Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement

Clinical Investigational Plan

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Version History

Version	Summary of Changes	Author(s)/Title
1A	Not Applicable, New Document	Charles Boldt/Sr Clinical Research Manager Sharla Chenoweth, Sr Principal Statisician Hongyan Qiao, Principal Statisician Michael Boulware, Clinical Research Manager
1B	Revised to incorporate feedback from FDA on 12 February 2016. 1. Clarfied sample size is up to 1256 subjects 2. Added statement to informed consent template regarding long term durability of TAVR	Charles Boldt/Sr Clinical Research Manager Sharla Chenoweth, Sr Principal Statisician
1C	1. Added EuroQol (EQ-5D) instrument to assess health-related quality of life at one year 2. Extended follow-up duration from 5 years to 10 years 3. Added exclusion criterion for "significant aortopathy requiring ascending aortic replacement" 4. Revised AS severity criteria to clarify that AVA, mean gradient, and max aortic velocity should be by TTE 5. Added inclusion criteria for asymptomatic patients with severe AS and LVEF < 50% 6. Reduced interval from PCI with BMS to randomization to 30 days 7. Added clause to clarify subjects with BAV after qualifying echo must meet AS severity criteria at time of submission to screening committee 8. Revised analysis section to indicate rates of prosthetic valve endocarditis, prosthetic valve thrombosis, all stroke, life-threatening bleed, and valve-related dysfunction requiring repeat procedure will be provided at 30 days, 6 months, 12 months, and annually thereafter through 10 years 9. Corrected typographical errors in Table 16 (Parameters for grading of aortic regurgitation) 10. Deleted role of legal representative (as vulnerable subjects are not allowed) 11. Added name of investigational device manufacturer, number of investigational devices, description of comparator device, and description of expectation for maintanence of equipment 12. Revised definition of adverse event relationships to be consistent with MEDDEV 2.7/3, revision 3 (May 2015) 13. Renamed "LVOT/Aortic Valve velocity ratio to "Doppler Velocity Index" 14. Revised AE reporting requirements to require reporting of only SAE and deviced-related AE after subject has completed his/her 2 year follow-up 15. Clarified that index PCI should be performed at study center, and PCI operators to be considered sub-investigators. 16. Modified the data analysis section to add analysis sets for "as treated" and "per protocol" 17. Sample size was changed to 1200 (previous is 1256 for mITT) for the AT sets for consistency. 18. Added Evolut 34R TAV size to the description of investigational devices	Charles Boldt/Sr Clinical Research Manager Hongyan Qiao, Principal Statistician Jessica Halverson, Clinical Research Manager

	19. Revised Intended Use statement (Section 2.3) to indicate trial data intended to support expanded indication to low risk patients.	
1D	1. Incorporated Medtronic TAVR 2.0 Devices 2. Increased investigational sites to up to 100 3. Clarified that the <3% predicted risk of mortality at 30 days is per multidisciplinary local heart team assessment and not the STS score 4. Clarified that revascularization decision during screening for stratification is determined by need for revascularization during SAVR 5. Removed the collection of cardiac enzymes 6. Added Health Economic Data Collection Language 7. Incorporated the Clinical Investigation Plan Addendum, Version 1A (10577419DOC Rev 1A) 8. Incorporated the Clinical Investigation Plan Addendum; Australia/New Zealand, Version 1A (10581435DOC Rev 1A) 9. Added Qualify of Life Questionairre Appendix 10. Removed Report of Prior Investigations 11. Corrected a typo in section 3.3.3.2.2 "…the additional outcome measures of **NYHA and quality of life** will use the AT set" 12. Clarified that surgical bioprostheses in the control arm must be commercially available in both the United States and the geography in which the study center is located. 13. Updated grammatical and formatting issues throughout the document	Lisa Slusser/Sr. Clinical Research Specialist
1E	1. Increased LTI sites to up to 50 worldwide	Lisa Slusser/Sr. Clinical Research Specialist
1F	1. Added Japan regional sponsor address 2. Clarified echocardiography inclusion criteria must be at rest 3. Added Japan for investigation sites and regions 4. Section 2.0 *Background* was updated with recent information 5. Added TAVR Implant Team definition 6. Added *and enrolled* to Screening Population once a patient provides informed consent 7. Added Intervention/repair of the mitral and/or tricuspid valve is only allowed during the SAVR procedure, but there must be no intent to perform the intervention/repair prior to the implant 8. Separated baseline assessments to clarify which are required prior to screening submission and which are required prior to the index procedure 9. Clarified the discharge window 10. Clarified that MRS assessment should be performed with any *suspected or confirmed* stroke event 11. Clarified that in countries where required, specifically the United States and Japan, the local heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of the TAVR procedure	Lisa Slusser/Sr. Clinical Research Specialist Morgan Lillehei/Clinical Research Specialist

	12. Added Name of secondary operator to TAVR Implant Procedure data collection 13. Added Name of primary surgeon to SAVR Implant Procedure data collection 14. Added commercial use for Evolut 34 mm devices if investigational devices are unavailable 15. Removed CEC and DSMB from Appendix VII (Leaflet Thickening/Immobility Sub-Study Protocol), section 4.10 16. Removed CoreValve 31 mm System 17. Removed the three year signature requirement for CVs 18. Updated Table 11 as requested by competent authority in Switzerland 19. Added the French Addendum reference in Section 3.3.5 20. Added applicable regulations for Japan 21. Added Japan monitoring requirements 22. Added to section 3.3.29.4 - "*Copies of source documents will be requested to support event adjudication by the Clinical Events Committee. In Japan, availability of source documentation may be limited due to hospital policies. If a specific source document is not available, necessary information may be transcribed onto the relevant CRF page.*" 23. Clarified subclavian access diameter requirements for eligibility criteria #30 24. Sample size language was changed from "up to" to "at least" 1200 subjects and "at least 300 evaluable subjects (150 TAVR and 150 SAVR)" in the LTI Sub-Study, allowing randomization up to 1400 subjects to complete the LTI Sub-Study and Japan enrollment requirements. 25. Increased LTI sites to "up to 100 globally" 26. In APPENDIX VII section 4.11 statistical analysis, "the frequencies and 95% confidence intervals of" was deleted based on FDA's suggestion. 27. Updated 3-year to 10-year annual visit windows to a +/- 60-day window 28. Added unscheduled visit criteria 29. Incorporated the EnVeo PRO delivery catheter system and EnVeo PRO loading system for the Evolut R and TAVR 2.0 systems and Incorporated the EnVeo R delivery system for the TAVR 2.0 system 30. Removal of anticoagulation as an exclusion for the LTI Sub-Study 31. Removal of The Australian Clinical Study Handbook reference	
1G	1. The allowance of randomized subjects was increased to up to 1540 subjects	Morgan Lillehei/Clinical Research Specialist
1H	1. Updated TAVR 2.0 to Evolut PRO to align with IFU 2. Added an additional interim analysis at the time when 850 subjects have had the chance to be followed for 12 months 3. Removed clinical assessments and echocardiographic exams for 6, 8, and 9 year visits	Morgan Lillehei / Clinical Research Specialist

	4. Changed the 6-month visit follow-up window to 183 to 213 days after the subject's index procedure 5. Corrected the Enveo PRO product number (Table 15) for the 23 mm Evolut PRO valve	
1J	1. Removed the language of stopping subject accrual associated with the timing of the first interim analysis. 2. Added Section 3.3.3.7 Multiplicity Considerations and clarified the primary endpoint superiority testing order. 3. Made formatting changes to Sections 3.3.3.5 and 3.3.3.6 to remove numbering of each endpoint. Additionally, removed Section 3.3.3.7 title "Additional Outcome Measures" to clarify all secondary effectiveness endpoints.	Hongyan Qiao, PhD / Sr. Principal Statistician

Medtronic approvals are maintained in an electronic document control system.

Contents

1.0 SYNOPSIS

Title	Transcatheter Aortic Valve Replacement (TAVR) in Patients with the Medtronic Transcatheter Aortic Valve Replacement System (TAVR) in Patients at Low Risk for Surgical Aortic Valve Replacement (SAVR)
Purpose	Evaluate the safety and effectiveness of the Medtronic TAVR System in patients with severe aortic stenosis at low risk for SAVR
Design	Multi-center, international, prospective, randomized, interventional, pre-market. Subjects will be randomized on 1:1 basis to either TAVR with the Medtronic TAVR system or to SAVR
Devices	Investigational Devices • Evolut R 23, 26, 29, and 34 mm Transcatheter Aortic Valve (TAV) • Enveo R Delivery Catheter System with EnVeo Inline Sheath and EnVeo R Loading System • Medtronic Evolut PRO TAV 23, 26, and 29 mm • Medtronic Evolut PRO Delivery Catheter System with InLine Sheath • Medtronic Evolut PRO Loading System • EnVeo PRO Delivery Catheter System and EnVeo PRO Loading System (US Only[i]) Control Devices Any commercially available bioprosthesis (stented or stentless) in both the United States and the geography in which the study center is located.
Primary Objective	Demonstrate that the safety and effectiveness of the Medtronic TAVR system as measured by rates of all-cause mortality or disabling stroke at two years is non-inferior to SAVR in the treatment of severe aortic stenosis in subjects who have a low predicted risk of operative mortality for SAVR
Exploratory Objective	Evaluate the incidence of Leaflet Thickening or Immobility (LTI) detected by Multi-Detector Computed Tomography (MDCT) following TAVR or SAVR (through sub-study)
Primary Endpoint	All-cause mortality or disabling stroke at 2 years
Secondary Endpoints	Safety • Composite of death, disabling stroke, life-threatening bleed, major vascular complication, or AKI (II or III) at 30 days • New permanent pacemaker implantation at 30 days • Prosthetic valve endocarditis at one year • Prosthetic valve thrombosis at one year • All stroke (disabling and non-disabling) at one year • Life-threatening bleed at one year • Valve-related dysfunction requiring repeat procedure at one year Effectiveness • Valve-related dysfunction (moderate or severe stenosis or regurgitation) at one year • Quality of Life as assessed by Kansas City Cardiomyopathy (KCCQ) at 30 days and one year • Repeat hospitalization for aortic valve disease at one year • Device Success (VARC II)

[i] The Delivery Catheter System and EnVeo PRO Loading System are limited for use at investigational sites located in the United States.

	• Hemodynamic performance metrics by Doppler echocardiography at one year • New York Heart Association (NYHA) functional classification at one year • Health-related quality of life at one year as assessed by EQ-5D survey instrument

1.0 SYNOPSIS (continued)

Investigation Sites	Up to 100 sites in the United States, Europe, Canada, Australia, New Zealand, and Japan
Number of Subjects	At least 1200 subjects, inclusive of at least 300 evaluable subjects (150 Medtronic TAVR and 150 SAVR) in LTI Sub-Study
Patient Population	Subjects with severe aortic stenosis with an indication for SAVR with a bioprosthesis whose predicted risk of mortality at 30 days is <3% per multidisciplinary local heart team assessment
Key Inclusion Criteria	• Patient is considered low risk for SAVR, where low risk is defined as predicted risk of mortality for SAVR <3% at 30 days per multidisciplinary local heart team assessment • Severe aortic stenosis, defined as: ▪ Symptomatic aortic stenosis Aortic valve area ≤1.0 cm2 (or aortic valve area index of ≤0.6 cm2/m2), OR mean gradient ≥40 mmHg, OR maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest ▪ Asymptomatic aortic stenosis: - Very severe aortic stenosis with an aortic valve area of ≤1.0 cm2 (or aortic valve area index of ≤0.6 cm2/m2), AND maximal aortic velocity ≥5.0 m/sec, or mean gradient ≥60 mmHg by transthoracic echocardiography at rest, OR - Aortic valve area of ≤1.0 cm2 (or aortic valve area index of ≤0.6 cm2/m2), AND a mean gradient ≥40 mmHg, or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, AND an exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia OR - Aortic valve area of ≤1.0 cm2 (or aortic valve area index of ≤0.6 cm2/m2), AND mean gradient ≥40 mmHg, or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, AND a left ventricular ejection fraction <50%. • Indicated for SAVR with a bioprosthesis
Key Exclusion Criteria	• Bicuspid aortic valve identified by echocardiography, MDCT, or Magnetic Resonance Imaging • Significant ascending aortopathy
Subject Evaluation (Main trial)	• Clinical assessment at pre and post-procedure, discharge, 30 days, 6 months, 1 year, 18 months, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years • Transthoracic echo at pre and post-procedure, 30 days, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years • Multi-Detector Computed Tomography at pre-procedure • Blood samples at pre- and post-procedure, discharge, and 30 days • 12-lead ECG at pre- and post-procedure, discharge, and 30 days

	• Adverse event review will be conducted at all visits and via telephone for the 6, 8, and 9 year follow-up visits
Subject Evaluation (LTI Sub-study)	• MDCT at 30 days and one year post-implantation

1.0 SYNOPSIS (continued)

Co-Principal Investigators	Jeffrey Popma, MD, Interventional Cardiologist. Beth Israel Deaconess Medical Center, Boston MA Michael Reardon, MD, Cardiothoracic Surgeon Houston Methodist Hospital, Houston TX
Professional Services	• Independent Echocardiography Core Laboratory • Independent Clinical Events Committee • Independent Data Safety Monitoring Committee • Independent MDCT Core Laboratory (for LTI Sub-Study) • Independent Explant Pathology Core Laboratory
Duration	Total study duration is estimated to be 12 years (time from first subject implanted to ten year follow-up on last subject implanted)

2.0 PURPOSE

2.1 Background and Rationale

Over the past ten years, transcatheter aortic valve replacement (TAVR) has emerged as a transformative technology for the management of severe aortic stenosis. TAVR has become the standard of care for patients with aortic stenosis who are inoperable or at extreme risk for surgical aortic valve replacement, [1, 2] and is the preferred alternative for patients with severe aortic stenosis who are at high risk for surgical aortic valve replacement. [3, 4] Following Cribier's first implantation in 2002,[5] TAVR has evolved to become a standard procedure at specialized heart centers worldwide, and is now performed with only moderate sedation rather than general anesthesia in many patients.

