Medtronic PERIcardial SurGical AOrtic Valve ReplacemeNt Pivotal Trial (PERIGON)

A multi-center, non-randomized trial to determine the safety and effectiveness of the Model 400 aortic valve bioprosthesis in patients with aortic valve disease.

Clinical Investigational Plan (CIP)

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Confidentiality Statement

Investigator Statement

Clinical Investigational Plan: Medtronic PERIcardial SurGical AOrtic Valve ReplacemeNt Pivotal Trial (PERIGON)

Title Clinical Investigational Plan: A multi-center, non-randomized trial to determine the safety and effectiveness of the Model 400 aortic valve bioprosthesis in patients with aortic valve disease.

Current Version: Version 1F 13March 2019

I have read the above named Clinical Investigational Plan and agree to conduct the trial as outlined and in compliance with country, local and internal institutional requirements.

Name of Institution: _____

Name of Investigator: _____

_____ _____

Investigator Signature Date: dd mmm yyyy

Version History

Version	Version date	Summary of Changes	Author(s)/Title
1A	16 July 2013	Version 1A: for internal use only and not distributed to clinical sites or regulatory agencies	Aimee Weber, Principal Clinical Research Specialist
1B	20 Nov 2013	• Change study title and valve name from Perigon™ to Model 400 • Increase number of centers • Separate out regulatory requirements for each geography • Update safety requirements • Add pathology core lab Minor administrative changes	Aimee Weber, Principal Clinical Research Specialist
1C	21 May 2014	• Updated Inclusion/Exclusion criteria based on requests from global regulatory agencies • Update to US Informed Consent template upon request from the U.S. FDA	Aimee Weber, Principal Clinical Research Specialist
1D	15 July 2014	• Updated study design elements based on recommendations from the U.S. FDA • Updated definitions based on requests from the U.S. FDA • Removed Appendix H: Device Return Instructions, due to an internal Medtronic process change • Updated CE mark status on accessories and added reporting requirements • Clarified regulatory requirements	Aimee Weber, Principal Clinical Research Specialist

1E	22 April 2015	• Increase study sample size to 1300 • Clarified requirement for 8 sites to enroll at least 30 subjects • Clarify unavoidable medical conditions resulting from the index procedure • Updated STS risk calculator information, based on STS Version 2.81, released Jan. 2015 • Changed discharge visit window to discharge, up to 30 days post-index procedure to accommodate geography differences in standard follow up • Clarified that subjects who are found intraoperatively to require concomitant procedures not allowed in Inclusion/Exclusion criteria should be exited and treated with a commercial valve to avoid confounding adverse event data • Updated Appendix E definitions to reflect revised STS definitions and clarify bleeding and PVL AE reporting requirements. • Update IFU's to current version	Aimee Weber, Principal Clinical Research Specialist
1F	13 Mar 2019	• Updated to clarify the valve sizes commercially available across geographies • Updated to allow the use of commercially available accessories • Administrative changes including small grammatical updates throughout • Administrative changes to match updated CIP template in SSMP • Updated Appendix G to allow upload of echoes into imaging portal (Medidata)	Stephanie Yong, Clinical Research Specialist

Medtronic approvals are maintained in an electronic document control system.

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Synopsis

Name of Trial	PERIGON Pivotal Trial
Title of Trial	A multi-center, non-randomized trial to determine the safety and effectiveness of the Model 400 aortic valve bioprosthesis in patients with aortic valve disease.
Name of Product	Model 400 aortic valve bioprosthesis
Purpose	To evaluate the safety and effectiveness of the Model 400 bovine pericardial stented aortic bioprosthesis in a patient population undergoing surgical aortic valve replacement. The collected data will be used to support regulatory applications in seeking market approval for the valve in Europe (CE Mark), the United States, Canada and other geographies.
Design	This is a prospective, interventional, non-randomized, worldwide, multi-site trial, with each center following a common protocol.
Objectives	To evaluate the safety and effectiveness of the Model 400 aortic valve bioprosthesis.
Endpoints	1. Safety: a. Thromboembolism b. Valve Thrombosis c. Hemorrhage d. Paravalvular leak e. Endocarditis f. Hemolysis g. Structural valve deterioration h. Non-structural dysfunction i. Reintervention j. Explant k. Death 2. Effectiveness: a. Hemodynamic performance metrics b. NYHA functional classification
Trial Sites	The trial will be conducted at up to 40 sites worldwide with approximately 14 in Europe, 4 in Canada and up to 22 in the United States.
Sample Size	A maximum of 1300 subjects will be implanted in the trial.
Patient Population	Patients requiring aortic valve replacement of the native or prosthetic valve.

Inclusion Criteria	1. Patient has moderate or greater aortic stenosis or regurgitation, and there is clinical indication for replacement of their native or prosthetic aortic valve with a bioprosthesis, with or without concomitant procedures, which are limited to any of the following: i. LAA ligation ii. CABG iii. PFO closure iv. Ascending aortic aneurysm or dissection repair not requiring circulatory arrest v. Resection of a sub-aortic membrane not requiring myectomy 2. Patient is geographically stable and willing to return to the implanting site for all follow-up visits 3. Patient is of legal age to provide informed consent in the country where they enroll in the trial 4. Patient has been adequately informed of risks and requirements of the trial and is willing and able to provide informed consent for participation in the clinical trial
Exclusion Criteria:	1. Patient has a pre-existing prosthetic valve or annuloplasty device in another position or requires replacement or repair of the mitral, pulmonary or tricuspid valve 2. Patient has had previous implant and then explant of the Model 400 aortic valve bioprosthesis 3. Patient presents with active endocarditis, active myocarditis or other systemic infection 4. Patient has an anatomical abnormality which would increase surgical risk of morbidity or mortality, including: • Ascending aortic aneurysm or dissection repair requiring circulatory arrest • Acute Type A aortic dissection • Ventricular aneurysm • Porcelain aorta • Hostile mediastinum • Hypertrophic obstructive cardiomyopathy (HOCM) • Documented pulmonary hypertension (systolic >60mmHg)

<table>
<tr><td></td><td>5. Patient has a non-cardiac major or progressive disease, with a life expectancy of less than 2 years. These conditions include, but are not limited to:
• Child-Pugh Class C liver disease
• Terminal cancer
• End-stage lung disease
6. Patient has renal failure, defined as dialysis therapy or GFR<30 mL/min/1.73 m^2
7. Patient has hyperparathyroidism
8. Patient is participating in another investigational device or drug trial or observational competitive study
9. Patient is pregnant, lactating or planning to become pregnant during the trial period
10. Patient has a documented history of substance (drug or alcohol) abuse
11. Patient has greater than mild mitral valve regurgitation or greater than mild tricuspid valve regurgitation as assessed by echocardiography
12. Patient has systolic EF<20% as assessed by echocardiography
13. Patient has Grade IV Diastolic Dysfunction
14. Patient has documented bleeding diatheses
15. Patient has had an acute preoperative neurological deficit or myocardial infarction and has not returned to baseline or stabilized ≥30 days prior to enrollment
16. Patient requires emergency surgery</td></tr>
<tr><td>Follow-up</td><td>For each subject, data will be collected preoperatively, intra-operatively, at hospital discharge up to 30 days, between 3 and 6 months post-operative, 1 year, 18 months, 2 years, 30 months, 3 years, and annually thereafter through 5 years, or until trial closure.</td></tr>
<tr><td>Estimated Time Course</td><td><table>
<tr><th>Activities</th><th>Timeline</th></tr>
<tr><td>Expected First Enrollment</td><td>Q2, 2014</td></tr>
<tr><td>Expected Enrollment Duration</td><td>Approximately 3 years or until commercial approval, whichever occurs first</td></tr>
<tr><td>Completion of Follow-Up</td><td>5 years, or until trial closure</td></tr>
<tr><td>Expected Trial Duration</td><td>8 years, or until trial closure</td></tr>
</table></td></tr>
<tr><td>Global Sponsor</td><td>Medtronic, Inc.</td></tr>
</table>

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1 Introduction

1.1 Background

Calcific or degenerative aortic stenosis and chronic aortic regurgitation are considered the most common valvular lesions[1-3] among elderly patients. The classic symptoms include angina, syncope, and dyspnea.[4] Once these symptoms develop, the cumulative mortality in untreated patients is high; with angina or syncope, the average survival is two to four years, whereas with congestive heart failure it is even less.[5-7]

For patients without increased risk for operative mortality or complications, conventional surgical aortic valve replacement (SAVR) with cardiopulmonary bypass is the established standard of care for patients with symptomatic severe aortic stenosis or chronic severe aortic regurgitation.[8,9] SAVR provides excellent functional outcomes, relieves symptoms, and improves survival. [10-14]

SAVR with a tissue bioprosthesis has become the preferred valve treatment for patients over 65 years of age, or those patients under 65 years of age who are unable or unwilling to be on lifelong anticoagulation with a mechanical heart valve.[8]

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).[15-18] 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%.[19] 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.[20] The Magna Ease uses the Magna design, with a lower profile and contoured sewing ring to enhance implantability.[21] The Perimount valves utilize anti-calcification treatments to inhibit the binding of calcium to the prosthetic leaflets.

Medtronic has developed the Model 400 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.[22-23] In order to evaluate the safety and effectiveness of the Model 400 aortic valve bioprosthesis, Medtronic will be conducting a worldwide, multi-center trial, with all sites following a common clinical protocol. The target population (those for whom the device is intended) includes all subjects who are candidates for a tissue prosthetic valve. The PERIGON Pivotal Trial is designed to enroll a maximum of 1300 subjects implanted with the Model 400 aortic valve bioprosthesis at a maximum of 40 sites worldwide.

1.2 Purpose

The purpose of this pivotal trial is to evaluate the safety and effectiveness of the Medtronic Model 400 aortic valve bioprosthesis [herein referred to as Model 400 valve] in a patient population undergoing SAVR. The collected data will be used to support regulatory applications in seeking market approval for the valve in Europe (CE Mark), the United States, Canada and other geographies. The Model 400 valve is commercially available (Avalus™) in the valve sizes: 19mm, 21mm, 23mm, 25mm, and 27mm after receiving FDA approval on July 31, 2017, Health Canada Approval on September 8, 2017, and CE mark approval on July 3, 2017. The size 17mm and 29mm valve sizes are still considered investigational in all geographies.

1.3 Objectives

1.3.1 Primary Objectives

The objectives of the trial are to evaluate the safety and effectiveness of the Model 400 valve in a patient population undergoing aortic valve replacement of his/her native aortic valve, or replacement of a failed prosthesis.

Trial endpoints are discussed in more detail in Section 7, Statistical Design and Methods.

1.4 Intended Use

The Medtronic Model 400 aortic valve bioprosthesis is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

2 Study Design

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

A maximum of 1300 subjects will be implanted at up to 40 sites with approximately 14 sites in Europe, 4 in Canada and up to 22 in the United States.

2.1 Rationale

Enrollment parameters are included in the study to avoid introduction of bias to the trial results due to disproportionate enrollment. Subjects will be enrolled at a minimum of 8 sites, with an expected minimum enrollment at each of these 8 sites of 15 subjects per EN ISO 5840:2009 and enrollment of 30 subjects per FDA Heart Valve guidance (2010). The maximum number of subjects enrolled per site will be no more than 260 (or 20% of the total trial population). The maximum number of subjects implanted in United States will not exceed 650 subjects.

