be recorded on the Unscheduled Follow-up eCRF and AE data on the AE eCRF.

9.1.2. Missed Follow-up Visits

Every effort should be made to ensure subjects return to the clinic for all protocol required follow-up visits. If the subject is unable to return for an in-person clinic visit, the Investigator (or designee) must document the reason the subject was unable to complete the visit and, if applicable, follow the requirements for deviation reporting as outlined in Section 9.8. The Investigator should also make every effort to contact the subject within the visit window, to collect the subject's information including potential adverse events.

9.2. SUBJECT EXIT FROM STUDY

Table 2 below details how the data will be handled for each scenario.

Table 2: Study exit scenarios

Scenario	Follow-up Required	CRFs Required
Subject enrolled, implanted with Avalus valve, and exits the study early due to explant	30 days post-explant for safety only	-All required/ Unscheduled Follow-up eCRFs through last visit completed -Valve Reintervention eCRF -AE eCRF (as applicable) -Trial Exit eCRF

Scenario	Follow-up Required	CRFs Required
Subject enrolled, implanted with Avalus valve, and exits the study early due to any of the following: - Lost to Follow-up - Death - Withdrawal	Through point of death, withdrawal, or last visit completed	-All required/ Unscheduled Follow-up eCRFs through last visit completed -AE eCRF (as applicable) -Trial Exit eCRF
Subject enrolled, implanted and completes the study requirements	Through 5 year follow-up	-All required/ Unscheduled Follow-up eCRFs -AE eCRF (as appropriate) -Trial Exit eCRF

9.3. TRIAL ASSESSSMENTS

9.3.1. NYHA Functional Classification

The New York Heart Association (NYHA) Functional Classification is a system for defining cardiac disease and related functional limitations into four broad categorizations as defined in Table 3.

Table 3: New York Heart Association (NYHA) Classification

Class I	Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

NYHA classification will be assessed at all in-office follow-up visits, and the results recorded on the appropriate eCRF. The NYHA classification should be assessed by a medical doctor.

9.3.2. 12-Lead ECG

A standard 12-Lead ECG should be taken at all in-office follow-up visits to assess cardiac rhythm, noting any cardiac arrhythmias and indications for pacing. The site will record ECG data on the appropriate eCRF.

The Investigator or Sub-Investigator should review and sign/date each 12-lead ECG recording conducted as part of the study requirements, verify or correct any automated diagnosis generated by the ECG machine, and note the clinical significance of any diagnosis/finding of the ECG. Any new abnormalities should be recorded on an Adverse Event eCRF.

9.3.3. Echocardiography

Transthoracic echocardiography (TTE) is required at all in-office scheduled follow up visits. The site will record echocardiography data on the Site Echo eCRF.

All TTE exams will be sent to the Echo Core Lab for central assessment; the Echo Core Lab will record the central assessment on the Echo Core Lab Assessment eCRF.

Details of the Echocardiography methods are provided in Appendix C: Echocardiography procedure. Additional information regarding the Echo Core Lab can be found in Section エラー! 参照元が見つかりません。.

9.3.4. Hematology/Chemistry

This section describes the laboratory parameters required at baseline and at each postoperative in-office interval.

- Complete Blood Count:
  - White Blood Cell (WBC) Count
  - Red Blood Cell (RBC) Count
  - Hemoglobin
  - Hematocrit
  - Plasma Free Hemoglobin*
  - Platelet Count
- Reticulocytes Count
- Haptoglobin
- Serum lactate dehydrogenase (LDH)

*Plasma free hemoglobin (PFH) will be the primary lab result used to diagnose hemolysis; however, if PFH results are inconclusive or not available, serum lactate dehydrogenase, haptoglobin and reticulocyte count may be used together to diagnose hemolysis, and may do so without reporting a protocol deviation. If neither PFH nor the combination of serum lactate dehydrogenase, haptoglobin and reticulocyte count are completed, the site must report a protocol deviation.

9.3.5. Hemostasis

The following blood labs are required for subjects on anticoagulation therapy (as appropriate for the type of anticoagulant):

- International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (aPTT)
- Prothrombin Time (PT)

For subjects continuing on anticoagulation therapy, coagulation panels should be performed as part of the follow-up assessments.

9.4. Medications

Use of the following medications will be collected at each postoperative interval and recorded on the appropriate eCRF:

- Anticoagulants
- Antiplatelets
- Aspirin

9.5. Subject Consent

9.5.1. Informed Consent Form

PI/ICF used for this study includes items described in section of "Article 5-(12)-3 Ethical Guidelines for Medical and Health Research Involving Human Subjects. PI/ICF may be modified per requirement of respective investigational site.

Site EC shall approve all informed consent documents prior to implementation in the study. EC must pre-approve all language changes to the PI/ICF throughout the course of the study prior to implementation; this includes initial submission, annual reviews (if applicable) and protocol amendment reviews. Medtronic will provide any important new information that impacts the health, safety or welfare of study subjects, for inclusion in PI/ICF updates as it becomes available. Sites should following any EC requirements for disseminating new information and re-consenting subjects during the course of the study.