TAVR was initially performed in patients at the highest risk for surgical aortic valve replacement, but data indicate that patients at intermediate risk are increasingly being treated with TAVR. A recent report from the United States national TVT Registry showed a median Society of Thoracic Surgeons Predicated Risk of Mortality (STS-PROM) at 30 days of approximately 7% in patients treated with TAVR from November 2011 through March 2013.[6] Several reports from European centers demonstrate a shift to intermediate risk patients, and have shown low mortality and stroke rates in these patients.[7-9] Large randomized trials are ongoing with the potential to confirm these early results in intermediate risk patients.[10] The PARTNER IIA trial involving the balloon-expandable Sapien valve (Edwards Lifesciences, Irvine CA, USA) has enrolled 2000 intermediate-risk patients with an STS-PROM between 4% and 8%. The SURTAVI trial, with an estimated enrollment of up to 2000 patients, includes patients with a predicted risk of mortality of ≥3% and <15% (by local heart team assessment) undergoing TAVR with the self-expanding Medtronic CoreValve system (Medtronic, Minneapolis, MN, USA). Both trials have a primary composite endpoint of all-cause mortality and disabling stroke at two years post-TAVR, randomized against surgical aortic valve replacement (SAVR). Data from the SURTAVI trial were submitted to the FDA and on July 10, 2017 the Medtronic CoreValve system was approved in the United States for patients at intermediate risk for SAVR.

Nonetheless, conventional surgical aortic valve replacement (SAVR) with general anesthesia, sternotomy, and cardiopulmonary bypass remains the gold standard for patients at low or intermediate operative risk.[11-13] Conventional SAVR is associated with low perioperative risk, and provides excellent functional outcomes with satisfactory long-term survival, even in elderly patients.[14-20] Therefore, evidence from rigorous clinical trials are needed to evaluate the application of TAVR in low-risk patients before it is assimilated into the overall management of patients with aortic stenosis who are good candidates for SAVR.

The Medtronic CoreValve TAVR system received the CE Mark in 2007, and FDA approvals for Extreme Risk and High Risk patient populations in 2014. To date, over 65,000 patients have been implanted with the Medtronic CoreValve in over 70 countries, with approximately 11,000 of these patients enrolled in post-approval registries or clinical trials that further confirm the safety and performance of the CoreValve product. There is now extensive published experience demonstrating the CoreValve system is fulfilling its intended role with a favorable risk/benefit ratio,[21-24] and rigorous clinical trials have established its safety and effectiveness, with improved mortality and quality of life compared with medical therapy in extreme risk patients,[2] and even superiority to SAVR among high operative risk patients.[4, 25]

While there have been significant improvements in TAVR outcomes due to better patient selection, increasing operator experience, and iterations in device technology, important issues remain. Clinical

challenges where further advances would be desirable include the occurrence of major procedural complications,[26-28] stroke,[29-31] paravalvular aortic regurgitation,[32, 33] vascular complications,[34, 35] and need for new permanent pacemaker implantation.[36-39]

To this end, Medtronic has developed modifications to the CoreValve frame and delivery catheter system to enable resheathing or full recapture of the device before it is released from the delivery system. These modifications are incorporated in the CoreValve Evolut R system (hereafter "Evolut R"). The ability to resheath or recapture the device allows the operator to reposition or remove the bioprosthesis if the initial implant positioning is sub-optimal (too high or too low). This feature is desirable in that it facilitates accurate final positioning which may mitigate risks associated with sub-optimal positioning such as paravalvular leak,[40, 41] acute migration,[28] and AV-conduction disturbance related to implant depth.[36] In addition, the EnVeo R Delivery Catheter System with EnVeo InLine Sheath provides physicians the option to use a lower profile introducer sheath (outer diameter), which may reduce the risk for major vascular complications.[42]

A comprehensive protocol of bench and animal testing of the Evolut R system has demonstrated its functionality, and has confirmed that changes to enable recapture have not impacted the structural integrity, hydrodynamic performance, or durability of the CoreValve bioprosthesis. Beginning in October 2013, clinical studies of the Evolut 23R, 26R, and 29R mm valve sizes involving 301 patients have been conducted in Australia, New Zealand, Europe, and the United States. These clinical studies confirm that TAVR with the Evolut R system can be performed with an acceptable incidence of procedural and device-related complications, that short term safety and clinical efficacy of the Evolut R system are similar to the predicate CoreValve system, and there is no new safety risks associated with the use of the resheath/recapture feature. Results from these studies were used to gain the CE Mark in February 2015 for the Evolut R 26 and 29 mm valve sizes, and FDA approval in June of 2015 for the Evolut R 23, 26 and 29 mm sizes.[43, 44]

In June 2016, enrollment began in the United States in a 60 subject study of the Evolut R 34 mm TAVR system. The Evolut R 34 mm IDE study is an addendum to the original Evolut R United States IDE study, and followed the same protocol. The purpose of this study was to assess the safety and efficacy of the Evolut R 34mm TAVR system, which is an extension of the Evolut R family, intended to extend the range of treatable annular diameters with the Evolut R TAVR system. Data from the initial 15 subjects with 30 day follow-up were submitted to FDA as PMA supplement, and on 26 October 2016, the Evolut R 34 mm was approved for use in the United States for subjects at high or extreme risk for SAVR. On July 10, 2017 the Evolut R 23, 26, 29 and 34 mm was approved in the United States for patients at intermediate risk for SAVR.

In order to continue striving for improvement with our TAVR systems, Medtronic has developed additional modifications to the Medtronic Evolut R system. An outer wrap covering the external frame on the first 1.5 cells of the inflow of the valve was added. The purpose of the wrap is to improve paravalvular leak (PVL) performance by enhancing sealing around the perimeter of the device inflow. It does this by reducing the open space and providing larger surface area contact between the device and native annulus over the 1.5 cells that it covers. This iteration of Evolut R is called the Medtronic Evolut PRO system.

Medtronic has completed a comprehensive protocol of bench testing that collectively has demonstrated the functionality of Evolut PRO, and that the changes associated with the modification to the valve have not

impacted the structural integrity, hydrodynamic performance, or durability of the Evolut PRO bioprosthesis. In May 2016, enrollment began in the United States to study the Evolut PRO system. Data from this trial were submitted to FDA and on March 20, 2017 the Evolut PRO system was approved for use in the United States for subjects at high or extreme risk for SAVR. On July 10, 2017 the Evolut PRO system was approved in the United States for patients at intermediate risk for SAVR.

Medtronic has also developed additional modifications to the Medtronic EnVeo delivery system and loading system components. The EnVeo PRO Delivery Catheter System (DCS) and the EnVeo PRO Loading System (LS) represent a modification to the EnVeo R DCS and EnVeo R LS components. There is no change to the Evolut R TAVs and Evolut PRO TAVs, or their intended use with the use of these additional modifications. The EnVeo PRO DCS and LS were submitted to the FDA and approved for high, extreme, and intermediate risk use in the United States on January 17, 2018.This trial will evaluate the safety and effectiveness of the Medtronic Transcatheter Aortic Valve Replacement system (CoreValve, Evolut R and Evolut PRO systems) in patients with aortic stenosis who are at low predicted risk for mortality at 30 days with SAVR. Data from this trial will be used to support regulatory submissions to seek an expansion of the approved indication to include patients who are indicated for aortic valve replacement with a low predicated risk of mortality with SAVR.

2.2 Medtronic Transcatheter Aortic Valve Replacement System

The Medtronic Transcatheter Aortic Valve Replacement (TAVR) system in this trial includes the following TAVR systems:

2.2.1 Evolut R system

The Evolut R System is a recapturable transcatheter aortic valve replacement system comprised of the following three components:

1. Evolut R Transcatheter Aortic Valve (TAV)
2. EnVeo R Delivery Catheter System (DCS) with EnVeo InLine Sheath or EnVeo PRO Delivery Catheter System (DCS)
3. EnVeo R Loading System (LS) or EnVeo PRO Loading System (LS)

2.2.2 Medtronic Evolut PRO System

The Medtronic Evolut PRO System is a transcatheter aortic valve replacement system comprised of the following three components:

1. Medtronic Evolut PRO Transcatheter Aortic Valve (TAV)
2. Medtronic Evolut PRO Delivery Catheter System (DCS) with InLine Sheath or EnVeo R Delivery Catheter System (DCS) with EnVeo InLine Sheath or EnVeo PRO Delivery Catheter System (DCS)
3. Medtronic Evolut PRO Loading System (LS) or EnVeo PRO Loading System (LS)

The Evolut R and Evolut PRO TAV treat aortic stenosis by displacing and functionally replacing the dysfunctional native valve with a bioprosthetic valve delivered on a catheter while the heart is still beating, thus avoiding the risks of cardiopulmonary bypass.[45-48] Their intended performance is to relieve aortic valve stenosis without inducing significant regurgitation, thereby restoring effective aortic valve function.

A detailed description of the Evolut R and Evolut PRO systems are provided in Section 5.0 Description of Investigational Devices.

2.3 Intended Use

Data from this trial will be used to support an expansion of the currently approved indication to include patients with aortic stenosis who are indicated for aortic valve replacement and are deemed at low predicted risk for mortality for SAVR, where low risk is defined as predicted risk of mortality for SAVR <3% at 30 days per multidisciplinary local heart team assessment.

2.4 Trial Objectives

2.4.1 Primary Objective

The primary objective of this trial is to demonstrate that the safety and effectiveness of the Medtronic TAVR systems, as measured by the rate of all-cause mortality or disabling stroke at 2 years, is non-inferior to SAVR in the treatment of severe aortic stenosis in subjects who have a low predicted risk of mortality at 30 days for SAVR.

2.4.2 Exploratory Objective

An exploratory objective is to evaluate the incidence of findings of prosthetic valve leaflet thickening or leaflet immobility (LTI) by Multi Detector Computed Tomography following TAVR with the Medtronic TAVR system or SAVR with commercially available surgical bioprotheses.

2.5 Trial Endpoints

The following endpoints will be used to evaluate the primary trial objectives:

2.5.1 Primary Safety and Effectiveness Endpoint

- The rate of all-cause mortality or disabling stroke at 2 years

2.5.2 Secondary Safety Endpoints

- The rate of the composite of death, disabling stroke, life-threatening bleed, major vascular complication, or AKI (II or III) at 30 days
- The rate of new permanent pacemaker implantation at 30 days
- The rate of prosthetic valve endocarditis at one year
- The rate of prosthetic valve thrombosis at one year
- The rate of all stroke (disabling and non-disabling) at one year
- The rate of life-threatening bleeding at one year
- The rate of valve-related dysfunction requiring repeat procedure at one year

2.5.3 Secondary Effectiveness Endpoints

- The rate of valve-related dysfunction, defined as moderate or severe prosthetic valve stenosis, or moderate or severe prosthetic regurgitation at one year (per VARC II)
- Quality of Life as assessed by Kansas City Cardiomyopathy (KCCQ) at 30 days and one year
- The rate of repeat hospitalization for aortic valve disease at one year
- Device Success (VARC II), defined as
  - Absence of procedural mortality, AND
  - Correct positioning of a single prosthetic heart valve into the proper anatomical location, AND
  - Intended performance of the prosthetic heart valve, defined as the absence of patient-prosthesis-mismatch and mean aortic valve gradient less than 20 mmHg (or peak velocity <3 m/sec), AND absence of moderate or severe prosthetic valve regurgitation.
- Hemodynamic performance metrics by Doppler echocardiography

- Mean aortic gradient at one year
- Effective orifice area at one year
- Degree of total, peri, and transvalvular prosthetic regurgitation at one year

- New York Heart Association (NYHA) functional classification at one year
- Health-related quality of life at one year as assessed by EQ-5D survey instrument

2.7 Rationale for Selection of Trial Endpoints

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

- They are clinically relevant and address important safety and effectiveness aspects of the Medtronic TAVR System compared to SAVR.
- They are objectively defined and measurable in the majority of subjects.
- They are consistent with current recommendations for endpoints in TAVR clinical studies.