Trial-wide, it is anticipated that a minimum of 15 valves of each size- 17, 19, 21, 23, 25, 27, 29 mm will be implanted. Up to 1300 valves will be implanted during the trial; more valves may be opened but not used. This estimate assumes that each subject will have one trial valve implanted.

At the moment of commercialization of each valve size in any of the geographies participating in the trial (EU, Canada or US, enrollment in that geography will cease. Enrollment may continue in the remaining geographies until commercialization for a geography is approved or the maximum of 1300 total trial subjects is reached, whichever occurs first. The estimated enrollment period, based upon the anticipated commercialization dates of EU, Canada and US, is approximately 36 months. Additional information regarding sample size justification is located in section 7.1.1.3.

2.2 Duration

Each implanted subject will be consented to be followed for 5 years, or until trial closure. A minimum follow-up of both 150 patients followed to 1-year and 400 patient-years will be completed to satisfy the requirements stated in EN ISO 5840:2009. A minimum follow-up of both 300 patients followed to 1-year and 800 patient-years will be completed to satisfy the requirements stated in the FDA Heart Valve Guidance. Total expected duration of the trial is approximately 8 years.

3 Selection of Subjects

3.1 Study Population

Patients who require aortic valve replacement (AVR) for any reason may be considered for this trial if they meet all of the inclusion and none of the exclusion criteria.

3.2 Subject Enrollment

The point of enrollment for this trial is once the IRB/MEC/REC-approved patient informed consent form has been signed and dated by all required parties.

3.3 Inclusion Criteria

Patients must meet all of the following criteria to be included in the trial.

1. Patient has moderate or greater aortic stenosis or regurgitation, and there is clinical indication for replacement of their native or prosthetic aortic valve with a bioprosthesis, with or without concomitant procedures, which are limited to any of the following:
   - LAA ligation
   - CABG
   - PFO closure
   - Ascending aortic aneurysm or dissection repair not requiring circulatory arrest
   - Resection of a sub-aortic membrane not requiring myectomy
2. Patient is geographically stable and willing to return to the implanting site for all follow-up visits
3. Patient is of legal age to provide informed consent in the country where they enroll in the trial
4. Patient has been adequately informed of risks and requirements of the trial and is willing and able to provide informed consent for participation in the clinical trial

3.4 Exclusion Criteria

1. Patients who meet any of the following criteria will not qualify for participation in the trial. Patient has a pre-existing prosthetic valve or annuloplasty device in another position or requires replacement or repair of the mitral, pulmonary or tricuspid valve
2. Patient has had previous implant and then explant of the Model 400 aortic valve bioprosthesis
3. Patient presents with active endocarditis, active myocarditis, or other systemic infection
4. Patient has an anatomical abnormality which would increase surgical risk of morbidity or mortality, including:
   - Ascending aortic aneurysm or dissection repair requiring circulatory arrest
   - Acute Type A aortic dissection
   - Ventricular aneurysm

- Porcelain aorta
- Hostile mediastinum
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Documented pulmonary hypertension (systolic >60mmHg)

5. Patient has a non-cardiac major or progressive disease, with a life expectancy of less than 2 years. These conditions include, but are not limited to:
   - Child-Pugh Class C liver disease
   - Terminal cancer
   - End-stage lung disease
6. Patient has renal failure, defined as dialysis therapy or GFR<30 mL/min/1.73 m^2.
7. Patient has hyperparathyroidism
8. Patient is participating in another investigational device or drug trial or observational competitive study
9. Patient is pregnant, lactating, or planning to become pregnant during the trial period
10. Patient has a documented history of substance (drug or alcohol) abuse
11. Patient has greater than mild mitral valve regurgitation or greater than mild tricuspid valve regurgitation as assessed by echocardiography
12. Patient has systolic EF<20% as assessed by echocardiography
13. Patient has Grade IV Diastolic Dysfunction
14. Patient has documented bleeding diatheses
15. Patient has had an acute preoperative neurological deficit or myocardial infarction and has not returned to baseline or stabilized ≥30 days prior to enrollment
16. Patient requires emergency surgery

4 Study Procedures

Subjects in whom the Model 400 aortic valve bioprosthesis is implanted will be evaluated at baseline, implant, hospital discharge (up to 30 days), between 3 and 6 months, 1 year, 18 months, 2 years, 30 months, 3 years, 4 years and 5 years, or until trial closure. Protocol-required evaluations should be performed at the investigative trial site.

4.1 Subject Screening

Patients identified with malfunctioning aortic valves requiring replacement will be screened by the site's investigative team for possible inclusion in the trial. All sites will be required to maintain a record of patients screened for the trial, including reason for screen failure if applicable.

Patients who meet all inclusion and no exclusion criteria will be asked to participate in the trial. If the patient agrees to participate, prior to any trial-specific tests or procedures, a personally signed and dated informed consent will be obtained, as detailed in Section 14 of this document. The point at which the informed consent is executed by all parties will be considered the point of enrollment, and the patient is from then on considered a trial subject. The subject's medical record must indicate that the subject is enrolled in the PERIGON Pivotal Trial. Sites will maintain a subject enrollment and identification log.

Failure to obtain a handwritten signed and hand-dated informed consent prior to any trial-specific procedures constitutes a protocol deviation, which is reportable to the IRB/MEC/REB (all henceforth referred to as an "Ethics Board"), the FDA/Health Canada, and other regulatory authorities as applicable. However, if any required baseline exams (e.g. Transthoracic Echocardiography (TTE), labs, 12-lead ECG) have been performed as standard of care for diagnostic purposes prior to consenting the patient, they can be used as the baseline/qualifying exams and will not be considered a protocol deviation, provided they meet the following criteria:

- The Principal Investigator (PI) determines that the exams contain the protocol-required data and are adequate for evaluation
- The exams were completed within 45 days (TTE within 90 days) prior to scheduled implant procedure

4.2 Schedule of Events

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

Table 1: Schedule of Events

Data Collection Requirement	Assessment Intervals								
	Baseline	Implant	Discharge up to 30 days	3-6 Months	1 Year	Annually years 2-5	18 & 30 month phone call	Un-scheduled Visits	Exit
Visit Window	-45 days/ -90 days for TTE from implant	Date of Model 400 Valve Implant	≤ 30 days	+90-180 days	± 30 days	± 60 days	547± 30 days & 912± 30 days	As necessary	Date of Exit
Demographics	X								
Physical Examination	X							X*	
Pregnancy Test	X**								
Medical History	X								
STS risk score	X								
NYHA Classification	X		X	X	X	X		X*	
12-Lead ECG	X		X	X	X	X		X*	
Blood Labs	X		X	X	X	X		X*	
Transthoracic Echo (TTE)	X		X	X	X	X		X*	
Transesophageal Echo (TEE)		X							
Adverse Event/ Device Deficiency	X	X	X	X	X	X	X	X	X
Relevant Medications	X	X	X	X	X	X	X	X*	
Vital Status							X		X
Operative Information		X							

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

**Pregnancy test is required for female subjects who are not exempt; see Section 6.1.

4.3 Baseline Procedures

The following baseline evaluations will be completed and recorded on the appropriate eCRF.

1. Demographics
2. Medical History (including diagnosis of valvular lesion and etiology of aortic valve disease)
3. Pregnancy Test (as applicable; see Section 6.1)
4. Physical examination
5. NYHA classification
6. Society of Thoracic Surgeons (STS) Score
7. 12-lead ECG
8. Hematology/chemistry data, including serum creatinine
9. Echocardiography examination (TTE)
10. Relevant medications
11. Adverse Events

Baseline evaluations are to be completed within 45 days of the scheduled implant procedure, with the exception of the TTE, which must be completed within 90 days of the scheduled implant procedure.

4.4 Implant Procedures

The implant technique for the Model 400 aortic bioprosthesis is expected to be similar to that for other stented aortic bioprosthetic valves. Detailed information is provided in the "Instructions for Use" included in each valve package.

4.4.1 Verification of Patient Status

The exclusion criterion, "Patient has had an acute preoperative neurological deficit or myocardial infarction and has not returned to baseline or stabilized ≥30 days prior to enrollment" must be reconfirmed prior to the planned SAVR procedure. Every subject should be evaluated on the day of procedure prior to entering the operating room, to ensure that there has not been an acute status change.

If there is an acute status change related to a neurological deficit or myocardial infarction between enrollment and the planned SAVR procedure:

- The surgeon will wait ≥30 days from the time that the subject either returns to baseline or the subject has stabilized, to implant the Model 400 valve
  or
- The surgeon will exit the subject from the trial, and continue with an alternative treatment plan (i.e., implant a commercially available device or other treatment).

Additionally, to avoid potentially confounding event data due to concomitant procedures, enrolled subjects who are intraoperatively found to require additional unplanned concomitant procedures that are not allowed per the inclusion and exclusion criteria, should be exited from the study prior to implant of the study valve. These patients should receive a commercially available valve per standard of care practices.

4.4.2 Index Procedure

The Index procedure is defined as the procedure where the Model 400 valve is implanted in the trial subject.

The following implant data will be collected and recorded on the Implant eCRF.

1. Procedure details including condition of explanted valve and any additional procedures or interventions (as applicable)
2. Serial number, valve size and disposition of implanted valve or opened valve packages
3. Documentation of device failure or malfunction (as applicable)
4. Peri-operative Transesophageal Echocardiography (TEE)
5. Adverse events/device deficiency
6. Relevant medications

4.4.3 Attempted Procedure

An attempted procedure is one where the trial subject has entered the Operating Room/Theater and the Investigator intends to implant the Model 400 valve, but the trial subject does not receive the Model 400 valve. The procedure could be aborted either before or during the attempted valve implant, or due to additional subject anatomic/medical considerations which would preclude the use of the Model 400 valve, or the Investigators' decision to use a product other than the Model 400 valve.

If the Model 400 valve (or accessories) passes the plane of the body, but the Model 400 valve is not implanted, the subject will be followed for safety reporting only for 30 days post-attempted implant, and then exited from the trial. AE data should be collected on the AE eCRF, and trial exit data on the Trial Exit eCRF.

4.4.4 Valve Reintervention

Any intervention post-index procedure, which is required to repair, remove, alter, or replace a previously implanted Model 400 valve is considered a valve reintervention. All Model 400 valve reinterventions are considered prosthesis-related. The details of a reintervention should be collected on a Reintervention eCRF and the reason for the reintervention should be collected on an AE eCRF.

If a subject's study valve is explanted, the subject will be followed for safety reporting only for 30 days post-explant. AE data should be collected on the AE eCRF, and trial exit data on the Trial Exit eCRF.

4.5 Discharge up to 30 Day Assessment

The discharge visit will occur at the time of subject's discharge from the hospital or up to 30 days post-procedure. The following evaluations will be completed and data recorded on the Discharge or 30 Day eCRF:

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

All evaluations may be performed any time during the discharge visit window through 30 days post-index procedure. Any data collected after 30 days will result in a protocol deviation.