9.5.2. Informed Consent Process

The Investigator or authorized designee must administer the approved PI/ICF to each prospective study patient without coercion or undue improper influence on, or inducement of, the patient to participate. During the consent discussion the Investigator (or designee) must fully inform the patient of all pertinent aspects of the study, using native non-technical language that is understandable to the patient. The patient must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the patient is otherwise entitled, and also informed that withdrawal from the study will not jeopardize their future medical care. The patient must also be informed that by participating in the study, they are not waiving their legal rights. The patient must have ample time and opportunity to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the patient. All items discussed in the ICF must be explained.

Informed consent will be obtained in writing from the patient. The date of consent and process by which the consent was obtained (including documentation of special circumstances, if applicable; see Section 9.5.3) will be documented in the patient's medical record prior to any study-specific procedures. Patient informed consent must be obtained in accordance with the national and local laws, regulations and guidelines of each site. The institutional standard procedure consent form does not replace the study PI/ICF.

The patient's signature and date of consent serve to document that they understand the written and verbal information that the Investigator (or designee) provides, and their agreement to participate. The Investigator or authorized delegate who conducted the informed consent process must provide their handwritten signature and date the consent was completed on the PI/ICF. The original signed consent

form will be retained in the patient's study records. A copy of the signed informed consent will be provided to the patient.

Informed consent should not be obtained from legally authorized representative.

9.5.3. Special Cercumstances for Informed Consent Process and Signature

If a patient cannot read or write, an impartial witness must be present during the entire informed consent discussion. The written informed consent form and any other information shall be read aloud and explained to the patient and witness. The witness signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given. The patient will sign and date if possible.

9.6. Assessment of Safety

Refer to Section 11, Adverse Event and Device Deficiency.

9.7. Recording Data

Same subject ID number (SID) designated in the preceded MDT-2215 study will be used in the PERIGON Japan study. SID for each subject was recorded on the subject log created for the preceded MDT-2215 study. Subject log is stored only at investigational sites and Medtronic will not collect the subject log.

9.7.1. Electronic Data Capture

Medtronic will use the Oracle Clinical Remote Data Capture database system for data collection. The database is located on a secure server at a Medtronic facility located in the United States. All users will be trained on the use of the database prior to obtaining access. Once access is granted, users will have a unique User ID and will create their own password. Data stored electronically shall be maintained in compliance with 21CFR Part 11. The database for this study will be maintained for the life of Medtronic, according to corporate policy and record retention schedule.

9.7.2. Data Collection

It is the responsibility of the participating Investigator to ensure the quality of the data being collected.

Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as indicated on the Sub-investigator and study collaborator list (RC) or the Delegation of Tasks List. The eCRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the study.

The primary investigator or delegated sub-investigator will electronically sign each eCRF.

The EDC system maintains an audit trail on entries, changes or corrections in eCRFs, once the eCRF is saved as complete. If changes are made to an already signed eCRF, the investigator or delegated sub-investigator shall re-sign this eCRF.

9.7.3. Data Validation

The sponsor and/or assigned designee will be responsible for the processing and quality control of the data (data management) per the Data Management Plan, which describes the procedures for data review, database cleaning and issue/resolution of data queries. Data will be collected and stored in a validated, password protected database. Data analysis will be conducted utilizing validated software and analysis programs by qualified biostatisticians.

Study data collected will be monitored and verified against source documents in accordance with ISO14155:2011 guidelines and international standards. Any data discrepancies will be addressed through queries posted within the EDC system.

9.7.4. Source Documents

Data entered must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

The eCRFs (or paper copies) may not serve as source documents. Source documentation for data elements not routinely captured in medical records (e.g. echocardiography variables) may vary from site to site; the site may use source document worksheets if identified as source documents.

The Investigator must ensure the availability of source documents from which the information on the eCRFs was derived. Where printouts of electronic medical records are provided as source documents, or where copies of source documents are retained as source documents, they should be signed and dated by a member of the investigational site team indicating they are a true reproduction of the original source document.

The source documents must be made available for monitoring or auditing by the sponsor's representative or representatives of the competent authorities and other applicable regulatory agencies.

9.8. Deviation Handling

A study deviation is any event in which the study is not conducted according to the CIP and/or agreement. Deviations may include, but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain Ethics Board approval before the start of enrolling subjects in the study
- Required testing and/or measurements not done or incorrectly done
- Subject did not attend follow-up visit
- Follow-up visit was completed outside window
- Source data permanently lost
- Enrollment of subjects during lapse of Ethics Board approval

The investigator is not allowed to deviate from the CIP, except when necessary to protect the life or physical well-being of a subject in an emergency situation. Study deviations must be reported to Medtronic on the Protocol Deviation eCRF.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the Ethics Board as well as Medtronic as soon as possible but no later than five (5) working days from the date of the deviation occurrence.