3.0 TRIAL PROTOCOL

3.1 Ethics and Regulatory Compliance

3.1.1 Applicable Regulations

This 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 trial will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the trial is being conducted. The trial will also be conducted in accordance with the Declaration of Helsinki. The principles of the Declaration of Helsinki are implemented in this trial by means of the Patient Informed Consent (IC) process, Ethics Board approval, trial training, clinical trial registration, pre-clinical testing, risk benefit assessment, and publication policy.

In the United States, the trial will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with 21 CFR Parts 11, 50, 54, 56 and 812, and ISO 14155:2011. In addition, the trial will be conducted in compliance with 21 CFR Part 11 and 54 in all participating geographies. In Europe and Canada, the trial 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. In Australia and New Zealand the trial will be conducted in compliance with local regulations and ISO 14155:2011. In Japan, the trial will be conducted in accordance with the ethical principles of the Japan GCP Ordinance, the Pharmaceutical and Medical Device Act as well as ISO 14155:2011.

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 trial 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)).

3.1.2 Institutional Review Board and Ethics Committee

The trial will be conducted in accordance with the requirements of local Institutional Review Boards and Ethics Committees. The responsible Institutional Review Board (IRB) or Ethics Committee (EC) at each investigational site must approve the trial protocol and informed consent form. Trial activities will not commence prior to receipt of documentation of IRB/EC approval by the site and Medtronic. The Investigator and trial staff must comply with the requirements of their IRB/EC, including any additional requirements imposed by the IRB/EC after initial approval.

Prior to enrolling subjects, each investigation site's IRB/EC will be required to approve the current CIP, the Informed Consent form, and any other written information to be provided to the subjects. Trial sites in the

United States must also utilize IRB approved Health Insurance Portability and Accountability Act (HIPAA) Authorization.

IRB/EC approval of the clinical trial must be received in the form of a letter and provided to Medtronic before commencement of the trial at an investigation site. The approval letter must contain enough information to identify the version or date of the documents approved. In addition the approval letter needs to be accompanied by an IRB/EC roster or letter of compliance, to allow verification that the investigator, other center trial staff, and/or Medtronic personnel are not members of the IRB/EC. If they are members of the IRB/EC, written documentation is required stating that he/she did not participate in the approval process. Investigators must inform Medtronic of any change in status of IRB/EC approval once the investigation site has started enrollment. If any action is taken by an IRB/EC with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

3.1.3 Regulatory Submissions

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

Each center is required to have documented approval from their local Regulatory Authority prior to their first subject enrollment. Medtronic will obtain a copy of the approval letter from the Regulatory Authorities.

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

- Monitoring Plan
- Data Management Plan
- Statistical Analysis Plan
- Safety Plan
- Electronic Case Report Forms (eCRFs)

If a regulatory authority imposes any additional requirements (eg, safety reports, progress reports), Medtronic will prepare the required documents and send them to the respective authority.

Any revisions or amendments to the CIP, Investigator Brochure, or Informed Consent documents will be submitted to all affected Regulatory Authorities. A final report will be submitted to all Regulatory Authorities upon trial closure.

3.1.4 Ethical Conduct of the Trial

The trial will be conducted in accordance with the design and specific provisions of this protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirements.

The principles of the Declaration of Helsinki have all been implemented by means of the patient informed consent process, IRB/EC approval, trial training, clinical trial registration, preclinical testing, risk benefit

assessment, and publication policy. Pediatric, legally incompetent, or otherwise vulnerable patients are not eligible for the trial. Further, the Medtronic TAVR system will not be used as an emergency treatment.

3.2 Trial Organization

3.2.1 Investigational Sites

This trial may be conducted at up to 100 sites in the United States, Canada, Europe, Australia, New Zealand, and Japan. Investigative sites will meet the following criteria:

1. The site will have extensive experience with TAVR and SAVR, including the following:
   - cardiothoracic surgeon with either ≥100 career AVRs, or ≥25 AVRs in a calendar year
   - an interventional cardiologist with ≥20 TAVR procedures in the prior year, or ≥40 TAVR procedures in the prior two years.
2. The site will have the presence or capacity of establishing an investigative team consisting of the following:
   - interventional cardiologist with expertise in transcatheter aortic valve replacement
   - cardiothoracic surgeon with expertise in aortic valve replacement
   - echocardiographer
   - trial coordinator
3. Sites that participate in the LTI Sub-Study will have capability of performing high quality retrospective ECG gated MDCT scans, and validated CT equipment that meets minimum requirements for temporal resolution.

Information on the investigational sites (eg, name, address, PI) will be maintained in a separate document.

3.2.2 Trial Site Investigative Team Members

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

3.2.2.1 Site Co-Principal Investigators

Each site will have two Co-Principal Investigators (PI), one who is an interventional cardiologist, and one who is a cardiothoracic surgeon. The Co-PIs have overall responsibility for the conduct of the trial at the site, including protecting the rights, safety, and welfare of the study subjects at their site, the integrity of the trial data generated by their site, and for ensuring the trial is conducted in compliance with the Clinical Investigation Plan, 21 CFR 812, and IRB/EC requirements.

3.2.2.2 Heart Team

Each site will utilize a local heart team to assess eligibility of the prospective subject for the trial.

At a minimum, the local Heart Team should include the following members:

1. A cardiothoracic surgeon
2. An interventional cardiologist
3. An echocardiographer

The site Co-PIs may also serve as a member of the Heart Team.

3.2.2.3 TAVR Implant Team

Each site will have a TAVR implant team with extensive experience with TAVR procedures. Operator 1 and Operator 2 must meet the minimum TAVR qualification as described in Section 3.2.1 (1).

3.2.2.4 Echocardiographer

Each site will have a designated cardiologist whose primary responsibilities are to ensure the required echocardiograms are performed in accordance with the CIP, and for reviewing and approving the site echocardiography eCRFs, if authorized by the PI. The designated echocardiographer may also serve as a member of the local Heart Team.

3.2.2.5 Trial Coordinator

Each site will have a designated trial coordinator whose responsibilities include coordination of trial activities, follow-up evaluations, and maintaining the records defined in the CIP.

3.2.2.6 Cardiovascular Imaging Specialist

Sites that participate in the LTI Sub-Study will have a designated cardiovascular imaging specialist, whose primary responsibilities are to ensure the required MDCT images are acquired in accordance with the LTI Sub-Study protocol and for review of the acquired images. The Cardiovascular Imaging Specialist is either a radiologist or cardiologist with expertise in MDCT.

3.2.3 Screening Committee

A Screening Committee will be used to ensure patient selection is appropriate and consistent among trial sites. The role of the Screening Committee will include the following:

- Confirmation that subjects are at low predicted risk of mortality at 30 days for SAVR
- Confirmation that subjects are anatomical suitable for implantation for both TAVR and SAVR

The Screening Committee will include interventional cardiologists and cardiac surgeons. Prior to the onset of the trial, the Screening Committee will establish a charter that describes its roles, responsibilities, and processes.

3.2.4 Publication Committee

A Publication Committee will provide direction and support in the development of clinical publications. The Publication Committee will consist of trial investigators and Medtronic representatives. The Publication Committee will be responsible to:

- Define the publication plan
- Review, approve, and prioritize publication proposals
- Provide input on the scientific merit and clinical relevance of ancillary publications
- Identify the manuscript/abstract first author(s)/writer(s)/presenter(s)
- Review publications prior to submission

3.2.5 Clinical Investigational Agreement and Financial Disclosure

A Clinical Investigation Agreement shall be signed by the participating investigation site and/or the principal investigator at each investigation center per the local legal requirements, and returned to Medtronic prior to trial center 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.

3.2.6 Curriculum Vitae

Signed and dated curriculum vitae shall be obtained for all investigators, including their current position at the investigation site in compliance with applicable local regulations.

3.2.7 Trial Training

Prior to investigational center activation or subsequent involvement in trial activities, Medtronic will provide training to the investigative team on the trial methods, procedures, and requirements. Training may be conducted via site initiation visits, investigator meetings, and/or other media sessions. Medtronic will maintain documentation of these training sessions. For new trial team members that join the trial after site activation, the PI may provide training on the trial with permission from Medtronic. Additionally, Medtronic representative(s) may be present at each site's implant procedures as part of the ongoing training process.

3.3 Methodology

3.3.1 Patient Population

The population includes males and females with severe aortic stenosis with a clinical indication for surgical aortic valve replacement with a bioprosthesis who are at low predicted risk of mortality at 30 days for surgical aortic valve replacement.

3.3.2 Trial Design

This is a multi-center, international, prospective, randomized, interventional trial. The primary trial objective will be accomplished by 1:1 randomization to TAVR and SAVR and assessing the clinical endpoints and outcome measures described in Section 2.5. The exploratory objective will be accomplished through evaluation of the data as described in the LTI Sub-Study, APPENDIX VII: LEAFLET THICKENING/IMMOBILITY SUB-STUDY PROTOCOL.

The trial methods include the following measures to minimize potential sources of bias:

- An external, independent Screening Committee will confirm subject eligibility and anatomical suitability.
- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and endpoint related adverse events. Safety endpoint results will be based on CEC adjudications.
- All sites will follow a standardized protocol for acquisition of echocardiographic endpoint data.
- An Echo Core Lab will evaluate all echocardiograms. Echocardiographic trial endpoint results will be based on Core Lab assessments.

- Trial sites should follow their institutional procedures for maintenance of echocardiography and laboratory equipment used for assessing the trial variables.

3.3.3 Statistical Aspects

3.3.3.1 Historical Data

Although the experience with surgical aortic valves in low surgical risk aortic valve replacement populations is extensive, it was not considered possible to leverage much of the data from these studies directly as surgical aortic valve replacement series typically enroll patient populations which include a proportion subjects with a bicuspid or unicuspid valve which may be as high as approximately 50%[50] and also include subjects with purely or primarily regurgitant lesions (also excluded from this trial) whose outcomes may differ from patients with aortic stenosis. As a result, series for which individual patient data were available or which were known to attempt exclusion of patients with bicuspid or unicuspid valves comprise the primary basis for the event rate estimate and additional series were considered only confirmatory in nature. Table 1 presents the rates of all-cause mortality at 24 months from studies which were considered in developing the event rate estimate. The simple weighted average from the studies was 11.4% which was adjusted up to 12% to account for the possibility that surgical candidates at extremely low risk (i.e. the healthiest and youngest potential subjects) may forego randomization into a TAVR trial until longer term data and data from lower surgical risk patients are available for TAVR.

Table 1. Surgical series supporting all-cause mortality event rate estimate

Surgical Series	Number in cohort	24-Month all-cause mortality K-M Rate
NOTION SAVR cohort[1]	134	9.8%
3f Pivotal cohort[1]	405	12.7%
Mosaic sub-analysis[2]	646	9.9%
Freestyle sub-analysis[3]	323	13.5%
Simple Weighted Average	1508	11.4%

[1]Entire cohort leveraged (data on file)
[2]Sub-group analysis excluding subjects <65 years of age, with congenital bicuspid valves or with a purely regurgitant lesion
[3]Sub-group analysis excluding subjects <65 years of age, with congenital bicuspid valves, with a purely regurgitant lesion or with the Freestyle valve implanted as a full-root replacement

The 24-month event rate estimate for non-fatal disabling stroke of 3% was generated primarily from the CoreValve US Pivotal High Risk Trial SAVR (3.9%) and TAVR (2.0%) cohorts which used event definitions consistent with this trial.[25] Additional sources of data considered include the NOTION SAVR cohort (4.6%) and the Mosaic and Freestyle cohort sub-analyses (which had rates of 2.0% and 2.3% respectively) all of which collected clinical stroke/cerebrovascular accidents.