4.6 3-6 Month Post-procedure Follow-up Assessment

Subjects will be seen in the office at 3-6 months (90-180 days) post procedure. The following evaluations will be completed and data recorded on the Follow-up eCRF:

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

4.7 1 Year Post-Procedure Follow-up Assessment

Subjects will be seen in the office at 1 year (± 30 days) post-procedure. The following evaluations will be completed and data recorded on the Follow-up eCRF:

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

4.8 18 Month and 30 Month Post- Procedure Follow-up Phone Call

Subjects will be contacted by phone at 18 and 30 months (± 30 days) post procedure to verify their health status. The following data will be collected and recorded on the Telephone Follow-up eCRF:

1. Vital Status (alive or deceased)
2. Relevant medications
3. Adverse events/device deficiency

In the event that the subject reports a new Serious Adverse Event (SAE) or device-related adverse event, at the discretion of the investigator, the subject may be asked to return to the office for an unscheduled visit and further assessment.

4.9 Annual Years 2-5 Post-Procedure Follow-up Assessment

Subjects will be seen in the office at 2, 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. Adverse events/device deficiency

5 Subject Accountability

5.1 Missed Follow-up Visits

Every effort should be made to ensure subjects return to the clinic for all protocol required follow-up visits (excluding 18 and 30 month phone 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 6.9. The Investigator should also make every effort to contact the subject within the visit window, to collect the subject's vital status (recorded on the Follow-up eCRF) as well as information related to potential adverse events (recorded on the AE eCRF).

5.2 Unscheduled Follow-up Visits

If a subject returns to the institution between the protocol-required follow-up visits, the visit will be treated as an unscheduled visit and 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 Follow-up eCRF and AE data on the AE eCRF.

5.3 Subject Withdrawal or Discontinuation

It is the subject's right to withdraw at any time from the trial and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled, and without jeopardizing their future medical care. The investigator may withdraw the subject at any time to protect the health, safety or welfare of the subject. At the last point of contact (if outside a trial-required visit), the subject's vital status should be recorded on a Trial Exit eCRF, and every effort should be made to collect the status of any ongoing adverse events. Sites shall request permission from the subject to follow-up outside of the trial, if issues arise with the investigational device safety or performance.

The subject may only be considered lost to follow-up after all efforts to obtain compliance are exhausted. At a minimum, four attempts must be made to contact the subject and documented in the subject's trial records:

- 3 telephone attempts to the subject's last known phone number, and if unsuccessful,
- 1 certified letter from the PI to the subject's last known address

If the site is unable to reach the subject after the documented attempts, the site should make every attempt to verify the subject's vital status (alive or deceased).

All subjects will be encouraged to remain in the trial through the last follow-up visit. Subjects who discontinue participation prematurely will be included in the analysis of results, but will not be replaced in the enrollment of total trial subjects. If the subject discontinues participating in the trial prior to

completing the trial requirements, the reason for withdrawal will be recorded in the subject's trial records and on the Trial Exit eCRF.

There are many scenarios in which a subject may exit the trial. Table 2 below details how the data will be handled for each scenario.

Table 2: Trial exit scenarios

Scenario	Follow-up Required	CRFs Required
Subject enrolled (informed consent signed), but the study device(s) (sizer, handle, valve) never contacts subject, and no Model 400 valve is implanted	None	-Inclusion/Exclusion eCRF -Baseline eCRF (as applicable) -AE eCRF (as applicable) -Unscheduled eCRF (as applicable) -Trial Exit eCRF
Subject enrolled, the study devices(s) (sizer, handle, valve) comes into contact with the subject (i.e., passes the body plane) but no Model 400 valve is implanted	30 days post-attempted implant for safety only	-Inclusion/Exclusion eCRF -Baseline eCRF (including labs/echo) -Implant eCRF -Discharge or 30 Day eCRF (including labs/echo) -AE eCRF (as applicable) -Other unscheduled eCRFs (as applicable) -Trial Exit eCRF
Subject enrolled, implanted with Model 400 valve, and exits the trial early due to explant	30 days post-explant for safety only	-All required/ unscheduled eCRFs through last visit completed -Valve Reintervention eCRF -AE eCRF (as applicable) -Trial Exit eCRF
Subject enrolled, implanted with Model 400 valve, and exits the trial 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 eCRFs through last visit completed -AE eCRF (as applicable) -Trial Exit eCRF
Subject enrolled, implanted and completes the trial requirements	Through 5 year follow-up	-All required/ unscheduled eCRFs -AE eCRF (as appropriate) -Trial Exit eCRF

6 Trial Assessments

6.1 Baseline

A careful medical history and physical examination should be taken prior to the implant procedure. Attention should be taken to document any chronic illnesses and pre-existing cardiac arrhythmias.

For any cardiac interventions, the date of the most recent intervention should be captured.

Use of the following medications will be collected at baseline; see Section 6.6 for additional information about specific data collection for medications:

- Anticoagulants
- Antiplatelets
- Aspirin (including Carbasalate Calcium)

Data to be collected at baseline:

- Gender
- Age at time of enrollment (in years and months)
- Race/Ethnicity- to be collected per the FDA Guidance for Collection of Race and Ethnicity Data in Clinical Trials (2005), in support of regulatory submissions in the United States (FDA) and Japan (PMDA). This requirement will be waived for subjects participating in countries where it is unlawful to collect race and ethnicity data.
- Co-existing cardiovascular conditions (including, but not limited to congestive heart failure, cardiomyopathy, peripheral vascular disease, coronary artery disease, previous myocardial infarction (MI), atrial enlargement, cardiac arrhythmias)
- Previous cardiovascular operations (including, but not limited to implanted cardiac device (pacemaker, defibrillator, CRT device), coronary artery bypass, coronary artery angioplasty, percutaneous valvuloplasty, operative valvuloplasty, previous aortic heart valve replacement, annuloplasty)
- Co-existing chronic and transient medical conditions (including, but not limited to liver, kidney, lung disease, substance abuse (alcohol/drug), diabetes (Type I or Type II), hypertension, endocarditis)
- 12-Lead ECG to collect cardiac rhythm (sinus rhythm, atrial fibrillation, atrial flutter, heart block, etc.)
- NYHA Classification
- STS risk score
- Hematology/chemistry, including serum creatinine to allow for the calculation of a EuroSCORE.

For female subjects of child-bearing potential, a pregnancy test will be done at baseline to confirm that the subject is not pregnant. Subjects exempt from this requirement are those who have been surgically sterilized, who are infertile, or who have been post-menopausal for at least 12 months (no menses).

6.1.1 STS Risk Scores

The Society of Thoracic Surgeons' risk models predict the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographic and clinical variables.

http://riskcalc.sts.org/stswebriskcalc/#/

The online calculator provides additional guidance for each of the parameters used to calculate the scores. Risk of Mortality and Risk of Morbidity or Mortality scores should be recorded on the Baseline eCRF. The STS Risk Scores should be printed from the online calculator and filed as source documentation for trial subjects.

6.2 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 baseline, discharge (up to 30 days), and all in-office follow-up visits, and the results recorded on the appropriate eCRF. The NYHA classification should be assessed by a medical doctor, physician assistant or nurse practitioner.

6.3 12-Lead ECG

A standard 12-Lead ECG should be taken at baseline, discharge (up to 30 days), and 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 trial 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.

6.4 Echocardiography

Transthoracic echocardiography (TTE) is required at baseline, discharge (up to 30 days), and all in-office scheduled follow up visits. The site will record echocardiography data on the Site Echo eCRF.

A peri-procedural Transesophageal Echocardiogram (TEE) is required before the subject leaves the operating room/theater to assess the valve implant and evaluate/characterize any paravalvular leak and peak /mean gradient. The site will record the TEE data on the Implant 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 G: Echocardiographic Procedures. Additional information regarding the Echo Core Lab can be found in Section 16.1.

6.5 Hematology/Chemistry

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

6.5.1 Hematology/Clinical Chemistry

- 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)
- Serum Creatinine (at baseline only, to allow for EuroSCORE to be calculated)

*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.

6.5.2 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.

6.6 Medications

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

- Anticoagulants
- Antiplatelets
- Aspirin (including Carbasalate calcium)

The physician will determine the appropriate anticoagulation therapy for each subject. Except where contraindicated, Medtronic recommends anticoagulation therapy during the initial healing stages after implantation in accordance with normal practices for bioprosthetic valves. Long-term anticoagulant and/or antiplatelet therapy should be considered for subjects with a dilated left atrium, a history of thromboembolic events, or a cardiac rhythm of atrial fibrillation or atrial flutter.

Subjects should be weaned off of anticoagulants per the Investigator's standard clinical practice.

6.7 Vital Status

A vital status (alive or deceased) should be confirmed for trial subjects at the 18 and 30 month phone calls and at trial exit and recorded on the appropriate eCRF.

6.8 Emergency Use

Given the investigational status of the Model 400 valve, and the availability of approved surgical valves, emergency cases are not allowed under this protocol.

6.9 Deviation Handling

A trial deviation is any event in which the trial 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 trial
- Implanted subject did not meet inclusion/exclusion criteria
- Required testing and/or measurements not done or incorrectly done
- Subject did not attend follow-up visit
- Follow-up visit was completed outside window
- Unauthorized use of investigational devices
- Adverse events/UADE or device deficiencies not reported in the required timeframe by country regulation or as specified in the CIP
- Control of trial devices not maintained
- Source data permanently lost
- Enrollment of subjects during lapse of Ethics Board approval
- Enrollment limits exceeded

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. Trial 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. Refer to Tables 13-18 for geography-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

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. Medtronic may provide center-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

6.10 Assessment of Safety

6.10.1 Definitions

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 Pivotal Trial

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) (EN 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 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.

Event Type	Definition
	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 Adverse Device Effect (UADE) (21 CFR 812.3)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
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.*

Event Type	Definition
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.*

6.10.2 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 trial subjects from the time they are consented until they are no longer participating in the trial.

All AEs that occur during the trial 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.

Unavoidable events are conditions which do not fulfill the definition of an Adverse Event, meaning those medical occurrences, clinical signs (including toward abnormal laboratory findings), diseases or injuries that are not untoward in nature, specifically those resulting from the intended injury such as the index surgical aortic valve replacement procedure.

The events in Table 5 below are expected and appropriate to occur with any open heart surgery and therefore do not fulfill the definition of Adverse Event, and do not need to be reported as Adverse Events, unless they occur outside of the stated timeframe, are otherwise considered to be an Adverse Event according to the treating investigator, or are suspected or confirmed to be device-related.

Table 5: Non-Reportable Medical Occurrences associated with Index Procedure

Body category	Occurrence	Timeframe (hours) from the Index Procedure
Hematologic	Blood transfusion and anemia occurring during the index procedure within expected ranges (part of the regular hospital protocol)	0
Hematologic	Any bleeding during the index procedure	0
Hematologic	Any bleeding after index procedure with < 3 units blood transfusion, or < 1 liter blood loss	24
Cardiac	Short transient episode of arrhythmia (including ventricular fibrillation) during index procedure	0
Central nervous system	Confusion, anxiety and/or disorientation (other than TIA/stroke) starting within 48 hours with or without medical intervention	120 (5 days)
Central nervous system	Temporary change in mental status (other than TIA/stroke) not requiring additional medical interventions or new medical assessments (e.g. CT)	72
Central nervous system	Dizziness and/or lightheadedness with or without treatment	24
Central nervous system	Headache with or without treatment	72
Central nervous system	Sleep problems or insomnia with or without treatment	120 (5 days)
Respiratory/pulmonary	Mild dyspnea or cough with or without treatment	72
Respiratory	Oxygen supply after extubation / "forced breathing therapy"	48
Gastrointestinal	Diarrhea with or without treatment	48

Gastrointestinal	Obstipation / Constipation with or without treatment	72
Gastrointestinal	Anesthesia-related nausea and/or vomiting with or without treatment	24
Body Temperature	Low-grade fever (<101.3˚F or <38.5˚C) without confirmed infection	48
Body Temperature	Low body temperature	6
Pain	Pain (e.g. back, shoulder) related to laying on the procedure table with or without treatment	72
Pain	Incisional pain (pain at access site) with or without standard treatment and patient not returning to clinic to have additional treatment	No time limit
Pain	Pain in throat and/or trachea due to intubation	72
Skin and subcutaneous System	Mild to moderate bruising or ecchymosis	168 (7 days)
Respiratory	Atelectasis / Pleural Effusion not requiring punctuation	168 (7 days)
General	Edema resulting in weight increase up to 4 kg / 9lbs from baseline	168 (7 days)

- The general process for reporting Adverse Events is as follows: Report the event to Medtronic as soon as possible but no later than the timeframes outlined in Table 7. Sites will be provided with the contact information of the appropriate Medtronic designee.
- 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 Model 400 valve
- Causal relationship of the event to the TruSize™ Sizer or Valve Handle
- 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

In addition, 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 16.4.1.