Reporting of all other study deviations should comply with Ethics Board policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of deviations must comply with Ethics Board policies, local laws, and/or regulatory agency requirements.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions which may include amending the CIP, conducting additional training, terminating the investigation, etc. Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment at that site until the problem is resolved or ultimately terminating the investigator's participation in the study.

9.9. Subject Withdrawal or Discontinuation

When a subject voluntarily withdraw his or her consent to participate in the study, the subject's will should be respected and the subject should be exited from the study. At the last point of contact (if outside a study-required visit), the subject's status of any ongoing adverse events. Subject withdrawal should be documented per the clinical site's SOP if applicable.

No additional subject will be enrolled to replace a subject withdrawn.

10. Risks and Benefits

10.1. Potential Risks

10.1.1. Description of Risk Analysis

10.1.1.1 Risk

Risks associated with any surgical procedure were identified and they were carefully monitored throughout the MDT-2215 study. No additional risks are expected for patients to participate in PERIGON Japan study. Risks associated with the Avalus aortic valve bioprosthesis are expected to be similar to commercially available tissue heart valves. Refer to Section 11 for adverse events and device deficiencies.

The following measures have been implemented to minimize risks to study subjects:

- Investigators will have expertise in aortic heart valve replacement procedures.

- Investigative sites will have comprehensive cardiology and surgery programs.
- Subjects receiving the Avalus valve will be rigorously followed over the course of the study. The protocol includes regular follow-up visits to assess device safety and effectiveness. These visits will enable detection of deterioration in Avalus valve function should it occur, and allow appropriate intervention. The safety events will be closely monitored by a panel of expert physicians.

Potential treatments for the foreseeable risks may include medication, surgery, medical monitoring or other applicable treatments, and will be provided at the discretion of the Investigator.

Any unanticipated or unforeseen complications will be reported by the principal investigator (or authorized designee) to the Ethics Board and to Medtronic. Medtronic will in turn report any necessary findings to the appropriate regulatory agencies/bodies.

Instruction for use (IFU) for the device will be utilized to address forseeable risks. Updated IFU will be distributed to the clinical sites.

10.1.1.2 Potential Benefits

There is no direct benefit associated to participation in this study, but the information obtained during this study will be used scientifically. The results of this study can help physicians understand the safety and effectiveness of the heart valve.

11. Adverse Event and Device Deficiencies

11.1. Definitions/Classifications

The definitions to be applied for the purposes of safety reporting are provided in Table 4.

Table 4: Definitions of Adverse Events for the PERIGON Japan Study

Event Type	Definition
Adverse Event (AE) (EN 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 persons, whether or not related to the investigational medical device. *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 persons, this definition is restricted to events related to investigational medical devices.*
Serious Adverse Event (SAE)	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
(EN ISO14155:2011 3.37)	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 foetal distress, foetal death or a congenital abnormality or birth defect. *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 (EN 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.* *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) (EN ISO14155:2011 3.36)	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Unanticipated Serious Adverse Device Effect (USADE) (EN ISO14155:2011 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.*
Device Deficiency (EN ISO14155 :2011 3.15)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.*

11.2. Potential Adverse Events

Potential failures/or adverse events associated with the heart valve replacement may include the

following:

- Device Failures/Adverse Events of significance
  - Thromboembolism,
  - Valve Thrombosis
  - Dehiscence of valve's basal portion or valve commissure
  - Endocarditis and other infection
  - Hemolysis
  - Hemolytic anemia
  - Hemorrhage, anticoagulant/antiplatelet-related
  - Leak, transvalvular or paravalvular
  - Nonstructural dysfunction (leaflet entrapment/impingement, obstructive pannus ingrowth, suture dehiscence, inappropriate sizing, other)
  - Prosthesis regurgitation
  - Structural deterioration (calcification, leaflet tear, stenosis, other)
  - Reintervention
  - Reoperation
  - Explant
  - Permanent disability
  - Death

- Device Failures/Adverse Events of others
  - Abrasion/or perforation which influenced suture or fabric covered stent
  - Damage with equipment handling
  - Patient - prosthesis mismatch
  - Native tissue injury for implantation treatment
  - Obstruction of coronary ostia by the stent and sewing ring
  - Ventricle rupture
  - Increase of transvalvular pressure gradient
  - Angina
  - Cardiac dysrhythmias
  - Heart failure
  - Myocardial infarction
  - Stroke

11.3. Reporting of Adverse Events

11.3.1. Evaluation and Documentation of Adverse Events and Device Deficiencies

Investigators are required to assess and document in the medical record all AEs and Device Deficiencies (per the definitions in Table 4) observed in study subjects until they are no longer participating in the study.

Suspected or confirmed device related adverse events, all SAE's regardless of device relatedness, and device deficiencies that occur during the study need to be reported to Medtronic via the AE eCRF. Documented pre-existing conditions are not considered to be reportable unless there is a change in the nature or severity of the condition. Pre-existing events should be reported as Adverse Events in the

situation where a new treatment has to be started or an existing treatment has to be changed to treat the adverse event and the event is accompanied with signs and symptoms.