The expected sample size for this trial was determined based on the primary endpoint of all-cause mortality or disabling stroke at 24 months. The assumed values $\pi_T = \pi_C = 0.15$ are based on an assumed rate of all-cause mortality of 12% at 24 months and a non-fatal disabling stroke rate of 3% at 24 months.

3.3.3.2 Analysis Sets

3.3.3.2.1 Screening Population

All subjects with severe aortic stenosis who provide an informed consent will be considered screened and enrolled and all available data will be entered into the Electronic Data Capture (EDC) system.

3.3.3.2.2 Randomized Population

If the subject signs informed consent, meets all inclusion and none of the exclusion criteria, and the Heart Team determines the subject is suitable for randomization in the trial, then the subject is reviewed by the Screening Committee. If the subject is approved by the Screening Committee and the subject is randomized to either TAVR or SAVR, the subject is added to the randomized population. Within the randomized population the following analysis sets are distinguished:

- **The intention to treat (ITT) set:** Subjects are reported according to the randomized assignment, SAVR or TAVR, regardless of what, if any, therapy was actually received.
- **The as treated (AT) set:** The AT set consists of all ITT subjects with an attempted implant procedure, defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed. Subjects will be analyzed according to their first attempted procedure (TAVR or SAVR).
- **The implanted set:** The Implanted set consists of all the AT subjects who are actually implanted with either the TAV or SAV.
- **The per protocol (PP) set:** The PP set will be defined based on the ICH E9 Statistical Principles, and will be specified in the statistical analysis plan (SAP).

The primary analysis for the primary objective, secondary safety objectives, secondary effectiveness objectives (except for valve dysfunction, hemodynamic performance metrics, and device success) will use the AT set. Valve dysfunction, hemodynamic performance metrics, and device success will use the implanted set.

3.3.3.3 Description of Baseline Variables

Baseline demographic and clinical variables will be summarized for each of the treatment groups for the ITT, AT, and implanted sets. Continuous variables will be summarized as means, medians, standard deviations, interquartile ranges, minima and maxima and compared between treatment groups using a Bayesian analog of a two-sample t-test or the non-parametric Wilcoxon rank-sum test. Categorical variables will be summarized as frequencies and percentages and compared between treatment groups using a Bayesian version of a comparison of proportions.

3.3.3.4 Primary Objective

The primary endpoint of all-cause mortality or disabling stroke at 24 months post procedure will be evaluated using the absolute difference of the TAVR rate and the SAVR rate for all-cause mortality or disabling stroke during a fixed follow-up of 24 months time. The hypothesis test is designed to show non-inferiority of TAVR to SAVR for the primary endpoint.

3.3.3.4.1 Hypothesis of Non-inferiority

The primary objective is to establish that TAVR is non-inferior to SAVR for the primary endpoint. The hypothesis of interest is:

$H: \pi_T < \pi_C + \delta$

where π_T and π_C denote binary rates of all-cause mortality or disabling stroke during a fixed follow-up of 24 months for the treatment (TAVR) and control (SAVR) groups, and $\delta = 0.06$. This trial is designed using Bayesian statistical techniques. TAVR will be declared to be non-inferior to SAVR if it can be established that the posterior probability $Pr(H_{\delta=0.06} \mid data) > \Psi$, where Ψ is a pre-specified threshold value. In addition, the primary endpoint (superiority) will be tested according to the testing order specified in Section 3.3.3.7 Multiplicity Considerations.

3.3.3.4.2 Randomization

Randomization will follow a 1:1 (treatment:control) allocation ratio and be stratified by site and need for revascularization, using a blocked randomization scheme with blocks of randomly varying sizes. The sample size for the AT population is 1200 subjects. The first interim analysis (timed to occur when 850 subjects are followed for 12 months) will be conducted for the purpose of possibly passing the primary objective. If the criterion for passing the primary objective is not met at this time, the second interim analysis (timed to occur when 1200 subjects are followed for 12 months) will again be conducted for the purpose of possibly passing the primary objective. If non-inferiority is not concluded at either of the interim analyses, follow-up will continue until all subjects have reached 24 months (24 months after the last LTI subject's procedure date), and a final analysis will occur.

3.3.3.4.3 Sample Size and Analysis

The sample size is guided by a standard frequentist non-inferiority power analysis. Under the assumptions of $\pi_T = \pi_C = 0.15$, non-inferiority margin δ=0.06, 1:1 randomization, α=0.05, and power = 85%, the method of Farrington and Manning[51] as implemented in PASS 2013[52] indicates that the required sample size for a single-look analysis is 1032. To allow for around 6% dropout, 1100 subjects must be accrued. Furthermore, to compensate for power lost in a three-look group sequential analysis plan with alpha spending, the sample size would have to be increased to 1200[53]. Two interim analyses for possible "early win" are planned when 850 subjects have reached 12 months, and when 1200 subjects have reached 12 months.

This trial is designed using Bayesian statistical techniques. The first interim analysis will be timed to occur 12 months after the 850th procedure date for the purpose of declaring an early win will occur. At this analysis, if $P(H_{\delta=0.06} \mid data) > \Psi$, non-inferiority will be declared at this time, and a regulatory submission will follow. Otherwise, follow-up will continue until the second interim analysis (timed to occur 12 months after the 1200th procedure date), where again if the posterior probability of non-inferiority $P(H_{\delta=0.06} \mid data) > \Psi$, non-inferiority will be concluded and a regulatory submission will follow. If non-inferiority is not concluded at either of the interim analyses, all subjects will be followed to 24 months (24 months after the last LTI subject's procedure date), when a final analysis will occur. At the final analysis, the standard for trial success will again be $P(H_{\delta=0.06} \mid data) > \Psi$. These three analyses are termed "Win Looks."

If non-inferiority is established at either interim analysis, a test of superiority may be performed (See Section 3.3.3.7 Multiplicity Considerations for additional requirements and testing sequence). If $P(H_{\delta=0} \mid data) > \Psi_{SUP}$, superiority will be established at this time. However, if $P(H_{\delta=0} \mid data) \leq \Psi_{SUP}$, subjects will continue to be followed until the full cohort has had the chance to be followed for 24 months (24 months after the last LTI subject's procedure date), at which time a delayed determination of superiority may be made if $P(H_{\delta=0} \mid data) > \Psi_{SUP}$.

The statistical approach for these analyses is Bayesian, and simulations for the trial design will be provided in a separate document. The prior distributions for π_T and π_C in these calculations are Beta (1,1). The threshold Ψ and Ψ_{SUP} will be specified in a separate document; this value is selected by trial-and-error to achieve a type I error (under simulation) of at most 0.05 for non-inferiority testing and at most 0.025 for superiority testing.

3.3.3.5. Secondary Safety Endpoints

- The rate of the composite of death, disabling stroke, life-threatening bleed, major vascular complications, or AKI (II or III) at 30 days
- The rate of new permanent pacemaker implantation at 30 days
- The rate of prosthetic valve endocarditis at one year
- The rate of prosthetic valve thrombosis at one year
- The rate of all stroke (disabling and non-disabling) at one year
- The rate of life-threatening bleeding at one year
- The rate of valve-related dysfunction requiring repeat procedure at one year

The incidence estimates for each endpoint above will be provided for the two treatment groups at the specified time point. The statistical method will be the Bayesian version of a comparison of proportions (with predictions). In addition, Kaplan-Meier estimates will be provided at the following time points: 30 days, 6 months, 12 months, and annually thereafter through 10 years.

3.3.3.6 Secondary Effectiveness Endpoints

- The rate of valve-related dysfunction, defined as moderate or severe prosthetic valve stenosis, or moderate or severe prosthetic regurgitation at one year (per VARC II)
  The incidence estimate will be provided for the two treatment groups at the specified time point. The statistical method will be the Bayesian version of a comparison of proportions (with predictions). The incidence estimates will also be reported at the following time points: 30 days, 6 months, one year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years.

- Quality of Life as assessed by Kansas City Cardiomyopathy (KCCQ) change from baseline at 30 days and one year
  The endpoint will be evaluated using a Bayesian analog of a two-sample t-test or the non-parametric Wilcoxon rank-sum test. The descriptive statistics for KCCQ change from baseline will also be reported at 30 days, 6 months, one year, and annually thereafter through 5 years.

- The rate of repeat hospitalization for aortic valve disease at one year.

The incidence estimate will be provided for the two treatment groups at the specified time point. The statistical method will be the Bayesian version of a comparison of proportions (with predictions). In addition, the Kaplan-Meier estimates will be provided at the following time points: 30 days, 6 months, 12 months, and annually thereafter through 10 years.

- Device Success (VARC II), defined as
  - Absence of procedural mortality, AND
  - Correct positioning of a single prosthetic heart valve into the proper anatomical location, AND
  - Intended performance of the prosthetic heart valve, defined as the absence of patient-prosthesis-mismatch and mean aortic valve gradient less than 20 mmHg (or peak velocity <3 m/sec), AND absence of moderate or severe prosthetic valve regurgitation.

  The incidence estimate will be provided for the TAVR group.

- Hemodynamic performance metrics by Doppler echocardiography
  - Mean aortic gradient at one year
  - Effective orifice area at one year
  - Degree of total, peri, and transvalvular prosthetic regurgitation at one year

  For mean gradient and effective orifice area, the descriptive statistics will be reported at each of the assessed time point (30 days, 6 months, one year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years). Prosthetic regurgitation severity will be reported as proportions at each of the assessed time point (30 days, 6 months, one year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years).

- New York Heart Association (NYHA) functional classification at one year.

  NYHA function classification will be reported as proportions at each of the assessed time point (30 days, 6 months, one year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years).

- Health-related quality of life at one year as assessed by EQ-5D survey instrument.

3.3.3.7 Multiplicity Considerations

It is recognized that with a multiplicity of tests comes an inflation in the chance of a false finding of superiority or non-inferiority. Therefore, for the purpose of seeking approved labeling claims on designated secondary objectives, the following standard will be used: if the primary objective demonstrates non-inferiority, claims will be sought for selected secondary non-inferiority and superiority objectives and for superiority on the primary objective metric. These will be tested via a hierarchical (sequential) testing order that preserves the overall study-wise type I error rate at the level of 0.05. The testing order is specified below. The following secondary objectives are tested in order, and testing continues if and only if all previous objectives have met their designated success criterion.

1. Transvalvular mean gradient at 1 year (non-inferiority)
2. Effective orifice area at 1 year (non-inferiority)
3. Change in NYHA classification from baseline to 1 year (non-inferiority)
4. Change in KCCQ score from baseline to 1 year (non-inferiority)

5. Transvalvular mean gradient at 1 year (superiority)
6. Effective orifice area at 1 year (superiority)
7. Change in KCCQ score from baseline to 30 days (superiority)

All of the above non-inferiority will be tested with a type I error standard of 0.05 and superiority tests will be tested with a type I error standard of 0.025. If all of the above tests meet their success criterion, the primary endpoint (superiority) will be tested using a type I error rate of 0.025.

For the purposes of seeking claims, these objectives will only be evaluated once, at the same time as non-inferiority of the primary objective is established. The only exception to this is the primary endpoint superiority test, which carries the possibility of a delayed determination of superiority and may thus meet its success criterion at a different time (see Section 3.3.3.4.3 Sample Size and Analysis).

The remaining secondary endpoints (see Section 3.3.3.5. Secondary Safety Endpoints and Section 3.3.3.6 Secondary Effectiveness Endpoints) may be of interest for scientific reasons but will not be the basis for supporting labeling claims; they are thus outside of the hierarchical testing procedure. Similarly, for those objectives that test non-inferiority, if non-inferiority is established, a test of superiority may also be conducted, but unless specifically itemized in the list, such superiority testing is not part of the hierarchical testing procedure; these superiority tests may be of interest for scientific reasons but will not be the basis for supporting labeling claims.

3.3.3.7.1 Ordered List of Secondary Objectives to be Tested to Support Labeling Claims

1. Transvalvular mean gradient at 1 year (non-inferiority). The hypothesis of interest is

   $$H: \mu_{TAVR} < \mu_{SAVR} + 5$$

   where μ_{TAVR} and μ_{SAVR} denote the average mean gradient at 1 year, measured in mmHg. This objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.95.

   Rationale for Delta: A difference less than 5 mmHg for mean gradient is not considered clinically relevant for the TAVR Low Risk Executive Committee.