6.10.3 Classification of Causal Relationships

For each reported AE, the causal relationship between the AE and the trial devices and implant procedure will be classified as related, not related or unknown. The causal relationships are defined in Table 6.

Table 6: Adverse Event Causal Relationship Definitions

Related to	Definition
Model 400 valve, TruSize™ Sizer or Valve Handle	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.
Model 400 valve implant procedure	Any AE that results from the implant procedure through 30 days post-implant. Events in this category are directly related to the general procedural sequelae.

6.10.4 Adverse Event and Device Deficiency Reporting Requirement

Adverse events and device deficiencies that occur during this trial are required to be reported to Medtronic via the AE or device deficiency eCRF, as soon as possible after the event occurs, but no later than the timeframes listed in Table 7 or local requirements, whichever is more stringent.

Table 7: Required 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 72 hours of the investigator's / site's first knowledge of the event
Adverse Device Effect (ADE) or Device Related Adverse Event	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Serious Adverse Device Effect (SADE)	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Unanticipated Adverse Device Effect (UADE)	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Unanticipated Serious Adverse Device Effect (USADE)	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Device Deficiency	No later than 72 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 72 hours of the investigator's / site's first knowledge of the event
Mandatory Problem Reporting Incident (Canada ONLY)	No later than 72 hours of the investigator's / site's first knowledge of the event, to Health Canada

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

The Sponsor is obligated to report adverse events and device deficiencies that occur during this trial to the Regulatory Authorities and Ethics Board as per local requirements. The applicable timeframes are described in the PERIGON Safety Plan.

6.10.5 Documentation and Reporting of Device Deficiencies

Device deficiency information will be collected throughout the trial 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).

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.

6.10.6 Vigilance Reporting

The Model 400 and accessories are commercially available in the United States, Canada, Europe, and Japan. The Model 400 valve is commercially available (Avalus™) in the valve sizes: 19mm, 21mm, 23mm, 25mm, and 27mm. The sizers are commercially available under both TruSize™ and Avalus sizer names. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements.

- Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.
- Vigilance Reporting: A system used to notify the Competent Authority (CA) about incidents with regard to medical devices that carry the CE mark. This system requires a manufacturer to notify the competent authority of incidents immediately on learning of them.
- Incident: Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health. Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic (i.e. the TruSize™ sizers and Valve Handles) regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately (within 48 hours) and via the regular channels for market released products.

6.10.7 Emergency Contact Details for Reporting Events and Device Deficiencies

Investigators should contact the Medtronic Trial 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.

7 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 trial report, along with justification for the deviation(s).

The safety and effectiveness analyses will be performed on those subjects implanted with the Model 400 valve (As Treated population).

The data from the subjects with attempted procedures, but who were not implanted with the Model 400 valve will be summarized separately, and reported as descriptive statistics. A sub-analysis of the operative mortality of this group will be included in the overall safety analysis. The subjects with attempted procedures will not be counted towards the total number of implants.

Additional exploratory analyses of the data may be conducted as deemed appropriate.

7.1 Primary Analysis

The statistical design for the primary analysis of the trial data is based on the recommendations of the FDA Heart Valve guidance document (2010) and EN ISO 5840:2009 standard for cardiac valve prostheses. This primary analysis will be used in a Pre-Market Approval (PMA) submission to the U.S. Food and Drug Administration (FDA), application for CE Mark in Europe, application for Medical Device License (MDL) to Health Canada, and may be used for other regulatory submissions.

7.1.1 Safety Objective

The objective is to evaluate the safety of the Model 400 valve with regard to valve-related adverse events and death.

7.1.1.1 Endpoints

Safety of the valve will be evaluated by the time-related incidence of valve-related adverse events and death. The following valve-related adverse events will be evaluated in this study: Thromboembolism, Thrombosis, Hemorrhage (all and major), Paravalvular leak (PVL, all and major), Endocarditis, Hemolysis, Structural valve deterioration, Non-structural dysfunction, Reintervention, Explant, and Death.

Definitions for the above valve-related adverse events are located in Appendix E.

7.1.1.2 Hypothesis

The safety objective will be assessed by comparing linearized valve-related adverse event rates from subjects implanted with the Model 400 valve to acceptable linearized valve-related adverse event rates following valve replacement as defined by FDA in the Heart Valve Guidance 2010 and EN ISO 5840:2009 as Objective Performance Criteria (OPC). The OPC for tissue valves (based on the linearized rate) are presented in Table 8.

Table 8: OPC for Tissue Prosthetic Heart Valves

Adverse Event	*Linearized Rate (% per Patient-year)*
Thromboembolism	2.5
Valve Thrombosis	0.2
All Hemorrhage	1.4
Major Hemorrhage	0.9
All Paravalvular Leak	1.2
Major Paravalvular Leak	0.6
Endocarditis	1.2

The trial is designed to test the hypothesis that the true linearized adverse event rate for the Model 400 valve ($R_{\_Model\ 400}$) is equal to or greater than twice the acceptable rate of commercially available tissue prosthetic valves ($R_{\_OPC}$). The null (H_0) and alternative (H_A) hypotheses are written as follows.

H_0: $R_{\_Model\ 400} \geq 2 \times R_{\_OPC}$

H_A: $R_{\_Model\ 400} < 2 \times R_{\_OPC}$

Where $R_{\_Model\ 400}$ is the linearized adverse event rate for the Model 400 valve and $R_{\_OPC}$ is the acceptable rate of commercially available tissue prosthetic valves. To reject the null hypothesis demonstrates statistically that the rate for the Model 400 valve is less than two times the acceptable rate.

7.1.1.3 Sample Size

Sample size estimation is based on the methods of Grunkemeier[24]. The amount of data required to test the null hypothesis using the smallest acceptable adverse event rate of 1.2% per patient-year (excluding Valve Thrombosis, Major Hemorrhage and Major PVL) is 800 patient-years. This estimation assumes a 95% confidence level, a power of 0.80, and an annual attrition rate of 5%. If all subjects are enrolled within a one year time frame, and followed for one year postoperatively, then a total of 556 implants are required. Accounting for potential variability in attrition and enrollment rate, a sample size of 650 was originally approved in protocol revisions 1B through 1D. With version 1E of the investigational protocol, the sample size has been increased to 1300. While the increased sample size adds exposure of the investigational device to a larger cohort of patients, the sample size is within acceptable limits based on the following justification:

- The current risk and benefit analysis suggests that the benefits of surgical aortic valve replacement far outweigh the risks associated with implant of an aortic bioprosthesis. Given the relatively low expected incidence of late valve-related adverse events and the assumed linearized occurrence of such events as detailed in the published OPC data from the FDA Heart Valve Guidance 2010 and ISO5840:2009, the increased risk to the overall population of subjects requiring SAVR is minimal.
- Due to the linearized OPC model utilized in the evaluation of the primary safety endpoints, an increased sample size will allow for a more rapid evaluation of the primary safety endpoints through faster accumulation of valve-years.
- A similar sample size has been used by both Medtronic and other industry sponsors in the evaluation of other tissue aortic valves that have a similar design, the same intended use, and the same primary safety endpoints as the PERIGON trial. Notably, the pivotal trial for the Medtronic Mosaic™ valve utilized a cohort of 1252 subjects for evaluation of the primary safety endpoints which were compared to the same published OPC. Likewise, the most recently approved tissue aortic valve, Trifecta™, which is manufactured by St. Jude Medical, utilized a cohort of 1014 subjects for evaluation of the primary safety endpoints compared to the same published OPC. Therefore, there is historical precedent that a cohort similar to that of the PERIGON trial is justified.

Additional rationale for increasing the sample size:

- An increased sample size provides a larger cohort from which to establish future long term safety, effectiveness and valve durability (e.g. follow-up beyond the current 5-year period).
- An increase of the trial cohort to up to 1300 subjects will allow for enrollment to continue until the point of anticipated commercialization, to avoid a significant interruption in access to surgeons of the latest surgical valve technology.
- All subjects will continue to be followed under the current rigorous clinical evaluation plan and follow-up schedule, including safety committee (CEC and DSMB) oversight.

7.1.1.4 Analysis Methods

Primary endpoint analyses for regulatory approval will be done on consecutive subjects, and according to the requirements of the guidance documents:

- ISO5840:2009: for regulatory submissions in geographies adhering to the ISO5840:2009 standards (minimum of 150 subjects with 1 year follow up and 400 patient years)
- FDA Heart Valve Guidance 2010 for US FDA PMA (minimum of 300 subjects with 1 year follow up and 800 patient years).

Early rates of adverse events will be calculated as the number of early adverse events divided by the total number of subjects, expressed as a percentage. Early events are events occurring on or before 30 days post-operative.

Linearized rates will be calculated as the number of late events divided by the cumulative late post-operative patient-years, expressed as a percentage. Late events are events occurring after 30 days post-operative. For those adverse events with OPC available, the linearized rates and their associated one-sided upper 95% confidence bounds will be compared to 2 x the OPC rate to show that they are within acceptable limits.

Kaplan-Meier survival analyses will also be performed to summarize the adverse event data.

In addition, control articles based on current literature of previously approved heart valves will be selected. Adverse event data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, and allow additional evaluation of the Model 400 adverse event data.

7.1.2 Effectiveness Objective

The effectiveness objective is to confirm the effectiveness of the Model 400 valve, with regard to NYHA Functional Classification and hemodynamic performance.

7.1.2.1 Endpoints

The effectiveness endpoints are

- NYHA Functional Classification (at discharge (up to 30 days), 3-6 months, 1 year and annually thereafter through 5 years)
- Hemodynamic Performance (at discharge (up to 30 days), 3-6 months, 1 year and annually thereafter through 5 years) including
  - effective orifice area (EOA)
  - effective orifice area index (EOAI)
  - peak pressure gradient
  - mean pressure gradient
  - valvular regurgitation
  - performance index
  - cardiac output
  - cardiac index

7.1.2.2 Analysis Methods

NYHA functional classification and echocardiographic hemodynamic data will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables. NYHA functional class will be evaluated based on the percentage of subjects in each specific NYHA class at each postoperative time-point and the percentage of subjects at each postoperative time-point who have improved, worsened, or not changed in NYHA class compared to preoperative baseline.