The general process for reporting Adverse Events is as follows:

- Report the event to Medtronic as soon as possible. Table 5 provides recommended reporting timeframes. These timeframes are not considered protocol requirements. Sites will be provided with the contact information of the appropriate Medtronic Safety designee for event reporting.
- Complete all sections of the Adverse Event eCRF.
- Each unique event/diagnosis must be documented separately.
- Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition.
- The Adverse Event eCRF must be reviewed and approved by the Investigator.

The following information should be collected on the Adverse Event eCRF:

- Date of onset or first observation
- Date of first awareness by investigator
- Description of the event
- AE code number (provided by Medtronic)
- Seriousness of the event
- Causal relationship of the event to the Avalus valve
- Causal relationship of the event to the implant procedure
- Action taken, including any medical or surgical intervention and date of intervention
- Outcome or status of the event; any reported event should be followed until it has resolved, has a stable level of sequelae, or is no longer clinically significant in the investigator's opinion

When possible and not otherwise prohibited by local regulation, for all endpoint-related adverse events and deaths, sites should submit relevant, de-identified source documents to Medtronic for the Clinical Events Committee (CEC) members to use in their adjudication of the event. The CEC may request source documentation on additional events, at their discretion and according to the CEC Charter. Additional information regarding the CEC is detailed in Section 12.1.

11.3.2. Classification of Causal Relationships

For each reported AE, the causal relationship between the AE and the study devices and implant procedure will be classified as related, not related or unknown. Definition of the causal relationship between the AE and Avalus aortic valve bioprosthesis 17mm is any AE involving the function of the device, or the presence of the device in the body. Included in this category are events that are directly attributed to the device.

11.3.3. Adverse Events and Device Deficiency Reporting Requirement

Adverse events and device deficiencies that occur during this study are required to be reported to Medtronic via the AE or device deficiency eCRF, as soon as possible after the event occurs. Table 5 provides recommended reporting timeframes. These timeframes are not considered protocol requirements.

Table 5: Timeframes for Adverse Event reporting to Medtronic

Event Type	Timeframe for Reporting
Adverse Event (AE)	No later than 10 working days of the investigator's / site's first knowledge of the event
Serious Adverse Event (SAE)	Immediately, but no later than 24 hours of the investigator's / site's first knowledge of the event
Adverse Device Effect (ADE) or Device Related Adverse Event	No later than 10 working days of the investigator's / site's first knowledge of the event
Serious Adverse Device Effect (SADE)	Immediately, but no later than 24 hours of the investigator's / site's first knowledge of the event
Unanticipated Serious Adverse Device Effect (USADE)	Immediately, but no later than 24 hours of the investigator's / site's first knowledge of the event
Device Deficiency	No later than 48 hours of the investigator's / site's first knowledge of the event
Device Deficiency that might have led to an SADE	Immediately, but no later than 24 hours of the investigator's / site's first knowledge of the event

In addition, Investigators are obligated to report adverse events in accordance with the requirements of their reviewing Ethics Board and local regulations.

Marketing approval was obtained for Avalus aortic valve bioprosthesis 17mm and this study is an observational study not involving invasive treatment, adverse events listed in Section 11.3.4 will be reported to the head of institution.

11.3.4. Regular Reporting of Adverse Event and Device Deficiencies (Annual Report)

The Sponsor is obligated to report adverse events and device deficiencies that occur during this study to the Regulatory Authorities and Ethics Board as per local requirements. Additionally the Sponsor should report adverse events reported from the clinical sites to the head of clinical department per internal procedure.

11.3.5. Documentation and 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 only.

Device deficiencies that did not lead to an AE should be reported on a Device Deficiency eCRF (one for each device deficiency).

Device deficiencies that did not lead to an adverse event but might have led to an SADE if a) a suitable action had not been taken, or b) an intervention had not been made, or c) circumstances had been less fortunate, should be reported to Medtronic immediately of the site's first learning of the event on a Device Deficiency eCRF.

Any device or accessory involved with a device deficiency should be returned to Medtronic (unless implanted) for analysis.

11.3.6. Emergency Contact Details for Reporting Events and Device Deficiencies

Investigators should contact the Medtronic Study Manager (listed in the synopsis of this document) if they have any questions regarding reportable events. Sponsor contact information is subject to change and will be maintained in a document separate from the protocol and provided to sites periodically.