2. Effective orifice area at 1 year (non-inferiority). The hypothesis of interest is

   $$H: \mu_{TAVR} > \mu_{SAVR} - 0.1$$

   where μ_{TAVR} and μ_{SAVR} denote the mean effective orifice area at 1 year, measured in cm^2. This objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.95.

   Rationale for Delta: A difference less than 0.1 cm^2 for effective orifice area is not considered clinically relevant for the TAVR Low Risk Executive Committee.

3. Change in NYHA classification from baseline to 1 year (non-inferiority). The hypothesis of interest is

   $$H: \mu_{TAVR} > \mu_{SAVR} - 0.375$$

   where μ_{TAVR} and μ_{SAVR} denote the mean number of classification improvements in NYHA from baseline to 1 year. For subjects with NYHA categories at both baseline and 1-year visit, the NYHA classification improvements will be calculated as $NYHA_{baseline} - NYHA_{12month}$. The objective will be evaluated using a

Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.95.

Rationale for Delta: A difference less than 0.375 for NYHA classification is not considered clinically relevant for the TAVR Low Risk Executive Committee.

4. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 1 year (non-inferiority). The hypothesis of interest is

$$H: \mu_{TAVR} > \mu_{SAVR} - 5$$

where μ_{TAVR} and μ_{SAVR} denote the mean changes in the KCCQ score from baseline to 1 year. For subjects with KCCQ score at both baseline and 1 year, the change in KCCQ will be calculated as $KCCQ_{1year} - KCCQ_{baseline}$. The objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.95.

Rationale for Delta: A 5-point improvement or decrease in KCCQ is the minimum difference that is clinically relevant. [54]

5. Transvalvular mean gradient at 1 year (superiority). The hypothesis of interest is

$$H: \mu_{TAVR} < \mu_{SAVR}$$

where μ_{TAVR} and μ_{SAVR} denote the average mean gradient at 1 year, measured in mmHg. This objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.975.

6. Effective orifice area at 1 year (superiority). The hypothesis of interest is

$$H: \mu_{TAVR} > \mu_{SAVR}$$

where μ_{TAVR} and μ_{SAVR} denote the mean effective orifice area at 1 year, measured in cm^2. This objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.975.

7. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 30 days (superiority). The hypothesis of interest is

$$H: \mu_{TAVR} > \mu_{SAVR}$$

where μ_{TAVR} and μ_{SAVR} denote the mean changes in the KCCQ score from baseline to 30 days. For subjects with KCCQ score at both baseline and 30 days, the change in KCCQ will be calculated as $KCCQ_{30day} - KCCQ_{baseline}$. The objective will be evaluated using a Bayesian version of a two-sample t-test. The posterior probability P(H | data) will be calculated and compared to a threshold of 0.975.

3.3.3.8 Missing Data

Every effort will be undertaken to minimize missing data. However, some missing data is inevitable, and the trial is designed with the expectation that there may be up to 6% of primary data missing at 24 months. The reasons for missing data will be described and evaluated for assessment of possible bias. The distribution of prognostic factors between subjects with data and those without data will be examined to evaluate any potential sources of bias.

3.3.3.9 LTI Analysis

The incidence of LTI will be assessed when at least 150 TAVR and at least 150 SAVR evaluable subjects have completed the 30 day MDCT scans and the 1 year MDCT scans. This analysis will not impact the Type I error rate of this trial as no decisions to alter the main trial are allowed based on this analysis.

3.3.4 Number of Subjects and Investigational Devices, Trial Duration

This trial will involve at least 1200 subjects in the AT population among all active sites. No site will implant more than 100 subjects without prior authorization from Medtronic. Subjects who exit from the trial after implantation will not be replaced.

Subjects will be consented for follow-up through 10 years. The enrollment period is estimated to be between 18 to 24 months; therefore the estimated total duration of the trial (first subject enrolled to last subject completing his/her last follow-up exam) is estimated to be 12 years. The number of investigational TAVR systems used in the trial is estimated to between 600 and 700 (based on sample size and 1:1 randomization).

Randomization will continue until the required number of subjects in the LTI Sub-Study and the Japan addendum are met, up to 1540 randomized subjects.

3.3.5 Subject Selection Criteria

3.3.5.1 Inclusion Criteria

Prospective subjects must meet all of following inclusion criteria to be eligible for implantation:

1. Severe aortic stenosis, defined as follows:
   a) For symptomatic patients:
   Aortic valve area ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **OR** mean gradient ≥40 mmHg, **OR** Maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest
   b) For asymptomatic patients:
      - Very severe aortic stenosis with an aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** maximal aortic velocity ≥5.0 m/sec, or mean gradient ≥60 mmHg by transthoracic echocardiography at rest, **OR**
      - Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** a mean gradient ≥40 mmHg or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** an exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia **OR**
      - Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** mean gradient ≥40 mmHg, or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** a left ventricular ejection fraction <50%.
2. Patient is considered low risk for SAVR, where low risk is defined as predicted risk of mortality for SAVR <3% at 30 days per multidisciplinary local heart team assessment.
3. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.

3.3.5.2 Exclusion Criteria

If any of the following exclusion criteria are present, the prospective subject is not eligible for implantation:

1. Any condition considered a contraindication for placement of a bioprosthetic valve (eg, subject is indicated for mechanical prosthetic valve).
2. A known hypersensitivity or contraindication to any of the following that cannot be adequately pre-medicated:
   a. aspirin or heparin (HIT/HITTS) and bivalirudin
   b. ticlopidine and clopidogrel
   c. Nitinol (titanium or nickel)
   d. contrast media
3. Blood dyscrasias as defined: leukopenia (WBC <1000 mm^3), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states.
4. Ongoing sepsis, including active endocarditis.
5. Any percutaneous coronary or peripheral interventional procedure with a bare metal stent within 30 days prior to randomization, or drug eluting stent performed within 180 days prior to randomization.
6. Multivessel coronary artery disease with a Syntax score >22 and/or unprotected left main coronary artery.
7. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 10 weeks of Heart Team assessment.
8. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.
9. Recent (within 2 months of Heart Team assessment) cerebrovascular accident (CVA) or transient ischemic attack (TIA).
10. Gastrointestinal (GI) bleeding that would preclude anticoagulation.
11. Subject refuses a blood transfusion.
12. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits).
13. Estimated life expectancy of less than 24 months due to associated non-cardiac co-morbid conditions.
14. Other medical, social, or psychological conditions that in the opinion of the investigator precludes the subject from appropriate consent or adherence to the protocol required follow-up exams.
15. Currently participating in an investigational drug or another device trial (excluding registries).
16. Evidence of an acute myocardial infarction ≤30 days before the trial procedure due to unstable coronary artery disease (WHO criteria).
17. Need for emergency surgery for any reason.
18. Subject is pregnant or breast feeding.
19. Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable

Anatomical exclusion criteria:

20. Pre-existing prosthetic heart valve in any position.
21. Severe mitral regurgitation amenable to surgical replacement or repair.

22. Severe tricuspid regurgitation amenable to surgical replacement or repair.
23. Moderate or severe mitral stenosis amenable to surgical replacement or repair.
24. Hypertrophic obstructive cardiomyopathy with left ventricular outflow gradient.
25. Bicuspid aortic valve verified by echocardiography, MDCT, or MRI.
26. Prohibitive left ventricular outflow tract calcification.
27. Sinus of Valsalva diameter unsuitable for placement of the self-expanding bioprosthesis.
28. Aortic annulus diameter of <18 or >30 mm.
29. Significant aortopathy requiring ascending aortic replacement.

For transfemoral or transaxillary (subclavian) access:

30. Access vessel mean diameter <5.0 mm for Evolut 23R, 26R, or 29R mm TAV, or access vessel mean diameter <5.5 mm for Evolut 34R mm or Evolut PRO TAV. However, for transaxillary (subclavian) access in patients with a patent LIMA, access vessel mean diameter <5.5mm for Evolut 23R, 26R, or 29R mm TAV, or access vessel mean diameter <6.0 mm for the Evolut 34R or Evolut PRO TAV[ii].

France

Inclusion and exclusion criteria required in France are included in the *Clinical Investigation Plan Addendum: France – Addendum for France to Clinical Investigational Plan Document Number 10234430DOC.*

3.3.6 Informed Consent

Prior to enrolling in the trial, patients should be fully informed of the details of trial participation as required by applicable regulations, the site's IRB and by Medtronic. Informed consent must be obtained from each patient prior to conducting any protocol-induced activities beyond standard of care, by using the informed consent form (ICF) approved by that site's IRB and by Medtronic. The ICF must be signed and dated by the patient and by the person obtaining the consent. Any additional persons required by the site's IRB to sign the informed consent form must also comply.

Prior to the patient signing the ICF, the investigator or authorized designee will fully explain to the patient the nature of the research, trial procedures, anticipated benefits, and potential risks of participation in the trial. The investigator or delegate will allow adequate time for the patient to read and review the consent form and to ask questions. Signing the ICF serves to document the written and verbal information that the investigator or authorized delegate provides to the patient, the patient's understanding of the information, and his/her agreement to participate. The investigator or authorized delegate must document in the patient's medical records that the patient was consented and the date on which the consent was obtained. The original signed consent form will be retained in the patient's trial records and a copy of the informed consent will be provided to the patient.

3.3.7 Revisions in Patient Information and Informed Consent Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's continued participation in the trial. The revised information will be sent to the investigator for

[ii] For subjects with a patent LIMA undergoing tranaxillary (subclavian) access, the minimal access vessel mean diameter is 5.5 mm for the Evolut 23R, 26R, and 29R TAV, and 6.0 mm for the Evolut 34R and Evolut PRO TAV.

approval by the IRB/EC. After approval by the IRB/EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated. The investigator or his/her designee should inform the subject in a timely manner.

3.3.8 Screening, Enrollment, and Randomization

The process of patient screening, subject enrollment, and randomization is as follows (Figure 1):

1. Patients identified by or presented to the trial site with aortic stenosis will be screened by the investigative team for the criteria described in 3.3.5, Subject Selection Criteria, using available medical records, including relevant imaging studies previously performed for diagnostic purposes.
2. If the patient is deemed a potential candidate for the trial, the investigational status of the Medtronic TAVR System and all aspects of the trial will be explained to the patient. The patient will then be invited to participate in the Low Risk Trial. Sites participating in the LTI Sub-study will also invite patients to consent for the LTI Sub-Study.
3. If the patient agrees to participate, written informed consent will be obtained. This will be considered the point of enrollment, and the subject will be assigned a Subject ID number.
4. The subject will undergo transthoracic echocardiography (TTE) to assess his/her degree of aortic stenosis.
5. Subjects who meet the criteria for aortic stenosis[iii] will undergo:
   a. Multi-Detector Computed Tomography (MDCT) of their peripheral vasculature and aortic annulus to assess anatomic suitability for the Medtronic TAVR , and
   b. Local Heart Team assessment to determine his/her operative risk profile for SAVR.
6. If the local Heart Team considers the subject anatomically suitable for implantation and at low risk for SAVR, the subject's clinical information will be submitted to the Screening Committee. The Heart Team assessment must be documented. The following information should be submitted to the Screening Committee:
   - Clinical assessments including STS-PROM, medical history and co-morbidities
   - TTE data on degree of aortic stenosis
   - MDCT data on anatomical suitability[iv]
7. The Screening Committee will review the clinical information to confirm the eligibility of the subject for implantation.
8. Subjects confirmed eligible for implantation by the Screening Committee will be randomized in a 1:1 fashion to either TAVR or SAVR, stratified by site and the need for coronary revascularization during SAVR. Coronary artery bypass graft (CABG) should be conducted during the index procedure. Concomitant percutaneous coronary intervention (PCI)[v] and TAVR is encouraged; however staging is left to the discretion of the operator. Intervention/repair of the mitral and/or tricuspid valve is only

[iii] If a subject has balloon aortic valvuloplasty after their qualifying TTE, they must have repeat TTE to confirm he/she meets criteria for severe aortic stenosis as described in Section 3.3.5.1 prior to submission to the screening committee.