Hemodynamic data will be summarized by valve size and visit. Control articles based on current literature of previously approved heart valves will be selected. Effectiveness data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, to allow for evaluation of the Model 400 valve effectiveness data.

7.2 Interim Analysis for Market Approval Outside of US

An interim analysis of the trial data is planned to evaluate the early safety profile of the Model 400 valve. The interim analysis will be included as supplementary information in a submission for CE Mark, and may be used for regulatory submissions in other geographies. There is no intention to evaluate or stop the study prematurely unless there is a safety concern regarding the Model 400 aortic bioprosthesis. The interim analysis results will not be distributed to US study sites, and will not be available on Medtronic's website for U.S. physicians to access. If material is published in peer reviewed journals, these results will not be distributed by Medtronic within the U.S. prior to FDA approval. Therefore, it is highly unlikely results from this interim analysis would present bias for the overall IDE study results.

7.2.1 Safety Objective

The safety objective is to evaluate the safety of the Model 400 valve with regard to valve-related adverse events and death.

7.2.1.1 Endpoints

Safety of the valve will be evaluated by the time-related incidence of valve-related adverse events and death. The following valve-related adverse events will be evaluated in this study: Thromboembolism, Thrombosis, Hemorrhage, Paravalvular leak, Endocarditis, Hemolysis, Structural valve deterioration, Non-structural dysfunction, Reintervention, Explant, and Death.

7.2.1.2 Hypothesis

The safety objective will be assessed by comparing a composite linearized adverse event rate from subjects implanted with the Model 400 valve to a composite linearized adverse event rate of valve-related Thromboembolism, Endocarditis, Major PVL and Thrombosis. The composite rate was developed using individual valve-related event rates from the Objective Performance Criteria (OPC) as defined by FDA in the Heart Valve Guidance 2010 and EN ISO 5840:2009. From Table 8, twice the composite linearized adverse event rate of Thromboembolism, Endocarditis, Major PVL and Thrombosis is 2 X (2.5 + 0.2 + 0.6 + 1.2) = 9%.

The trial hypothesis is to test that the true composite linearized adverse event rate of Thromboembolism, Endocarditis, Major PVL and Thrombosis for the Model 400 valve ($P_{\_Model\ 400}$) is equal to or greater than twice the composite linearized adverse event rate of commercially available tissue prosthesis valves.

The null (H_0) and alternative (H_A) hypotheses are written as follows.

H_0: $P_{\_Model\ 400} \geq 9\%$

H_A: $P_{\_Model\ 400} < 9\%$

Where $P_{\text{Model 400 is}}$ the composite linearized adverse event rate for the Model 400 valve.

7.2.1.3 Rationale for the Composite Endpoint

The composite rate was chosen because it provides an overall evaluation of safety of the device by incorporating significant device-related events that are clinically relevant to evaluating a new bioprosthetic heart valve.

7.2.1.4 Sample Size

A fixed sample size group sequential design with O'Brien-Fleming boundaries for one interim analysis will be utilized. A fixed sample size design of 400 patient-years with one interim analysis at 200 patient-years achieves at least 90% power.

The assumptions for sample size / power calculation:

- P_{Baseline} (the baseline rate: observed in the literature) = 3.5%
- $P_{\text{Model 400}}$ (the assumed rate for the Model 400 valve) = 3.5%
- Type I error (α) =0.05
- One interim analysis at 200 patient-years

The objective will be evaluated with a fixed sample size group sequential design with one interim analysis at 200 patient-years and one possible second analysis at 400 patient-years.

7.2.1.5 Analysis Method

This trial will have up to two analyses of this objective. The first analysis will occur when 200 patient-years of data are collected and the second analysis may occur when 400 patient-years of data are collected. Spending function with boundaries similar to that for O'Brien-Fleming will be used to control the Type I and Type II error probabilities. The table below illustrates the O'Brien-Fleming boundaries and the associated z-statistic and p-value for each analysis under an assumption that 200 patient-years of data are observed at the interim analysis. However, if the observed patient-years of data are different at the time of the interim analysis, the boundaries and p-values will be recalculated to reflect the appropriate percentage of the total sample size observed at the time of the interim analysis.

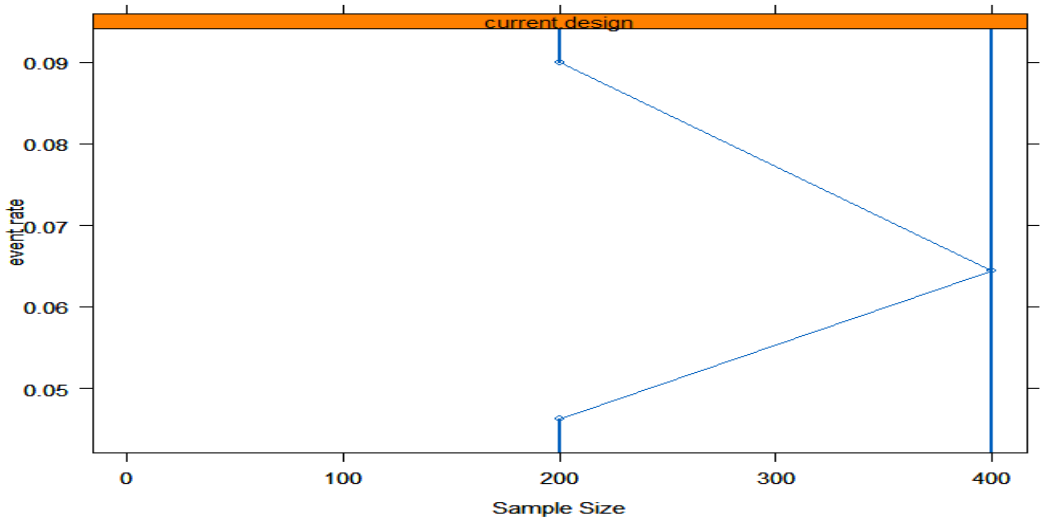
Table 9: O'Brien-Fleming boundary at the interim and 400 patient-year analysis

Analysis	Z-statistic	P-value
Interim	-2.3585, 0.0000	0.0092, 0.5000
400 patient-years	-1.6677	0.0477

*S-Plus 8.2/S+ SeqTrial used with the O'Brien-Fleming Type I error spending function.

The above sample rate boundaries are also shown in Figure 1:

Figure 1: Event Rate boundaries using O'Brien-Fleming Method



Since there may be up to two analyses, there are two thresholds for which the observed test statistic will be evaluated. Call this set of thresholds $Z_t = (Z_1, Z_2)$. Each of these thresholds will be a standard normal Z statistic evaluated at the nominal alpha level for the analysis. For example, in the table above, the nominal alpha level for the interim analysis is 0.0092 with an associated Z statistic of -2.3585. Thus, if the Z statistic is smaller than -2.3585, the null hypothesis may be rejected at the interim analysis. Similarly, if the null hypothesis cannot be rejected at the interim analysis, the null hypothesis may be rejected at the 400 patient-years analysis provided the Z statistic is smaller than -1.6677. To reject the null hypothesis demonstrates statistically that the Model 400 valve composite adverse event rate is less than 9%. This method preserves the Type I error rate at 5% since the conservative O'Brien-Fleming rules are utilized in setting the rejection thresholds Z_t.

- At the interim analysis (200 patient-years), if the data support the alternative hypothesis that the Model 400 valve composite rate is <9%, the results will be summarized and submitted for CE Mark approval. The 400 patient-year analysis will not be performed under this scenario.
- If the criteria are not met at the 200 patient-year interim analysis, the trial will continue to gather data to at least 400 patient-years and then summarize the data and submit for CE Mark approval.

Each component of the composite adverse event rate will also be summarized and described.

Kaplan-Meier survival analyses will also be performed to summarize the adverse event data.

In both scenarios, the trial conduct will not be altered, and the trial will not stop, but continue until at least 800 patient-years of data are collected.

7.2.2 Effectiveness Objective

The effectiveness objective is to confirm the effectiveness of the Model 400 valve with regard to the NYHA Functional Classification and hemodynamic performance.

7.2.2.1 Endpoints

The effectiveness endpoints are:

- NYHA Functional Classification (at discharge or within 30 days, 3-6 months, 1 year and annually thereafter through 5 years)
- Hemodynamic Performance (at discharge or within 30 days, 3-6 months, 1 year and annually thereafter through 5 years) including
    - effective orifice area (EOA)
    - effective orifice area index (EOAI)
    - peak pressure gradient
    - mean pressure gradient
    - valvular regurgitation
    - performance index
    - cardiac output
    - cardiac index

7.2.2.2 Analysis Methods

NYHA functional classification and echocardiographic hemodynamic data will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables. These data will also be summarized by valve size and visit. Contemporary control articles based on current literature of previously approved heart valves will be selected. Effectiveness data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals; and allow evaluation of the Model 400 valve effectiveness data.

7.3 Additional Analysis Information

7.3.1 General Summaries

Baseline demographic and clinical variables will be summarized. Continuous variables will be summarized as means, medians, standard deviations and ranges. Categorical variables will be summarized as frequencies and percentages.

7.3.2 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.

7.3.3 Poolability of Data

A poolability analysis among geographies, investigational sites and baseline data will be performed for the safety endpoint and will be described in detail in the SAP. In addition, the endpoints will be evaluated for possible differences between genders.

7.3.4 Controls

The clinical trial will include appropriate controls including literature-based objective performance criteria (OPCs) for safety data and contemporary literature articles and reports for both safety and effectiveness data.

7.3.5 Minimizing Bias

Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical trial.

Selection of subjects, treatment of subjects and evaluation of trial data are potential sources of bias. Methods incorporated in the trial design to minimize potential bias include (but are not limited to):

- For sites that are participating in other SAVR studies which may have similar enrollment criteria as the PERIGON Pivotal Trial, a written process for avoiding selection bias is required
- Subjects will be screened to confirm trial eligibility with defined inclusion/exclusion criteria prior to enrollment. Sites are required to maintain a log of all subjects screened and enrolled for the trial.
- Demographics and medical history will be collected at baseline in order to later assess possible characteristics that may influence endpoints
- Data collection requirements and trial procedures will be standardized across all geographies
- All geographies will follow the same version of the CIP and eCRFs
- No more than 20% of expected enrollments may come from a single site
- All trial investigators will be required to meet the requirements of 21CFR Part 54, Financial Disclosure by Clinical Investigators
- All trial site and Medtronic personnel will be trained using standardized training materials
- Regular monitoring visits will be conducted to verify adherence to the CIP and source data
- An independent Clinical Events Committee (CEC) will be utilized to regularly review and adjudicate reported adverse events
- An independent Data Safety Monitoring Board (DSMB) will be utilized to review data, help safeguard the interests of trial subjects and monitor the overall conduct of the trial

8 Risk Analysis

8.1 Description of Risk Analysis

Medtronic has determined the Model 400 valve to be a significant risk medical device. Therefore, in accordance with the FDA Heart Valve Guidance (2010) and EN ISO5840:2009 requirements, Medtronic is required to conduct a human trial and obtain appropriate regulatory approvals to do so.

In the United States, Medtronic will obtain an Investigational Device Exemption from the United States Food and Drug Administration. Medtronic will obtain approval from country-specific Competent Authorities in the EU, and approval from Health Canada to conduct the human trial.