12. Data Review Committees

12.1. Echocardiography Core Lab

The Echocardiography Core Laboratory (Echo Core Lab) is responsible for developing protocol requirements, reviewing echo exams, interpreting subject echo data, and providing feedback on the quality of the echo exams to participating sites. The Echo Core Lab will review, analyze, and record data on the Echo Core Lab Assessment eCRF. The Echo Core Lab Cardiologist's interpretation of all echocardiograms (up to PMDA approval) will be used for the data analyses. All transthoracic echocardiography recordings will be evaluated by the team of Dr. Neil J. Weissman at:

Cardiovascular Core Labs
MedStar Health Research Institute
100 Irving Street, NW
East Building, Room 5123
Washington, DC 20010 USA
Phone: +1-202-877-0223
Fax: +1-202-877-0206

Medtronic will conduct audit to MedStar Health Research Institute if it is required based on annual audit plan. Also, annual business evaluations are conducted and improvements are requested as necessary. If non-compliance and / or deviations are identified, discuss immediately and develop appropriate improvements.

12.2. Pathology Lab

All explanted study valves will be independently analyzed by CVPath Institute, Inc., 19 Firstfield Road, Gaithersburg, MD 20878.

Medtronic will conduct audit to CVPath Institute if it is required based on annual audit plan. Also, annual business evaluations are conducted and improvements are requested as necessary. If non-compliance and / or deviations are identified, discuss immediately and develop appropriate improvements.

12.3. Clinical Event Committee (CEC)

An independent Clinical Events Committee (CEC) will be established prior to the first enrollment of the study. The purpose of the CEC is to conduct a medical review and classify/adjudicate, at a minimum, all deaths and endpoint related adverse events for seriousness and relatedness to the study device/procedure according to definitions and processes outlined in the protocol and the CEC charter. The CEC will consist of qualified cardiologists, and cardiothoracic surgeons (including a chairperson), who are not participants in the study. Additional specialists, such as echocardiologists, may also be selected as part of the CEC.

Prior to the onset of the study, the CEC charter will be drafted to establish explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify/adjudicate a study endpoint related clinical event. The charter will be approved by Medtronic.

All deaths and potential endpoint events will be reviewed and adjudicated by CEC as described in CEC Charter. CEC decisions will be documented in meeting minutes, which will be maintained in the study master file.

Additional details about the CEC will be outlined in the CEC charter.

12.4. Data Safety and Monitoring Board (DSMB)

A DSMB will be established to review accumulating data from the study, and advise Medtronic on the continuing safety of current and future study participants, and the continuing validity and scientific merit of the study. The board will be independent of Medtronic and the study investigators and will be comprised of at least 3 experts (including a chairperson) and at a minimum, one cardiothoracic surgeon, one cardiologist and one statistician.

A DSMB charter will be developed and approved by Medtronic and the DSMB members prior to the first subject enrollment, and include:

- Criteria for study termination recommendations if safety concerns warrant. These DSMB recommendations may include recommendations on study status such as continuing the study without modifications, continuing the study with modifications, stopping the enrollment in the study, or recommendations about study conduct including recommendations around enrollment or protocol deviations.
- Frequency of meetings
- Handling of emergency situations
- Documentation procedures of the DSMB meetings

The DSMB will meet at least 2 times during the study to monitor adverse events. Meetings will consist of both open and closed sessions. Following each full DSMB meeting, the board will report to Medtronic in writing and may recommend changes in the conduct of the study. The DSMB 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 and returned to the study statistician at the closure of the DSMB meeting.

Additional details about the DSMB will be outlined in the DSMB charter.

13. Statistical Design and Methods

Statistical analysis will be performed by Medtronic employed statisticians or their designated representatives. A separate Statistical Analysis Plan (SAP) will be developed to further describe pre-specified statistical methods, data handling rules, and analyses that will be employed. Any deviation from the original statistical analysis plan will be reported in the final study report, along with justification for the deviation(s).

13.1. Missing Data

Every effort will be undertaken to minimize missing data. Missing (accidentally, due to withdrawal, missing follow-up or loss-to-follow up etc.), unused and spurious data will remain identifiable in the database. The number of subjects included in the analysis will be reported, so the impact of missing data can be assessed. Unless otherwise specified in each objective, no statistical techniques will be used to impute missing data.

14. Ethics

14.1. Statement(s) of Compliance

14.1.1. Applicable Laws and Regulations

The PERIGON Japan Study was designed to reflect the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Education and Ministry of Health, Labor and Welfare notification No. 3 in 2014) and Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices (The law No. 145 in 1960).

The following items in "Article 8-(1), Ethical Guidelines for Medical and Health Research Involving Human Subjects" are not applicable.

⑯ Procedure regulated by Article 13 (including procedure of explanation) when obtaining informed assent

⑰ How to deem if the all requirements in Article 12-6 are met when the research regulated by the Article is performed

㉑ Provision of medications to subjects after the research specific activities on the research exceed to regular treatment

㉒ Handing of the research results (including accidental findings) when an important knowledge as to subjects' health and genetic characteristics etc. which can be inherited by descendants can be obtained

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 (PIC) process, Ethics Board approval, study training, clinical study registration, pre-clinical testing, risk benefit assessment, and publication policy. In addition, the study will be conducted in compliance with FDA 21 CFR Part 11 and 54.