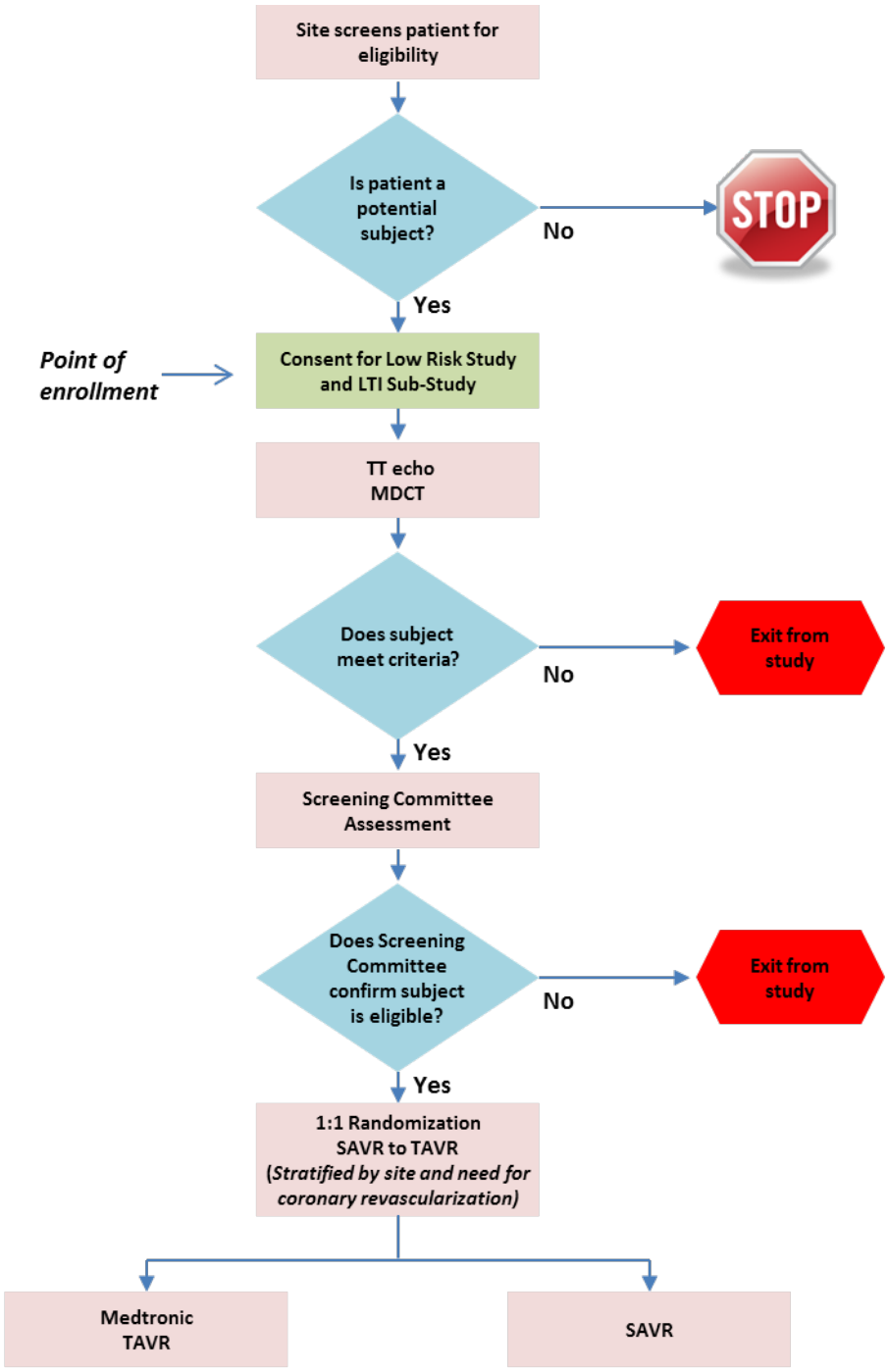
[iv] Anatomical suitability will be confirmed by Medtronic Screening Lab. Information on MDCT procedures and sizing recommendations is provided in Appendix II, Section 4.0.

[v] Index PCI should be performed at the TAVR implanting center; index PCI operators will be considered investigators.

allowed if deemed necessary during the SAVR procedure, but there must be no intent to do this type of intervention/repair prior to implant.

9. Trial randomization will not be blinded. Once randomization is complete and a treatment arm is assigned, crossover from SAVR to TAVR treatment is not permitted. The sponsor will strictly monitor device dispensation to ensure that only those subjects randomized to the Medtronic TAVR treatment arm receive the Medtronic TAV. Distribution of the subjects within the trial groups will be controlled at the implanting sites by means of central randomization using interactive voice/web randomization service (IXRS). The randomization scheme will be securely stored at the IXRS provider.
10. Implantation should occur within 90 days of Screening Committee approval.
11. Subjects who consent to participate in the LTI study will also follow the LTI sub-study protocol as described in APPENDIX VII: LEAFLET THICKENING/IMMOBILITY SUB-STUDY PROTOCOL

Patients should give written consent before undergoing any protocol-required testing. However, if any of protocol-required baseline/screening evaluations (eg, echocardiography, MDCT, coronary arteriography, lab work) have been performed for clinical diagnostic purposes prior to consenting, they can be used as the protocol-required exams, provided they were obtained within the protocol-required time windows and contain the necessary information.



Notes
1. TTE, MDCT, coronary arteriography, or labs performed for diagnostic purposes prior to consent may be used for the baseline/screening exams, provided they were performed within window and contain the necessary data.
2. Only the sites participating in the LTI Sub-study will consent for both the main study and LTI Sub-study.
3. Subjects who give consent for LTI Sub-study will follow sub-study protocol in addition to main protocol.

Figure 1. Flow diagram of trial entry process.

3.3.9 Required Evaluations

Follow-up protocol required evaluations should be performed at the trial site. The protocol required evaluations for each trial interval are listed as follows, and summarized in Table 2 and Table 3.

Baseline/Pre-implant Required prior to Screening Committee Submission (within 12 weeks prior to submission to the Screening Committee; except for MDCT and coronary arteriography) [vi]

- Clinical assessment and history (eg, clinical history, STS-PROM, co-morbidities, NYHA) [v]
- Coronary arteriography
- TTE
- Heart Team assessment
- MDCT (peripheral vasculature and aortic annulus)
- Adverse Events

Baseline/Pre-implant Required prior to Index Procedure

- 12-lead ECG
- Complete blood count, creatinine,
- Modified Rankin Score
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Euro-Qol (EQ-5D) Quality of Life survey
- Anti-thrombotic medications
- Adverse Events

Implant Procedure (TAVR subjects)

- Post-deployment hemodynamics and aortography (final result)
- Adverse Events

12 to 24 Hours Post Procedure

- 12 lead ECG
- Adverse Events

18 hours to 7 days Post Procedure (Device Success)

- TTE (for device success)
- Creatinine
- Adverse Events

Discharge (7 days post procedure or discharge, whichever comes first)

- Clinical assessment (NYHA not assessed at discharge)
- 12 lead ECG
- Modified Rankin Score
- Anti-thrombotic medications
- I.N.R. (for subjects on VKA)
- Adverse Events

[vi] Pre-implant MDCT and Coronary arteriography should be performed within 365 days of submission to the screening committee date

[v] Definitions of STS risk factors and other co-morbidities are provided in Appendix III

30 days (between 30 to 45 days post implant)

- Clinical assessment
- TTE
- 12 lead ECG
- Creatinine
- Modified Rankin Score
- KCCQ
- EQ-5D
- Anti-thrombotic medications
- I.N.R. (for subjects on VKA)
- Adverse Events

Six Months (between 183 to 213 days post implant)

- Clinical assessment
- TTE
- Modified Rankin Score
- KCCQ
- EQ-5D
- Anti-thrombotic medications
- I.N.R. (for subjects on VKA)
- Adverse Events

One Year (between 365 and 395 days post implant)

- Clinical assessment
- TTE
- Modified Rankin Score
- KCCQ
- EQ-5D
- Anti-thrombotic medications
- I.N.R. (for subjects on VKA)
- Adverse Events

18 Months (between 545 and 575 days post-implant)

- Clinical assessment
- Modified Rankin Score
- Anti-thrombotic medications
- I.N.R. (for subjects on VKA)
- Adverse Events

Two Year (between 730 and 760 days post-implant)

- Clinical assessment
- TTE
- Modified Rankin Score
- KCCQ
- Anti-thrombotic medications
- I.N.R. (for subjects on VKA)
- Adverse Events

Annually from 3 years through 5 years (between implant anniversary date and +/-60 days after)

- Clinical assessment
- TTE
- Modified Rankin Score
- KCCQ
- Anti-thrombotic medications
- I.N.R. (for subjects on VKA)
- Adverse Events

6 years, 8 years and 9 years (between implant anniversary date and +/-60 days after)

- Adverse Event review conducted via telephone

7 years and 10 years (between implant anniversary date and +/-60 days after)

- Clinical assessment
- TTE
- Adverse Events

Other Evaluations

- Creatinine clearance will be derived by the trial database system using the Cockcroft-Gault equation.
- A Modified Rankin Score assessment should be conducted at 1 and 3 months following any suspected or confirmed stroke event.

Table 2. Summary of visit schedule and required evaluations through 5 years

	Baseline (Pre-Implant)	Implant	12 to 24 Hrs	18 Hrs to 7 Days (Device Success)	Discharge	30 Days	6 Months	1 Year	18 Months	Annual (through 5 Years)
Clinical Assessment	X				X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Coronary Arteriography	X									
MDCT	X									
TTE	X			X		X	X	X		X
12-lead ECG	X		X		X	X				
Modified Rankin Score	X				X	X	X	X	X	X
Hemodynamics		X								
Aortography		X								
Complete Blood Count	X									
Creatinine	X			X		X				
I.N.R.					X	X	X	X	X	X
Anti-thrombotic medications	X				X	X	X	X	X	X
KCCQ	X					X	X	X		X
EQ-5D	X					X	X	X		

Table 3. Summary of visit schedule and required evaluations from 6 through 10 years

	Years 6, 8, and 9	Years 7 and 10
Clinical Assessment		X
Adverse Events	X	X
TTE		X

Visit Windows

Baseline	Within 12 weeks prior to submitting to the screening committee (except for MDCT and coronary arteriography) as noted in Section 3.3.9)
Discharge	Discharge from index procedure or 7 days post implant, whichever comes first
30 Days	Between 30 and 45 days post implant
6 Months	Between 183 and 213 days post implant
1 Year	Between 365 and 395 days post implant
18 Months	Between 545 and 575 days post-implant
2 Year	Between 730 and 760 days post-implant
3 – 10 years	Between implant anniversary date and +/-60 days after

Notes

1. NYHA assessment not required at discharge
2. TTE for device success should be performed within 18 hours to 7 days post-procedure
3. Adverse events should be assessed at each visit
4. Hemodynamics and aortography for TAVR subjects only
5. I.N.R. only required for subjects on VKA
6. TTE can be collected at 8 year follow-up visit if missed during 7 year visit

Throughout this trial, UB-04 summary bills and itemized hospital bills for TAVR and SAVR subjects will be collected by the Baim Institute at select clinical sites in the US. Prior to the collection of billing information, patients will be asked to provide the information and permission to obtain such billing records for the length of their follow-up period. All related data will be kept in a secure and confidential database.

3.3.10 Post-Implant Anti-thrombotic Therapy

Management of subject's anti-thrombotic regimen will be per the discretion of the investigator, in accordance with the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease.[13]

The recommended post implant anti-thrombotic regimen for TAVR subjects will be 30 days or more of Dual Anti-Platelet Therapy (DAPT) followed by aspirin through 12 months.

The recommended post implant regimen for SAVR subjects will be a Vitamin K Antagonist (VKA) or aspirin in accordance with current guidelines.

3.3.11 Subject Disposition

Sites will maintain a log of subjects consented, his/her assigned treatment group, date attempted and implanted, as well as the Subject ID numbers assigned to each patient. Subjects who are consented but are not taken to the procedure room for implantation will be exited from the trial, and will not be followed beyond the date of trial exit.

Subjects who are taken to the procedure room for implantation but do not receive a TAV or surgical valve for any reason will be followed for the trial duration. Subjects that have their TAV or SAVR bioprosthesis explanted will be followed for the trial duration.

3.3.12 Implant Procedure (TAVR)

The implantation procedure is performed according to the standard procedures of the implanting physicians. In countries where required, specifically the United States and Japan, the local heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of the TAVR procedure. Procedural aspects specific to the Medtronic TAVR system should be performed according to the Instructions for Use, with the exception of the use of pre-deployment balloon aortic valvuloplasty[vii]. The following variables will be collected regarding the TAVR implantation procedure:

- Name of the primary and secondary operator
- Anesthesia type (general or local)
- Delivery catheter access site and vessel diameter of access site
- Use of EnVeo InLine Sheath alone, OR use of separate introducer sheath size and type
- Pre-deployment BAV (yes/no)
- Use of rapid pacing during BAV and deployment (yes/no)
- Size of TAV implanted
- Post-implant dilation (yes/no)
- Post-implant pressures at final result (LV systolic and end-diastolic, aortic systolic and diastolic)
- Implantation of TAV within the desired location (yes/no)
- Post-implant degree of prosthetic regurgitation by angiography (Sellers criteria)[55]
- Post-implant degree of prosthetic paravalvular regurgitation by TEE, if performed
- Post-implant degree of prosthetic transvalvular regurgitation by TEE, if performed
- More than one TAV implanted (yes/no)
- Patency of coronary arteries post-implant (yes/no)
- Estimated contrast volume used
- Total procedural time(minutes): time in procedure room to exit from procedure room
- Information on use of resheath/recapture feature[viii]
- Occurrence of adverse events
- If TAV implantation not attempted, reason why

[vii] For this trial, the use of pre-deployment BAV is per the discretion of the implanting physician. It will not be considered a deviation if pre-deployment BAV is not performed.