Risk Analysis procedures were completed in accordance with EN ISO 14971:2012, and the results are detailed in the Investigator Brochure/Report of Prior Investigations.

8.2 Risks and Benefits

8.2.1 Potential Benefits

Potential benefits from use of the device are similar to those associated with commercially available bioprosthetic valves. The primary benefit is restoration of heart blood flow control by replacement of the diseased heart valve. The chosen tissue (bovine pericardial) has proven durable performance, as demonstrated in currently approved valves. [19]

This valve is designed to incorporate the proven attributes of the leading bovine pericardial heart valves: a flexible, radiopaque, low-profile stent, a contoured sewing cuff, and anti-calcification agent (AOA™).

The Model 400 valve may offer the following benefits:

- The valve tissue is treated with an alpha amino oleic acid (AOA™) anti-mineralization process that has been shown to mitigate calcification of bioprosthetic valves.
- The base frame PEEK material is impregnated with barium sulphate to allow for radiographic visualization to use it for potential TAVI procedures in the future.
- The valve has a low profile, so that the chance of obstructing the coronary ostia is minimized.
- Wide range of available sizes
- Pliable sewing ring with enhanced needle penetration, facilitating implant suturing and seating.

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

8.2.2 Potential Risks

There are risks associated with any surgical procedure. Risks associated with the Model 400 aortic valve bioprosthesis are expected to be similar to commercially available tissue heart valves. These risks include:

- angina
- cardiac dysrhythmias
- endocarditis or other infection
- heart failure
- hemolysis
- hemolytic anemia
- hemorrhage, anticoagulant/antiplatelet-related
- leak, transvalvular or paravalvular
- myocardial infarction
- nonstructural dysfunction (leaflet entrapment/impingement, obstructive pannus ingrowth, suture dehiscence, inappropriate sizing, other)
- prosthesis regurgitation
- stroke
- structural deterioration (calcification, leaflet tear, stenosis, other)
- thromboembolism
- valve thrombosis

These complications could lead to:

- reintervention
- explant of the bioprosthesis
- permanent disability
- death

The Model 400 valve has not been studied in humans; however, the expected rates of adverse device effects are well characterized in the ANSI/AAMI/EN ISO 5840:2009 “Cardiovascular implants- Cardiac valve prostheses”, Table R1, objective performance criteria (OPC). Table 10 lists the highest anticipated rates (2 x the OPC rates) for these OPC events. It is expected that the rates of risks of the Model 400 valve will be similar to currently-market approved bioprosthetic aortic valves.

Table 10: Upper bound (2 x OPC) of expected rates of ADEs in the PERIGON Pivotal Trial

Adverse Event	Rate (2x OPC) (% per patient-year)
Endocarditis	2.4%
Hemorrhage	2.8%
Paravalvular leak	2.4%
Thromboembolism	5.0%
Valve thrombosis	0.4%

Preoperative evaluation and close postoperative monitoring will minimize foreseeable risk and discomfort.

There are no expected additional risks due to subject participation in the trial.

The following measures will be implemented to minimize risks to trial subjects:

- Investigators will have expertise in aortic heart valve replacement procedures.
- Investigative sites will have comprehensive cardiology and surgery programs.
- Investigators will be trained on the use of the Model 400 valve and accessories.
- Subjects receiving the Model 400 valve will be rigorously followed over the course of the trial. The protocol includes regular follow-up visits to assess device safety and effectiveness. These visits will enable detection of deterioration in Model 400 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 in each of the respective geographies.

8.2.3 Risk-Benefit Rationale

It has been demonstrated that implantation of aortic tissue valves can be performed safely, and that these devices provide competent valve function.

Given the poor prognosis of patients with aortic valve deficiencies, and the expectation that risks of the Model 400 valve are similar to current market-released aortic tissue valves, the potential benefits outweigh the risks and the investigation of this valve is justified.

8.3 Analysis of Adverse Device Effects

The Model 400 valve has undergone extensive pre-clinical testing and has demonstrated comparable results to other commercially available tissue heart valves. A summary of pre-clinical testing is included in the Investigator Brochure/Report of Prior Investigations.

9 Product Description

The Medtronic Model 400 aortic valve bioprosthesis (manufactured by Medtronic, Inc.) is indicated for the replacement of a diseased, damaged, or malfunctioning native or prosthetic aortic valve.

The Model 400 valve (Figure 2) 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 2: Model 400 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. The Model 400 valve 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.

A disposable valve holder (Figure 3) is attached to the outflow of the valve to facilitate implantation. The disposable holder is designed to fit the reusable Medtronic Valve Handle (Medtronic Valve Handle, manufactured by Medtronic, Inc.) (Figure 4), and features a single cut point to remove the holder from the valve.

Figure 3: Valve Holder

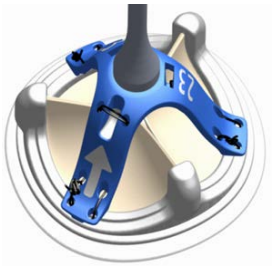
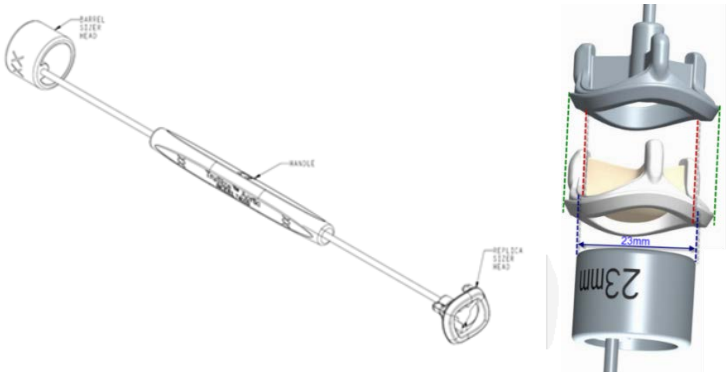


Figure 4: Medtronic Valve Handle

Double-ended, reusable TruSize™ sizers (Figure 5) (manufactured by Medtronic, Inc.) are used to select the appropriate valve size; the barrel end represents the valve orifice, and the replica end imitates the prosthesis geometry.

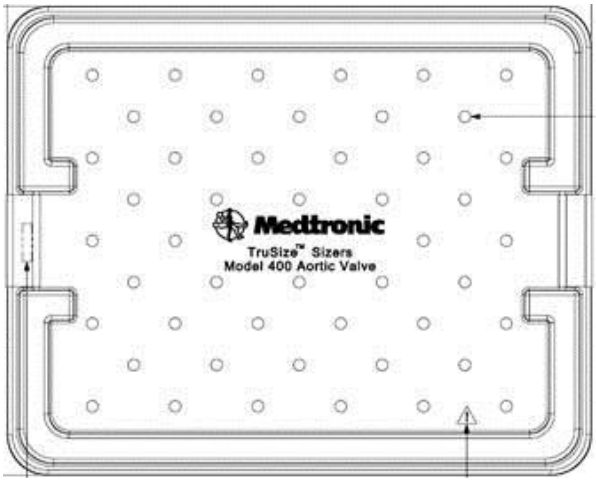
Figure 5: TruSize™ Sizer



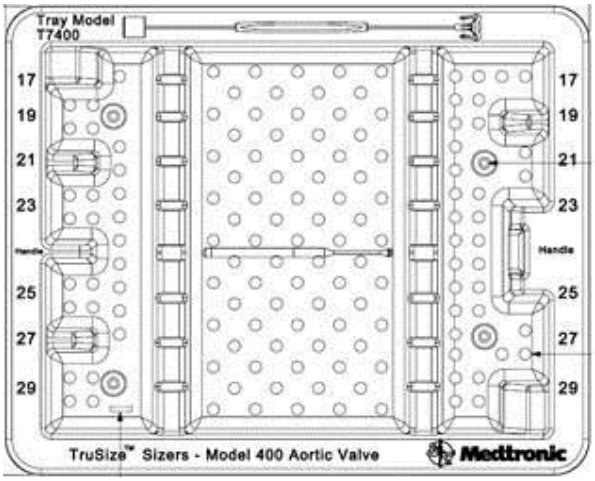
The Valve Handle and TruSize™ sizers are housed in an optional accessory tray (Figure 6)

Figure 6: Model 400 Accessory Tray

(a) Tray Lid



(b) Tray bottom



Device model numbers are listed in Table 11:

Table 11: Model 400 aortic valve bioprosthesis /Implant Accessory Model Numbers

Valves	Model Number
17mm	40017
19mm	40019
21mm	40021
23mm	40023
25mm	40025
27mm	40027
29mm	40029
Accessory Parts	
TruSize™ Sizer	7400S
Avalus™ Sizer (commercial)	7400S
Medtronic Valve Handle	7420
Model 400 Accessory Tray	T7400
Complete Accessory Kit (sizer, handle and tray)	7400K

The Model 400 valve and accessories (sizer/handle) are commercially available (Avalus™) in the valve sizes: 19mm, 21mm, 23mm, 25mm, and 27mm after receiving FDA approval on July 31, 2017, Health Canada Approval on September 8, 2017, and CE mark approval on July 3, 2017. The size 17mm and 29mm valve sizes are still considered investigational in all geographies and will be labeled as such (see Section 13.1 for specific language on the device label). Use of the valve is limited to the clinical investigation and according the Clinical Investigational Plan (CIP) for the 17mm and 29mm valve sizes. Commercially available accessories may also be used during implant of the Model 400 valve according to the CIP. Complete Instructions for Use are included in Appendix B. The device classification of the Model 400 valve and its accessories are listed in Table 12.

Table 12: **Device Classification**

Device	Classification by Geography		
	USA (FDA)	Europe (MDD)	Canada (Health Canada)
Model 400 aortic bioprosthetic valve	Class III	Class III	Class IV
TruSize™ Sizer[1]	Class I	Class IIa	Class II
Valve Handle	Class I	Class IIa	Class II
Model 400 Accessory Tray	Not a medical device	Not a medical device	Class I

[1]Sizers are commercially named Avalus sizers in Europe

10 Ethics

10.1 Statements of Compliance

The PERIGON Pivotal Trial 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. 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, Ethics Board approval, study training, clinical trial 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 CFR Parts 11, 50, 54, 56 and 812. In addition, the study will be conducted in compliance with 21 CFR Part 11 and 54 in all participating geographies.

In Europe and Canada, the study will be conducted in compliance with ISO 14155:2011.

In Canada, SOR/98-282, Section 79-88 will also be followed.

In Europe, MDD 93/42/EEC and MEDDEV 2.7/3 will also be followed.

Regulatory authority notification/approval to conduct the trial is required in all participating geographies. Investigational sites will be not be activated, nor begin enrolling subjects until the required approval/favorable opinion from the respective regulatory agency 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 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, Section 810(a)).

11 Study Administration

11.1 Regulatory Submissions

The PERIGON Pivotal Trial will be used to support application for market release in several targeted geographies, particularly the United States, Canada and Europe.

For commercialization in the United States, the trial will be conducted to meet the requirements detailed in the FDA Draft Heart Valve Guidance, 2010.

Likewise, for commercialization in other markets including Canada and Europe, the study will be conducted in accordance with ISO 5840:2009 Cardiovascular implants- Cardiac valve prostheses.