Ethics Board notification/approval to conduct the study is required at all participating sites. Investigational sites will be not be activated, nor begin enrolling subjects until the required approval/favorable opinion from the respective Ethics Board has been obtained (as appropriate). Additionally, any requirements imposed by a local regulatory agency or Ethics Board shall be followed, as appropriate.

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

14.1.2. Investigational Site Initiation and Management

14.1.2.1 Investigator Selection

The following criteria will be used to select investigators and sites for participation:

- The presence or capacity of establishing an investigative team capable of managing the duties of the clinical study
- Access to the necessary cardiovascular facilities and services to complete protocol required study procedures and follow-up.
- Willingness to comply with the requirements described in this CIP

14.1.2.2 Research Agreement and Conflict of Interest

A Clinical Investigation Agreement shall be signed by the participating investigational site and/or the principal investigator at each investigational site per the local legal requirements, and returned to Medtronic prior to study activation. The investigator is required to indicate their approval of the CIP (and any subsequent amendments), by signing and dating the agreement.

14.1.2.3 Training of Investigative Staff

Medtronic will provide training to the investigative team, according to the Training Plan, on the study requirements and EN ISO 14155:2011. Training required per local law will occur prior to site activation at each site, and will include the following topics:

- CIP overview and study procedures
  - Investigator and sponsor responsibilities
  - Procedures for obtaining informed consent
  - Adverse event/device deficiency reporting procedures
  - Deviation reporting procedures
  - Site record maintenance and retention
- Ethics Board requirements
- Monitoring requirements and expectations
- Case report form (CRF) completion and management, including electronic data entry

- Potential regulatory inspections and audits by the regulatory authorities
- Investigational site and subject compensation
- Any additional regulatory requirements

14.1.2.4 Site Activation

Investigational sites will receive a formal letter of site activation, upon receipt of or completion of the following:

- A signed research agreement
- Disclosure of Conflict of Interest from the investigators
- A copy of the Ethics Board approval letter, along with the voting roster
- The Ethics Board approved patient informed consent form
- Documented training of the investigative team
- Sub-investigator and study collaborator list (RC) or DTL
- Lab certificate and lab normal values/ranges
- Confirmation of adequacy of equipment/facilities

14.1.2.5 Study Site Investigative Team Members – Roles and Responsibilities

The following is a description of the key personnel who will form the investigative team at each study site.

14.1.2.5.1 Principal Investigator

Each site will have a Principal Investigator (PI), who is a cardiothoracic surgeon. The PI has overall responsibility for the conduct of the study at the site and for the integrity of the study data generated by their site. Specifically, the PI is responsible for the following:

- Protecting the rights, safety, and welfare of the subjects in their care
- Obtaining written informed consent of all subjects prior to any study-related procedures, and only after Ethics Board and regulatory approval of the study
- Obtaining and maintaining Ethics Board approval
- Conducting the investigation in accordance with the signed agreement, investigational plan, applicable laws and regulations, and any conditions of approval imposed by an Ethics Board or regulatory body
- Reporting adverse events and device deficiencies in accordance with the CIP and according to country regulations
- Approving all case report forms; approval of the case report form indicates the data represented are accurate and have been reviewed.
- Maintaining accurate, complete, and current records, including:
    - All correspondence with another investigator, the sponsor, the monitor, the Ethics Board (including required reports), or regulatory agency
    - Records of receipt, use, or disposition of investigational devices
    - Records of each consented subject's case history, signed and dated informed consent(s), exposure to the device, eCRFs, and source documents
    - The CIP, and documentation of dates of and reasons for each protocol deviation
    - Any records required by a regulatory agency

- Allowing time with the study monitor and Sponsor study staff members during Sponsor site visits
- Managing suppliers per site's SOP if any of the study related work is outsourced.

14.1.2.5.2 Cardiologist/Echocardiographer

Each site should consider having a designated cardiologist/echocardiographer as a sub-Primary Investigator.

14.1.2.5.3 Other Study Support Staff

The PI will ensure that the investigative site has the appropriate support staff to maintain the study. Additional staff may include sub-investigators, study coordinators, and other specialized health care professionals.

14.2. Ethics Board Information

All necessary documents (CIP and PI/ICF) will be provided by Medtronic to the site for submission to their Ethics Board. Documented approval of the Ethics Board affiliated with the site is required before enrollment can begin. The documented approval must include:

- The Ethics Board approval date
- Version and/or date of the documents approved (including CIP, ICF and other written study materials)
- Any specific Ethics Board requirements relative to the study (if applicable)

The investigator and study staff must comply with any additional requirements imposed by the Ethics Board. Investigators must inform Medtronic of any change in status of Ethics Board approval once the investigation site has started enrollment.

The approval letter needs to be accompanied by an Ethics Board roster to allow verification that the investigator or other site study staff members are not members of the Ethics Board. If they are members of the Ethics Board, written documentation is required stating that he/she did not participate in the approval process.