[viii] Definitions of resheath/recapture use are provided in Appendix IV.

3.3.13 Implant Procedure (SAVR)

Surgical aortic valve replacement should be performed according to the implanting surgical team's standard routine. Procedural aspects specific to the bioprosthesis should be performed according to the Instructions for Use for the respective bioprosthesis. The following variables will be collected regarding the SAVR implantation procedure:

- Name of primary surgeon
- Valve size implanted
- Manufacturer of implanted valve
- Valve positioning (supra-annular, intra-annular, sub-annular)
- Concomitant procedures performed
- Post-implant degree of prosthetic paravalvular regurgitation by TEE, if performed
- Post-implant degree of prosthetic transvalvular regurgitation by TEE, if performed

3.3.14 Clinical Assessment

Clinical assessment is required at the following post-implant intervals: discharge, 30 days, 6 months, 1 year, 18 months, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years. The following variables will be documented at each protocol-required follow-up interval:

- Follow-up status
- NYHA functional classification (except at discharge)
- Modified Rankin Score (except at years 6 through 10)
- Prescribed antithrombotic medications (except at years 6 through 10)
- KCCQ (except at discharge, 18 months, and years 6 through 10)
- EQ-5D (except at discharge, 18 months, and years 2 through 10)
- Documentation of any adverse events
    - Adverse Events will be collected via telephone at 6 year, 8 year, and 9 year visits

3.3.15 Echocardiography

Transthoracic echocardiography (TTE) is required at the following intervals: pre-implant, 18 hours to 7 days (for device success), 30 days, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 7 years and 10 years. Exams will be sent to the Echo Core Lab for central assessment. Further details of the echocardiography methods are provided in APPENDIX I: ECHOCARDIOGRAPHY PROCEDURES. Sites will acquire the necessary views and measurements in order for the Echo Core Lab to assess the following variables at each protocol-required exam:

- Height (cm or in) and weight (kg or lb)
- Heart rate
- Left ventricular outflow tract (LVOT) diameter in mid systole
- Max aortic/prosthetic valve velocity (V_2) by CW Doppler
- Aortic valve velocity time integral (VTI) by CW Doppler
- Mean gradient across aortic valve (MGV_2) by CW Doppler
- LVOT VTI by PW Doppler
- Grade of aortic/prosthetic transvalvular regurgitation (post-implant only)

- Grade of aortic/prosthetic paravalvular regurgitation (post-implant only)
- Grade of prosthetic total (transvalvular plus paravalvular) regurgitation (post-implant only)
- Grade of mitral regurgitation
- Grade of tricuspid regurgitation
- Max tricuspid regurgitant (TR) jet velocity (if TR is present)
- Left ventricular internal dimension at end diastole
- Left ventricular internal dimension at end systole
- Interventricular septal thickness at end diastole
- Left ventricular posterior wall thickness at end diastole
- Left atrial diameter (anterior-posterior linear dimension) at systole
- Left ventricular ejection fraction by visual estimate
- Grade of diastolic dysfunction (if present)

In addition, the following variables will be derived by the central database from the appropriate measurements reported by the site:

- Body surface area (Dubois and Dubois)[56]
- Peak aortic pressure gradient
- Aortic valve area (AVA)/effective orifice area (EOA) by continuity equation
- Aortic valve area index (AVAI)/effective orifice area index (EOAI)
- Doppler Velocity Index (DVI)
- Estimated right ventricular systolic pressure (RVSP)

Derived variables will be displayed on the eCRF upon entry of the appropriate raw measurements. The pre-implant qualifying AVA or AVAI must be based on the site reported variables for LVOT diameter, LVOT VTI, aortic valve VTI, height, and weight.

3.3.16 Missed Follow-up Visits

Every effort should be made to ensure subjects return to the clinic for all protocol required follow-ups. If the subject is unable to return for an in-person clinic visit, the Investigator, or designee, should document in the subject record the reason the subject was unable to complete the visit and, if applicable, follow the requirements for deviation reporting as outlined in section 3.3.18 Protocol Deviations.

The investigator should also make every effort to contact the subject within the visit window to collect the subject's vital status as well as information related to potential adverse events, safety data, and hospitalizations.

3.3.17 Unscheduled Follow-up Visits

If a subject returns to the study site or is contacted via telephone between their scheduled follow-up visits for an event potentially related to a study endpoint, the visit or telephone call will be treated as an unscheduled follow-up, and the assessments completed at this visit will be conducted at the discretion of the investigator. eCRFs are provided for unscheduled visits.

3.3.18 Protocol Deviations

A protocol deviation is defined as an event where the clinical investigator or site personnel did not conduct the study according to the protocol or the Investigator Agreement. Examples of protocol deviations 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 IRB approval before the start of the study
- Implanted subject did not meet inclusion/exclusion criteria[ix]
- Required testing and/or measurements not done or incorrectly done
- Subject does not attend follow-up visit or follow-up visit outside window
- Unauthorized use of investigational devices
- Adverse events not reported in the required time frame as required by regulation or as specified in the CIP
- Control of study devices not maintained
- Source data permanently lost
- Enrollment of patients during lapse of IRB approval
- Enrollment limits exceeded

Investigators should obtain prior approval from Medtronic before initiating any change or deviation from the CIP, except where necessary to protect the life or physical well-being of a subject in an emergency situation. Such approval shall be documented in writing and maintained in the Investigator Site File. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control (eg, subject did not attend scheduled follow-up visit).

Deviations will be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Study deviations should be reported to Medtronic via the Study Deviation eCRF (one eCRF for each protocol deviation).

Investigators should report the following deviations to Medtronic and their reviewing IRB/EC within 5 working days of the occurrence of the deviations:

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

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

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

[ix] Subjects must meet all inclusion/exclusion criteria to be eligible for implantation. However, it will not be considered a protocol deviation if study related testing (eg. echo, MDCT, labs, coronary arteriography, Heart Team assessment, or Screening Committee assessment) of a consented subject identifies implantation eligibility criteria that are not met.

3.3.19 Trial Materials and Trial Specific Equipment

Medtronic will control the supply of investigational devices and trial materials (eg, Investigator Site File, eCRF access). Investigational devices will not be sent to the site until the site is activated. Medtronic will not provide any trial-specific equipment to the sites. Equipment used for assessing study variables (eg, echocardiographic systems) should be maintained per the site's standard procedures.

3.3.20 Device Accountability

The Evolut R TAV, the EnVeo R DCS with EnVeo InLine Sheath, the EnVeo R LS, the EnVeo PRO DCS, the EnVeo PRO LS, and the Evolut PRO TAV, DCS, and LS are not approved for use in low risk patients, and therefore are considered investigational devices. As such, they should be stored as labeled and in a secure location. The method of storage should prevent the use of these investigational devices for applications other than mentioned in this CIP. The investigator shall maintain adequate records of the receipt and disposition of all investigational devices.

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

- Investigational device name
- TAV serial number
- Lot number (for delivery catheter system and loading system only)
- Date of receipt of device
- Name of person receiving the device
- Name of person using the device
- Date of implant or use
- ID number of subject receiving or using the device
- Disposition (implanted, disposed of, or returned to Medtronic)

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

- TAV serial numbers
- Lot numbers (for delivery catheter system and loading system only)
- The quantity and reason for the device being returned to Medtronic or disposed of
- Name of the person who returned or disposed of each device
- Date of shipment back to Medtronic

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

3.3.21 Device Malfunction or Explant

In the event of a device malfunction of the Medtronic TAVR system prior to implant, or in the event a TAV or surgical bioprosthesis is explanted after implant (due to reintervention or autopsy), the TAV or surgical bioprosthesis, and/or affected components Medtronic TAVR system should be sent to Medtronic at the following address:
Medtronic

Attn: Explant Lab [PE#]
1851 E. Deere Avenue
Santa Ana, CA 92705-5720

Additional details surrounding the device return process are contained within the Medtronic explant kit that will be provided upon notification of a device malfunction or explant.

3.3.22 Subject Withdrawal or Discontinuation

All subjects will be encouraged to remain in the trial through the last follow-up visit at 10 years. Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of total trial subjects. If a subject is discontinued from the trial early, the reason for discontinuation should be documented in the subject file and a Trial Exit eCRF must be completed.

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

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

3.3.23 Early Suspension or Termination of the Trial

Medtronic may decide to suspend or prematurely terminate the trial (eg, if information becomes available that the risk to study subject is higher than initially indicated, if interim analysis indicates that the results significantly differ from the clinical study objectives or statistical endpoints). If the trial is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators and regulatory authorities of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB/EC. Medtronic will, as soon as possible, provide a written statement to the investigators to enable prompt notification of the IRB/ECs. If trial enrollment is terminated early, follow-up visits will continue for all enrolled subjects.

3.3.24 Early Suspension or Termination of a Trial Site

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

3.3.25 Revisions or Amendments to the Clinical Investigational Plan

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

Medtronic will submit any significant amendment to the CIP, including a justification for the amendment, to all affected regulatory agencies and to the investigators to obtain approval from their IRB/EC. The investigator will only implement the amendment after approval of the IRB/EC, regulatory agencies, and Medtronic. Administrative amendments to the CIP will be submitted to the IRB/EC for notification. Furthermore, investigators shall sign any approved amendment for agreement.

3.3.26 Adverse Events, Adverse Device Effects, and Device Deficiencies

3.3.26.1 Definitions

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

Table 4. Adverse event definitions for reporting requirements

Event Type	Definition
Adverse Event (AE) (ISO14155:2011 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other parties, whether or not related to the investigational medical device.[57] *NOTE 1: This definition includes events related to the investigational medical device or the comparator.* *NOTE 2: This definition includes events related to the procedures involved.* *NOTE 3: For users or other parties, this definition is restricted to events related to investigational medical devices.*
Serious Adverse Event (SAE) (ISO14155:2011 3.37)	Adverse event that a) led to death, b) led to a serious deterioration in the health of the subject, resulting in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect.[57] *NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.*
Adverse Device Effect (ADE) or Device Related Adverse Event (ISO14155:2011 3.1)	Adverse event related to the use of an investigational medical device. *NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.[57]* *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) (ISO14155:2011 3.36)	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.[57, 58]
Unanticipated Adverse Device Effect (UADE) (21 CFR 812.3)	Any serious adverse effect on health or safety of a patient, or any life-threatening problem or death caused by or associated with the device, if the effect, problem, or death has not been previously identified in nature, severity, or degree of incidence in the investigational plan or application, (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.[59]

Table 3. Adverse event definitions for reporting requirements (continued)

Event Type	Definition
Unanticipated Serious Adverse Device Effect (USADE) (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,[57] *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	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.[57] *NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.*
Mandatory Problem Reporting Incident (SOR/98-282 59-61.1(2))	An incident that (a) is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or in the directions for use, and (b) has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur. *NOTE: this definition and reporting requirement pertains to events that occur within Canada only.*
Significant Safety Issue (SSI) *(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016)*	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Urgent Safety Measure (USM) *(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016)*	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from Human Research Ethics Committees (HREC) or institutions.

3.3.26.2 Evaluation and Documentation of Adverse Events and Device Deficiencies

Investigators are required to evaluate and document in the subject's medical records all adverse events (AE) and device deficiencies (per the definitions in Table 4) observed in trial subjects from the time they are enrolled until they are exited from the trial. All AE should be followed through their resolution.

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 AE 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. In addition, after the subject has completed his/her two year follow-up visit, only SAE and device-related AEs need to be reported to Medtronic.

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 SAVR or TAVR procedure. The events listed in Table 4 are expected for patients undergoing SAVR or TAVR, and do not need to be reported as AE, unless they occur outside of the stated timeframe, are otherwise considered to be an AE according to the treating investigator, or are suspected or confirmed to be device-related.