11.2 Investigational Site Initiation and Management

11.2.1 Investigator Selection

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

- Experience in cardiothoracic surgery and surgical aortic valve replacement
- The presence or capacity of establishing an investigative team capable of managing the duties of the clinical trial

- Access to the necessary cardiovascular facilities and services to complete protocol required study procedures and follow-up.
- A sufficient patient population to meet enrollment expectations (minimum enrollment of 15 subjects expected at each site, with a maximum of 130 subjects (or 20% of the total trial population))
- Willingness to comply with the requirements described in this CIP

11.2.2 Research Agreement and Financial Disclosure

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 trial activation. The investigator is required to indicate their approval of the CIP (and any subsequent amendments), by signing and dating the agreement.

All investigators will be asked to complete financial disclosure statements provided by Medtronic prior to their participation in the trial.

11.2.3 Training of Investigative Staff

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

- Technical overview of device(s)
- CIP overview and trial procedures
- Investigational device disposition and accountability procedures
- Procedures for returning unused/explanted devices
- Case report form (CRF) completion and management, including electronic data entry
- Investigator and sponsor responsibilities
- Procedures for obtaining informed consent
- Ethics Board requirements
- Adverse event/device deficiency reporting procedures
- Deviation reporting procedures
- Monitoring requirements and expectations
- Potential regulatory inspections and audits by the sponsor or sponsor representative
- Site record maintenance and retention
- Device/product reimbursement information (based on geographic regulations)
- Investigational site and subject compensation
- Any additional regulatory requirements

Site personnel (including new personnel) must be trained and activated by Medtronic prior to performing any protocol related duties.

11.2.4 Site Activation/Supply of Trial Materials

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

- Curriculum vitae of the principal and sub-investigators and all key site staff
- A signed research agreement
- Financial disclosure from the investigators
- Competent Authority/FDA/Health Canada approval (as applicable to the geography)
- 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
- Delegated Task List
- Lab certificate and lab normal values/ranges
- Confirmation of adequacy of equipment/facilities

Medtronic will control the supply of devices and trial materials, and will only ship investigational devices once the above activation criteria are met, and the site receives a formal activation letter from Medtronic.

11.3 Trial Site Investigative Team Members- Roles and Responsibilities

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

11.3.1 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 trial at the site and for the integrity of the trial 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 trial-related procedures, and only after Ethics Board and regulatory approval of the trial
- 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

- For Canadian sites: Investigators must comply with Subsection 81(k) of Canadian Medical Devices Regulations (SOR /98-282)

- Providing accurate financial disclosure to the sponsor, including any relevant changes during the course of the trial and for 1 year after the completion of the trial.
- Ensuring control and accountability of the investigational devices, and return or disposal of the devices at the close of the trial per Sponsor instructions.
- Reporting adverse events and device deficiencies in accordance with the CIP and according to country regulations
- Approving all case report forms (or authorizing a sub-investigator to do so); 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 trial monitor and Sponsor trial staff members during Sponsor site visits

11.3.2 Cardiologist/Echocardiographer

Each site will have a designated cardiologist/echocardiographer whose primary responsibilities are to assure echocardiography exams are performed in compliance with the CIP.

11.3.3 Other Trial Support Staff

The PI will ensure that the investigative site has the appropriate support staff to maintain the trial. Additional staff may include sub-investigators, trial coordinators, and other specialized health care professionals. The PI will document authorization of delegated tasks using the Delegation of Tasks Log provided by Medtronic.

11.4 Medtronic Representative Involvement at the Site

Medtronic representatives will provide administrative support for the sites, as is standard when conducting a clinical research trial. Medtronic representatives may also attend the implant procedures, in order to assure that all study requirements are met.

11.5 Device Accountability / Disposition and Return Instructions

11.5.1 Device Accountability and Disposition

The Model 400 aortic valve bioprosthesis 17mm and 29mm valve sizes are considered investigational and must be stored as labeled and placed in a secure/locked location which meets the labeling requirements for device storage. The Model 400 aortic valve bioprothesis accessories (sizers/handle) are commercially available for use and will not be required to be maintained on the device records. Sites are required to maintain investigational device records on only the investigational valves that contain the following information on all components shipped to the site for the trial:

- Investigational device name
- Device serial/model number
- Date of receipt of device
- Name of person receiving the device
- Name of person using/opening the device (if applicable)
- Date of implant or use (if applicable)
- Subject Identification Number (SID) of subject receiving or using the device(if applicable)
- Disposition (implanted, disposed of, or returned to Medtronic)

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

- The reason for the device being returned to Medtronic or disposed of
- Name of the person who returned or disposed of each device
- Date shipped to Medtronic, if returned
- If device is disposed of, the method of disposal

At the end of the trial enrollment period, all remaining investigational devices must be returned to Medtronic.

11.5.2 Device Explant and Return Procedures

In the event of a device malfunction of the Model 400 valve prior to, during or after implant (due to reintervention or autopsy), the device should be returned to Medtronic. Sites should contact their Medtronic clinical trial representative to obtain further instruction on device return procedures. All explanted devices will be analyzed by an independent lab.

11.6 Data Management

Trial sites will designate a unique subject ID number (SID) at the point of subject enrollment, which is assigned by Medtronic in the Electronic Data Capture system. Records of the subject/SID relationship will be maintained by the trial site.

11.6.1 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 trial will be maintained for the life of Medtronic, according to corporate policy and record retention schedule.

11.6.2 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 Delegation of Tasks List. The eCRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the trial.

The investigator (or authorized 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 shall re-sign this eCRF.

11.6.3 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.

Trial 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.

11.6.4 Recording Data

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 trial).

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.

11.6.5 Confidentiality

All information and data sent to parties involved in trial conduct concerning subjects or their participation in this trial will be considered confidential. Trial sites will assign a unique subject ID number (SID) to each subject. Records of the subject/SID relationship will be maintained by the trial site. The SID number is to be recorded on all trial 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.

In the United States, "Protected Health Information" (PHI) will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). To maintain confidentiality, the subject's name or any other PHI should not be recorded on any trial document other than the informed consent form, as required by EN ISO5840: 2009. This scenario will be covered in the Patient Information-Informed Consent Form. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel.

Data relating to the trial 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.

11.6.6 Record Retention

All trial-related documents must be retained for a period of at least 2 years after the last approval of a marketing application (or longer if required by local law) and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational device. Medtronic will inform the investigator/site when these documents are no longer required to be retained.

No trial 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 trial records to another party or move them to another location, advance written notice must be given to the Sponsor.

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

11.7 Suspension or Early Termination

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. In all geographies, the study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Each lead cohort may have independent study closure timelines.

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

Termination of the Study is discontinuance, by sponsor or by withdrawal of Ethics Board or FDA approval, or local regulatory body of an investigation before completion. This is possible for the whole study, for all centers in a country, 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, for all centers in a country or a single center.

11.7.1 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
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (medically/ethically justifiable) where the study is operating under regulatory body authority

11.7.2 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
- Consistent non-compliance to the CIP (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups, etc.)
- Lack of enrollment

- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- 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)

11.7.3 Procedures 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).

11.7.3.1 Medtronic-initiated

In the case of study termination or suspension for reasons other than a temporary Ethics Board approval lapse, the investigator will promptly inform the 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.

In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic. Subjects already enrolled should continue to be followed out of consideration of their safety, rights, and welfare.

11.7.3.2 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

11.7.3.3 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

11.8 CIP Amendments

Any revisions or amendments to the CIP, Investigator Brochure/Report of Prior Investigations, or Informed Consent document, along with a statement of justification for the changes, will be submitted to all affected Regulatory Authorities (FDA, CA, and Health Canada) and governing Ethics Boards, 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). Approval by regulatory agencies and Ethics Board must be obtained prior to implementing a CIP revision at the site.

11.9 Publication and Use of Information

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

Medtronic, as the Sponsor of this trial, recognizing the seminal importance of this investigation, is committed to the widespread dissemination of all endpoint results. At the conclusion of the trial, a multisite abstract reporting the primary results will be prepared by the Coordinating Principal Investigators (in collaboration with others including, but not limited to, the Steering Committee and CEC) and presented at an annual scientific meeting (e.g. STS, AATS or EACTS). 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 trial 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 trial requires approval by the Coordinating Principal Investigators after review by the Steering Committee.

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

11.10 Liability

Medtronic, Inc. (including all wholly owned subsidiaries) maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the Ethics Board.

Medtronic will provide subject indemnification according to local laws where this trial will be conducted.

12 Monitoring

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

According to the Monitoring Plan, the trial data will be 100% source document verified through market approval. A risk-based monitoring strategy may be implemented once market approval has been obtained in the target geographies (EU, US and Canada); Medtronic will update the Monitoring Plan and notify the Investigators, Ethics Boards and regulatory agencies under separate cover from this CIP.

12.1 Site Initiation Visit

Medtronic will conduct a site initiation visit prior to first implant, to prepare the site to conduct the trial. 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 trial):

- Have received and understand the requirements and contents of
  - CIP
  - Investigator Brochure (IB)
  - 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
- Have been trained in the use of the investigational device
- Are familiar with the responsibilities of the Principal Investigator

12.2 Periodic Monitoring Visit

Periodic monitoring visits will be made at all active investigational sites throughout the clinical trial 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 accurate with respect to the subject source documentation
- Facilities remain acceptable
- Subject informed consent is being obtained and properly documented
- The CIP is being followed
- Complete records are being maintained
- Appropriate and timely reports have been made to Medtronic and/or its designees and the Ethics Board
- Device and Device inventory are controlled
- The Investigator is carrying out all agreed activities
- Any equipment to be used for assessing the clinical investigation variables are maintained/calibrated according to the site's standard protocol

The progress of the trial will be monitored by:

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

12.2.1 Trial Closure

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

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

12.3 Audits and Inspections

Medtronic may conduct audits at participating clinical sites. The purpose of an audit is to verify the performance of the monitoring process and the trial conduct, independently of the personnel directly involved in the trial. Regulatory bodies, such as the Food and Drug Administration, 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.

13 Labeling

13.1 Device Labeling

The labeling of the Model 400 valve 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. The following are the required statements on the labeling for the geographies where this study is being conducted:

- Europe: "Exclusively for clinical investigations"
- United States: "CAUTION: Investigational Device. Limited by Federal Law (USA) to Investigational Use"
- Canada: "Investigational Device. To Be Used by Qualified Investigators Only"

A copy of the current device labeling can be found in Appendix C. If changes are made to the labeling, they will be provided under separate cover to the appropriate authorities per local requirements.

13.2 Investigator Brochure

The Investigator Brochure for the Model 400 valve will be provided under separate cover. Medtronic will update the Investigator Brochure in accordance with EN ISO14155:2011, and provide those updates to sites and regulatory agencies. For geographies under EN ISO14155:2011, documentation of receipt of the Investigator Brochure by each site's Ethics Board is required for all versions of the Investigator Brochure.

14 Subject Consent

14.1 Consent Materials

Geography-specific templates of the Patient Information and Informed Consent Form (PI/ICF) can be found in Appendix A. These template may be modified to suit the requirements of the individual site. For US sites, this must include Health Insurance Portability and Accountability Act (HIPAA) Authorization language. This language may be incorporated into the consent form or if required by the IRB, included as a separate document.