15. Study Administration

15.1. Management of Study Contact Information

Medtronic (Medtronic Japan, Medtronic plc and its subsidiaries) is responsible for creating study-related materials, monitoring, audit, statistical analysis, data management, safety, handling of personal information and publication as a research representative. These study-related data are collected by using Medtronic's electronic data management system for research.

This information might be updated during the period of this research. The updated information will be reported to the head of research sites on regular basis.

A list of participating investigational sites and the Investigators is provided as attachment.

15.2. Monitoring

Monitoring and monitoring oversight will be provided by Medtronic Japan and detailed in a Monitoring Plan separate from this CIP. Representatives of Medtronic (i.e. contractors and designees) may also act as the study monitors to the site. A list of the study monitors will be kept separate from this document, and the Sponsor will provide updated lists to the investigative sites.

Follow-up letter will be provided to PI at investigational site after monitoring visit is conducted.

15.2.1. Site Initiation Visit

Medtronic will conduct a site initiation visit prior to first implant, to prepare the site to conduct the study. Medtronic may conduct Investigator Meetings in place of, or in addition to on-site initiation visits. Monitors (and/or other Medtronic representatives) will ensure that the PI and study staff (depending on their role in the study):

- Have received and understand the requirements and contents of
  - CIP
  - Patient Information/Informed Consent Form (PI/ICF)
  - Electronic CRFs
  - IFU
  - Any written clinical investigation agreements (as appropriate)
- Have access to an adequate number of investigational devices
- Are familiar with the responsibilities of the Principal Investigator

15.2.2. Periodic Monitoring Visit

Periodic monitoring visits will be made at all active investigational sites throughout the clinical study to ensure the safety and wellbeing of the subjects, verify that the Investigator obligations are fulfilled, and all applicable regulations and guidelines are being followed. Monitors will review at a minimum:

- Data submitted on eCRFs are complete and complete records are being maintained
- Subject informed consent is being obtained and properly documented
- The CIP is being followed
- Appropriate and timely reports have been made to Medtronic and/or its designees and the Ethics Board
- The Investigator is carrying out all agreed activities

The progress of the study will be monitored by:

- On-site review, as deemed appropriate by the sponsor
- Telephone communications between the site personnel (e.g., Investigator, other supporting staff) and study monitors
- Review of eCRFs and the associated clinical records
- Review of regulatory documents

15.2.3. Study Closure

Upon study completion Site Closeout Visits will be conducted, as outlined in the Monitoring Plan.

15.3. Data Management

Refer to Section 9.7 Recording Data.

15.4. Direct Access to Source Data/Documents

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

15.5. 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 ID number (SID) to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the site.

Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

15.6. Liability

Compensation in this research is not applicable because events exceeding regular treatment, regulated by "Article 5-1-(3), Ethical guidelines of medical research for human," are not applicable.

15.7. Subject Compensation

Subject compensation may be paid per agreement between Sponsor and cinical site in the research study. It should be documented in PD/PIC if subject compensation is payable.

15.8. Report to the Head of Research Site

Any revisions or amendments to the CIP or Informed Consent document, along with a statement of justification for the changes, will be submitted to Ethics Board, according to applicable regulations. If the CIP is amended, a review of the CRFs will be completed to determine if amendment to the forms is necessary. All amendments to the CIP shall be agreed between the sponsor and the Principal Investigator(s). Any required approvals by regulatory agencies and Ethics Board must be obtained prior to implementing a CIP revision at the site.

15.9. Clinical Investigation Plan Amendments

Medtronic Japan will report the following matters to the head of the research site. Each research site will also report the following matters to the head of the research site, depending on the site's SOP.

- Case that significant concerns occurred from the point of subject's human right and that of performance of this research such as study-related information leakage
- Case that facts or information which appropriateness of performance or reliability of research result are lost are obtained
- Case that fact or information which ethical validity and/or scientific rationality are lost are obtained and affect to the continuation of this research
- Case that Unanticipated Serious Adverse Device Effect (USADE) occurred in the research site
- Progress of this research, occurrence of adverse events and regular basis report of storage condition of study-related information (Annual report: in accordance with the SOP of Medtronic Japan)
- Case that this research is completed, suspended or stopped
- Case that site audit is performed (in accordance with audit plan)
- Approved status of performance and continuation of this research by other research site's Ethics Board

15.10. Records and Report

All study-related documents must be retained for a period of at least 3 years after study closure. Medtronic will inform the investigator/site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between the Sponsor and the investigator. Measures shall be taken to prevent accidental or premature destruction of documents. 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 the Sponsor.

The sponsor will retain the study records for the life of Medtronic, according to Medtronic corporate policy and record retention schedule.

Table 6 shows record creation and retention policy for the study. Monitor will confirm subject's informed consent via source data verification or alternative monitoring method (such as remote monitoring) and record it in monitoring report.