Medtronic, the Competent Authorities (CA), and site Ethics Board shall approve all informed consent documents prior to implementation in the trial. Medtronic, Ethics Board, and CAs, where applicable must pre-approve all language changes to the PI/ICF throughout the course of the trial prior to implementation; this includes initial submission, annual reviews (if applicable) and protocol amendment reviews. The original Ethics Board-approved PI/ICF must be retained at the investigational site, and a copy sent to Medtronic prior to device shipment. Any updated PI/ICF must be sent to Medtronic upon approval of the materials by the Ethics Board.

Medtronic will provide any important new information that impacts the health, safety or welfare of trial subjects, for inclusion in PI/ICF updates as it becomes available. Sites should following any Medtronic, CA or Ethics Board requirements for disseminating new information and re-consenting subjects during the course of the trial.

14.2 Informed Consent Process

The Investigator or authorized designee must administer the approved PI/ICF to each prospective trial 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 trial, using native non-technical language that is understandable to the patient. The patient must be informed about their right to withdraw from the trial 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 trial will not jeopardize their future medical care. The patient must also be informed that by participating in the trial, they are not waiving their legal rights. The patient must have ample time and opportunity to inquire about details of the trial, and to decide whether or not to participate in the clinical trial. All questions about the trial should be answered to the satisfaction of the patient. All items discussed in the PI/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 Section14.2.1) will be documented in the patient's medical record prior to any trial-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 trial 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 trial records. A copy of the signed informed consent will be provided to the patient and a copy of the signed consent will be placed in the patient's medical record.

14.2.1 Special Circumstances 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.

15 Ethics Board Information

All necessary documents (CIP, PI/ICF, and Investigator Brochure/Report of Prior Investigations) 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, PI/ICF and other written trial materials)
- Any specific Ethics Board requirements relative to the trial (if applicable)

The investigator and trial 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 trial 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.

Medtronic will provide a complete listing of participating sites and Ethics Board chairpersons to participating investigational sites and regulatory agencies (if required), within 6 months of the first enrollment in the trial.

16 Other Institutions

16.1 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 FDA 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

16.2 Pathology Lab

All explanted study valves will be independently analyzed by CVPath Institute, Inc., 19 Firstfield Road, Gaithersburg, MD 20878. A pathology protocol will be provided under separate cover.

16.3 Steering Committee

The Steering Committee will be an advisory body to Medtronic. Their roles and responsibilities may include, but are not limited to the following:

- Overall conduct of the trial with regard to
  - CIP development and implementation
  - Trial progress
  - Subject safety

- Data quality and integrity
- Quality performance at individual sites
  - The Steering Committee will support site investigators in resolving any clinical or procedural issues that may impact subject well-being or integrity of the trial
  - Any site placed on probation for any reason may be terminated from the trial after an appropriate review by the Steering Committee
- Review of all Data Safety Monitoring Board (DSMB) recommendations
- Review and provide input on the publication strategy:
  - Defining and refining the Publication Plan
  - Overseeing the development of manuscripts, abstracts, and presentations
  - Identifying and appointing the manuscript/abstract first author(s)/writer(s)/presenters(s)
  - Reviewing the publication
- Assess requests for sub-studies
- Assist with Publication efforts by disseminating trial information through appropriate scientific sessions and publications
  - All requests for abstract and manuscript preparation and submission require Steering Committee review and approval. All final decisions will be made by Medtronic; however, the recommendations made by the Steering Committee will be highly considered
- Participate in Investigator Meetings (and other trial related meetings)
- Serve as a contact for other trial investigators (providing peer consultation)

The Steering Committee will establish a charter and a Publication Plan. The Steering Committee charter and Publication Plan will be approved by Medtronic and the Steering Committee members.

16.4 Data Review Committees

16.4.1 Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will be established prior to the first enrollment of the trial. 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 trial 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 trial. Additional specialists, such as echocardiologists, may also be selected as part of the CEC.

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

All deaths and potential endpoint events will be reviewed and adjudicated by a minimum of two CEC members. All other events will be reviewed and classified by the Sponsor, by qualified internal Medtronic safety individual(s) to ensure they should not be adjudicated by the full CEC and that the events are appropriately classified by the investigator.

CEC decisions will be documented in meeting minutes, which will be maintained in the trial master file.

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

16.4.2 Data Safety Monitoring Board (DSMB)

A DSMB will be established to review accumulating data from the trial, and advise Medtronic on the continuing safety of current and future trial participants, and the continuing validity and scientific merit of the trial. The board will be independent of Medtronic and the trial 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 trial termination recommendations if safety concerns warrant. These DSMB recommendations may include recommendations on trial status such as continuing the trial without modifications, continuing the trial with modifications, stopping the enrollment in the trial, or recommendations about trial 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 trial 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 trial. The DSMB may call additional meetings if, at any time, there is concern about any aspect of the trial. All data presented at the meetings will be considered confidential and returned to the trial statistician at the closure of the DSMB meeting.

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

17 Records and Reports

17.1 Responsibilities of the Investigator

The Investigator is responsible for the preparation, review, and signature (as applicable), and retention of the records listed as follows:

- 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
- The approved CIP, PI/ICF, IB and any amendments
- Insurance certificate, where applicable
- Ethics Board approval documentation and voting list
- Sample eCRFs
- Regulatory authority notification and approval documentation
- List of sponsor contacts and monitoring contact list
- List of investigation sites
- Training records

- Disclosure of conflict of interest
- Certification of adequacy of equipment
- Lab certificate/lab normal ranges
- Subject ID and enrollment log
- Sponsor's statistical analyses and clinical investigation report

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 13, Table 14, and Table 15. 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. For Adverse Event reporting requirements, see Table 7.

Table 13: Investigator records and reporting responsibilities applicable to the United States

Investigator Reports 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))*

Investigator Reports Applicable to the United States		
Report	**Submit To**	**Description/Constraints**
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 14: Investigator Reports Applicable to Europe

Investigator Reports Applicable to Europe		
Report	**Submit To**	**Description/Constraints**
Withdrawal of MEC approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing MEC of the investigator's part of the investigation within 5 working days of the date of withdrawal. *(Medtronic Requirement)*
Progress Report	Sponsor and Ethics Board	Provide if required by local law or MEC. (ISO 14155:2011)
Study Deviations	Sponsor and Ethics Board and Regulatory Authority	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, MECs, competent authorities or the appropriate regulatory bodies should be informed. (ISO 14155:2011) 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 investigator report	Ethics Boards 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. *(Medtronic Requirement)*

Table 15: Investigator Reports Applicable to Canada

Investigator Reports 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	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)*

17.2 Responsibilities of the Sponsor

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

- All essential correspondence related to the clinical trial
- 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
- Device complaint documentation
- 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
- Trial training records for site participants and internal trial staff members
- Contact lists of all participating investigators/investigative sites, Ethics Board information, trial 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 investigation 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 16, , and Table 18.

Table 16: Sponsor records and reporting responsibilities applicable to the United States

Sponsor Reports for United States		
Report	**Submit To**	**Description/Constraints**
Premature termination or suspension of the clinical investigation	Investigators, IRB, and Relevant authorities	Provide prompt notification of termination or suspension and reason(s). *(*ISO 14155:2011*), (MHLW Ordinance 36, Article 32)*
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))*

Sponsor Reports for United States		
Report	**Submit To**	**Description/Constraints**
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)*

Table 17: Sponsor records and reporting responsibilities applicable to Europe

Sponsor Reports for Europe		
Report	**Submit To**	**Description/Constraints**
Unanticipated Serious Adverse Device Effects (USADE)	MEC, Investigators, Competent Authorities	Medtronic will notify investigators and MEC in all geographies as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. For reporting to Regulatory authorities, all UADEs are classified as SADEs and should follow the applicable reporting requirements. (ISO 14155:2011) and Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 3.A.1). Reporting timeframe as per local competent authority.(ISO 14155:2011 3.42)
Serious Adverse Event (SAE)	MEC, Competent Authorities	Submit to MEC per local reporting requirement. Submit to Competent Authority per local reporting requirement. Reports will be in compliance with MDD 93/42/EEC and MEDDEV 2.7/3 requirements.
Serious Adverse Device Effects (SADE)	MEC, Competent Authorities	Submit to MEC per local requirement (ISO 14155:2011). Submit to regulatory authority as per local competent authority reporting timelines.
Device Deficiency that might have led to an SADE	MEC, Competent Authorities	Submit to MEC per local requirement. Submit to regulatory authority as per local competent authority requirement.
Premature termination or suspension of the clinical investigation	Investigators, MEC, Relevant Authority	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2011)

Sponsor Reports for Europe		
Report	**Submit To**	**Description/Constraints**
Withdrawal of MEC approval	Investigators, MEC, Relevant Authority	All applicable investigators will be notified only if required by local laws or by the MEC.
Withdrawal of Competent Authority approval	Investigators, MEC, and Regulatory Authority	Investigators and MECs will be notified only if required by local laws or by the MEC.
Progress Reports	MEC, Regulatory Authority (upon request)	This will be submitted to the MEC and/or Regulatory Authority only if required.
Final Report	CA, Investigators, MEC, and Regulatory Authority (upon request)	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	MEC and Regulatory Authority	Ensure that the MECs and Regulatory Authorities are informed of significant new information about the clinical investigation (ISO 14155:2011)

Table 18: Sponsor records and reporting responsibilities applicable to Canada

Sponsor Reports for 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))

Sponsor Reports for Canada		
Report	**Submit To**	**Description/Constraints**
Serious Adverse Device Effects (SADE)	REB, 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, 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, Head of Institution, 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	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)

Sponsor Reports for Canada		
Report	**Submit To**	**Description/Constraints**
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)

17.3 Final Report

Medtronic will provide a final written report of the trial results according to applicable regulations, and will include:

- Identification of the device(s)
- Description of the methodology and design of the clinical investigation
- Summary of the deviations from the CIP
- Statistical analysis of the trial data
- Critical appraisal of the aims of the trial

Medtronic will submit this final report to the PIs for review and comment, and shall document and disseminate discrepant comments to all trial PIs. The coordinating investigators will provide their signatures, indicating their agreement with the content of the final report.

All required trial reports will be submitted to regulatory authorities per local reporting requirements/regulations.

18 Report of Prior Investigations of the Device and Justification for the Trial

The complete Report of Prior Investigations is available under separate cover.

The use of human subjects is required as part of an EN ISO 5840:2009 clinical trial to evaluate the safety and effectiveness of the use of device in humans which includes evaluations that cannot be made using bench testing. Therefore, the conduct of the PERIGON Pivotal Trial is justified.

19 Glossary

Acronym	Term
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 – Mark	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

Acronym	Term
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IFU	Instructions for use
INR	International Normalized Ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
LDH	Lactate Dehydrogenase
MEC	Medical Ethics Committee
MI	Myocardial Infarction
mL	Milliliters
mm	Millimeters
NYHA	New York Heart Association
OPC	Objective Performance Criteria
PE	Product Experience
PEEK	Polyetheretherketone
PERIGON	Medtronic PERIcardial SurGical AOritc Valve ReplacemeNt Pivotal Trial
PI	Principal Investigator

Acronym	Term
PI/ICF	Patient Information/ Informed Consent Form
PPM	Patient Prosthesis Mismatch
PT	Prothrombin time
PVL	Paravalvular leak
REB	Regulatory Ethics Board
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SAVR	Surgical Aortic Valve Replacement
SID	Subject Identification
SOP	Standard Operating Procedures
STS	Society of Thoracic Surgeons
SVD	Structural Valve Deterioration
TAVI	Transcatheter Aortic Valve Implantation
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect

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