Table 6: Method of record creation and retention

Record Item	Provider	Receiver (Medtronic Japan and/or Medtronic plc and its subsidiaries)
Receiver's Name: Medtronic Japan and/or Medtronic plc and its subsidiaries	CIP and CIP Supplement (if necessary, notification form as to the provision of existing samples and information to other research institutions) to be stored for 3 years after the report date of this research completion (it is acceptable for Receiver to store instead)	CIP to be stored permanently
Name of responsible person of Receiver: Refer to CIP Attachment	CIP and CIP Supplement (if necessary, notification form as to the provision of existing samples and information to other research institutions) to be stored for 3 years after the report date of this research completion (it is acceptable for Receiver to store instead)	CIP to be stored permanently
Provider's Name: refer to CIP Attachment		CIP to be stored permanently
Researcher's Name: refer to Researchers and Sponsor		CIP to be stored permanently
Data Item: refer to Sample Case Report Forms	CIP and CIP Supplement (if necessary, notification form as to the provision of existing samples and information to other research institutions) to be stored for 3 years after the report date of this research completion (it is acceptable for Receiver to store instead)	CIP to be stored permanently
Background of obtaining information colleted by electronic data management system		CIP to be stored permanently

Subjects' personal information including names	Signed informed consent form to be stored for 3 years after the report date of this research completion	Provided information to be stored permanently in the electronic data management system in the condition not to be identified specific individuals
Obtaining informed consent from subjects	Signed informed consent form to be stored for 3 years after the report date of this research completion	Provided information to be stored permanently in the electronic data management system in the condition not to be identified specific individuals
Provider's address		Contract to be stored permanently
Name of the head of Provider		Contract to be stored permanently

15.11. Publication and Use of Information

Preceded MDT-2215 trial was registered at http://clinicaltrials.gov before first enrollment in the trial. Trial data and results will be made available as required per regulations.

At the conclusion of the study, a multisite abstract reporting the primary results may be prepared in collaboration with Principal Investigator and with others including, but not limited to, CEC members, 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 Investigators will be solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications regarding the endpoints from the study requires approval by the Coordinating Principal Investigator.

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

15.12. Use of Subject Data in the Future

Medtronic should store study-related information collected from subjects strictly after completion of this research as well. A statistical analysis which is not planned might be performed by using the data. The data might be also used in newly planned research in future.

15.13. Suspension or Early Termination

15.13.1. Planned Study Closure

Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigational Plan and/or by a decision by Medtronic or regulatory authority, whichever occurs first. Study Closure is a process initiated by distribution of an initial study closure letter.

For each center, Ethics Board approval renewals are required per regulation until the study closure process is complete at that center.

15.13.2. Early Termination or Suspension

Termination of the Study is discontinuance, by sponsor or by withdrawal of Ethics Board approval before completion. This is possible for the whole study or for a single center. Study suspension is a temporary postponement of study activities related to enrollment and distribution of the investigational product(s). This is possible for the whole study or a single center.

15.13.3. Criteria for Study-wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study for all centers include but are not limited to:

- AEs and device deficiencies associated with the system or product under investigation which might endanger the safety or welfare of subjects
- Decision by Medtronic or regulatory body (medically/ethically justifiable) where the study is operating under regulatory body authority

15.13.4. Criteria for Investigator/Center Termination or Suspension

Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Failure to obtain initial Ethics Board approval or annual renewal of the study
- Lack of enrollment
- Ethics Board suspension of the center
- Fraud or fraudulent misconduct (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

15.13.5. Procedure for Planned Study Closure, Termination, or Suspension

Medtronic will promptly inform the clinical investigators of the reasons for a study termination or suspension and inform the regulatory authority (ies) (where required per regulatory requirements).

15.13.5.1 Medtronic-initiated

In the case of study termination or suspension for reasons other than a temporary Ethics Board approval lapse, Medtronic will promptly inform the principal investigator and the Head of Institution (if needed, the Director of Ethics Board).

In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided.

15.13.5.2 Investigator-initiated

- The investigator will promptly inform:
  - Medtronic and provide a detailed written explanation of the termination or suspension
  - The institution (where required per regulatory requirements)
  - The Ethics Board
  - The subjects and may inform the personal physicians of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension:
  - Subject enrollment must stop until the suspension is lifted
  - Subjects already enrolled should continue to be followed out of consideration of their safety, rights, and welfare

15.13.5.3 Ethics Board-initiated

- The investigator will promptly inform:
  - Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
  - The institution (where required per regulatory requirements)
  - The subjects and may inform the personal physicians of the subjects, with the rationale for the study termination or suspension
- In the case of a study suspension:
  - Subject enrollment must stop until the Ethics Board suspension is lifted
  - Subjects already enrolled should continue to be followed in accordance with Ethics Board policy or its determination that an overriding safety concern or ethical issue is involved

16. References

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17. Appendices

Appendix A： Instruction for Use

Appendix B： Definitions

Appendix C： Echocardiography Procedures

Appendix D： Informed Consent Form

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not applicable	Mizuho Nakagaki, Sr. Clinical Research Specialist