Table 4. Non-reportable medical occurrences associated with the index implant procedure

Event	Timeframe (hours) from the Index Procedure
Short transient episode of arrhythmia (including ventricular fibrillation) during index procedure	0
Confusion, anxiety and/or disorientation (other than TIA/stroke) starting within 48 hours with or without medical intervention	120 (5 days)
Temporary change in mental status (other than TIA/stroke) not requiring additional medical interventions or new medical assessments (eg, CT)	72
Dizziness and/or lightheadedness with or without treatment	24
Headache with or without treatment	72
Sleep problems or insomnia with or without treatment	120 (5 days)
Mild dyspnea or cough with or without treatment	72
Oxygen supply after extubation/"forced breathing therapy"	48
Diarrhea with or without treatment	48
Obstipation/Constipation with or without treatment	72
Anesthesia-related nausea and/or vomiting with or without treatment	24
Low-grade fever (<101.3°F or <38.5°C) without confirmed infection	48
Low body temperature	6
Pain (eg, back, shoulder) related to laying on the procedure table with or without treatment	72
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 in throat and/or trachea due to intubation	72
Mild to moderate bruising or ecchymosis	168 (7 days)
Atelectasis/Pleural Effusion not requiring punctuation	168 (7 days)
Edema resulting in weight increase up to 4 kg/9lbs from baseline	168 (7 days)

For all observed AEs, investigators should assess and document the following information on the Adverse Event eCRF:

- Date of onset or first observation
- AE code number
- Description of the event
- Seriousness of the event
- Causal relationship of the event to the TAV or surgical valve
- Causal relationship of the event to the EnVeo R DCS and/or LS
- Causal relationship of the event to the EnVeo PRO DCS and/or LS
- Causal relationship of the event to the SAVR or TAVR implant procedure
- Treatment required
- Outcome or status of the event
- Date of resolution

For all deaths, investigators should assess and document the following information on the Death and Adverse Event eCRF

- Date of death
- Primary death category
- Causal relationship of the event to the TAV or surgical valve
- Causal relationship of the event to the EnVeo R DCS and/orLS
- Causal relationship of the event to the EnVeo PRO DCS and/or LS
- Causal relationship of the event to the implant procedure

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.

Definitions of safety endpoints, the AE code list, and guidelines for accessing causal relationships are provided in APPENDIX V: DEFINITIONS: SAFETY ENDPOINTS AND EFFICACY EVENTS.

3.3.26.3 Anticipated Adverse Events

Adverse events that are anticipated for subjects participating in this trial are described in Section 4.2, Risks.

3.3.26.4 Adverse Event Reporting Requirements for Clinical Sites

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 5 or local requirements, whichever is more stringent.

Table 5. 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 a SADE	Immediately, but no later than 72 hours of the investigator's/site's first knowledge of the event
Additional event types	**Additional Time Frame for Reporting**
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
Significant Safety Issue (SSI) (Australia ONLY)	No later than 72 hours of the investigator's/site's first knowledge of the event
Urgent Safety Measure (USM) (Australia ONLY)	Immediatley, but no later than 24 hours of the investigator's/site's first knowledge of the event

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

The Sponsor is obligated to report adverse events and device deficiencies that occur during this trial to the Regulatory Authorities and IRB/EC as per local requirements. The applicable timeframes are described in the Safety Plan associated with this trial.

3.3.26.5 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 as soon as possible but no later than 72 hours after the investigator first learns of the event.

3.3.26.6 Emergency Contact Details for Reporting SAE, SADE, UADE, and Device Deficiencies

Investigators should contact their Medtronic clinical trial monitor if they have any questions regarding reportable AEs. Medtronic will provide and maintain a listing of current contact details for each site.

3.3.27 Clinical Events Committee

A Clinical Events Committee (CEC) will provide independent medical review and adjudication of adverse event data used in the safety assessment of the investigational device. The CEC will adjudicate all deaths and safety endpoint-related adverse events reported by the investigators. The CEC will follow the recommendations of VARC II[49] for classifying adverse events that relate to clinical safety endpoints. The analysis of the trial safety data will be based on CEC adjudicated events. Safety endpoint definitions are provided in APPENDIX V: DEFINITIONS: SAFETY ENDPOINTS AND EFFICACY EVENTS.

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

- Cardiac surgery
- Interventional cardiology
- Neurology
- Electrophysiology

A CEC charter will be developed and approved by Medtronic prior to the first subject enrollment.

3.3.28 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will assess interim trial data and provide recommendations to Medtronic regarding trial conduct, should they identify any issues that may affect the safety of the trial subjects. DSMB members will be free from bias towards the trial and will be independent from both the study and investigators and Medtronic. The DSMB will consist of a minimum of 3 members:

1) a cardiologist with expertise in the management of aortic stenosis
2) a cardiothoracic surgeon with expertise in aortic valve replacement
3) a statistician

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

The DSMB will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for safety data review, chairman appointment, and guidelines for trial recommendations. The DSMB will meet on a periodic basis to perform a comprehensive data review, including at a minimum, all SAEs and deaths, and will meet more frequently when needed. Safety-related endpoints may also be

reviewed at these meetings. DSMB meetings may consist of both open and closed sessions. Medtronic personnel may facilitate the DSMB meeting but will not have voting privileges.

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

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

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.

3.3.29 Role of Sponsor Representatives

Representatives from Medtronic will provide confirmation of anatomical criteria prior to implant of each subject. In addition, representatives from Medtronic may provide technical support during the implant procedures to the implanting physicians and trial site staff relative to the use of the investigational devices.

3.3.30 Data and Quality Management Procedures

3.3.30.1 Data Collection

Trial sites will assign a unique ID number to each subject. Records of the subject/subject ID relationship will be maintained by the trial site. Individual subject medical information obtained as a result of this trial will be considered confidential.

This trial will utilize an Oracle Clinical Remote Data Capture (RDC) system that is the property of Medtronic. Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as indicated on the Delegation Task List (DTL). Trial personnel delegated for eCRF completion and/or approval per the DTL will be trained on the use of the RDC system and thereafter provided with a user name and password to access the system. The eCRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the trial. The investigator (or approved sub-investigator) will electronically sign the appropriate pages of each eCRF.

Data from the core lab will be entered into the Oracle Clinical RDC system by core lab personnel per their procedures established for the trial. The core lab cardiologist will approve core lab eCRFs.

The Oracle Clinical RDC system maintains an audit trail of entries, changes, and corrections in eCRFs. If a person only authorized to complete eCRFs makes changes to an already signed eCRF, the investigator shall re-approve this eCRF.

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

No trial document or image should be destroyed without prior written agreement between Medtronic and the investigator. 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 Medtronic.

3.3.30.2 Time Windows for Completion and Submission of eCRFs

The Device Use Notification eCRF should be completed as soon as possible after device use. All other eCRFs should be completed and approved within 2 weeks of the applicable follow-up visit.

3.3.30.3 Data Review and Processing

Medtronic will be responsible for the processing and quality control of the data. Data review, database cleaning and issuing and resolving data queries will be done according to Medtronic internal SOPs and the Data Management Plan for this trial. The trial database will be developed and validated per the Data Management Plan for this trial, and will employ validation programs (eg, range and logic checks) on entered data to identify possible data entry errors and to facilitate data validation. The trial database will maintain an audit trail of all changes made to the eCRFs.

3.3.30.4 Source Documents

Entered data must be traceable to source documents. Source documentation is defined as the first time the data appear and may include all clinical records, hospital records, procedural reports, autopsy reports, and any other material that contains original information used for trial data collection or adverse event reporting. Identified descrepancies between source documents and the eCRFs will be resolved through the on-line query resolution process per the Data Management plan.

The eCRFs may not serve as source documents. Source documentation for data elements not routinely captured in medical records (eg, echocardiography variables, MDCT variables, cath and surgical procedural data variables, local heart team assessment, Modified Rankin Score) may vary from center to center: the site may use technical worksheets if identified as source documents.

Source documents must be retained by the investigational site for a period of two years after trial conclusion (or longer as required by local law) and made available for monitoring or auditing by the sponsor's representative or representatives of the FDA and other applicable regulatory agencies or IRB/EC.

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 investigation site team indicating they are a true reproduction of the original source document.

Copies of source documents will be requested to support event adjudication by the Clinical Events Committee. In Japan, availability of source documentation may be limited due to hospital policies. If a specific source document is not available, necessary information may be transcribed onto the relevant CRF page.

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

3.3.30.5 Subject 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 is to be recorded on all trial documents to link them to the subject's medical records at the site. To maintain confidentiality, the subjects' name or any other personal identifiers should not be recorded on any trial document other than the informed consent form. In the event a subject's name is included for any reason, it will be masked as applicable. In the event of inability to mask the identification (eg, digital media), it will be handled in a confidential manner by the authorized personnel.

3.3.31 Records and Reports

3.3.31.1 Responsibilities of the Investigator

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

- All essential correspondence that pertains to the investigation
- Device use/disposition records
- Records of each subject's case history and exposure to the device. Case histories include the eCRFs and supporting data (source documentation), including, for example:
  - Signed and dated consent forms
  - Medical records, including, for example, progress notes of the physicians, the subject's hospital chart(s) and the nurses' notes
  - All adverse event/device deficiency information
  - A record of the exposure of each subject to the investigational device (eg, 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, Patient Information/Informed Consent Form, Investigator Brochure, and any amendments
- Insurance certificate, where applicable
- IRB/EC Approval documentation and voting list
- 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
- Records indicating of adequacy of echocardiography 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 6,

Table 7, Table 8, and Table 9 for their respective geographies. 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. Requirements for reporting Adverse Events to Medtronic are described in Table 5.

Table 6. Investigator records and reporting responsibilities applicable to the United States

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

Table 7. 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)
Trial 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 trial completion or termination of the investigation or the investigator's part of the investigation. *(Medtronic Requirement)*

Table 8. 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)*
Trial 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 trial completion or termination of the investigation or the investigator's part of the investigation. (*Medtronic Requirement)*

Table 9. Investigator reports applicable to Australia and New Zealand

Events to Report	Reporting Requirement and Timeframe	Submit to
All SAEs and DDs with potential SADE	Without unjustified delay. All SAEs should be reported immediately to the sponsor except those that the protocol or other document (eg, IB) identifies as not requiring immediate reporting. The immediate reports should be followed promptly by detailed, written reports. *(5.17.3 NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 part 2 section C.2 and other applicable local laws and regulations)*	Sponsor
USADE	Report to their institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event. *(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 part 2 section C.2.g)*	HREC, Institution
Significant Safety Issues	• Urgent Safety Measure (USMs): Within 24 hours *(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 part 2 section C.2.c)* • All other significant safety issues: without undue delay and no later than 72 hours of the principal investigator becoming aware of the event *(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 part 2 section C.2.g)*	Sponsor HREC, Institution
Death	For reported deaths, the investigator should supply the sponsor and the HREC with any additional requested information (e.g., autopsy reports and terminal medical reports). *(According to applicable local laws and regulations)*	Sponsor/HREC

3.3.31.2 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, 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 10, Table 11, Table 13, and Table 14.

Table 10: Sponsor records and reporting responsibilities applicable to the 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))*
Trial 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 11: Sponsor records and reporting responsibilities applicable to 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)
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 (per local reporting requirements/regulations)	This will be submitted to the MEC and/or Regulatory Authority only if required.
Final Report	CA, Investigators, MEC, and Regulatory Authority (per local reporting requirements/regulations)	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)
Trial 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 12: Sponsor records and reporting responsibilities applicable to Europe (continued)

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 13: Sponsor records and reporting responsibilities applicable to Canada

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

Table 13. Sponsor records and reporting responsibilities applicable to Canada (continued)

Report	Submit To	Description/Constraints
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)
Trial deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators quarterly. (ISO 14155:2011)
Significant new information	Ethics Board and Health Canada	Ensure that the Ethics Boards and Regulatory Authorities are informed of significant new information about the clinical investigation (ISO 14155:2011)

Table 14. Sponsor reports applicable to Australia and New Zealand

Events to Report	Submit to	Reporting Requirement and Timeframe
Fatal or life-threatening Australian USADEs	TGA	No later than 7 calendar days after being made aware of the case with any follow up information within a further 8 calendar days. *(ARGMD, v1.1, May 2011, Access to unapproved therapeutic goods- clinical studies in Australia October 2004, NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 part 2 section C.1.f and other applicable local laws and regulations)*
Other Australian USADEs	TGA	No later than 15 calendar days after being made aware of the case. *(ARGMD, v1.1, May 2011, Access to unapproved therapeutic goods- clinical studies in Australia October2004, NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 part 2section C.1.f and other applicable local laws and regulations)*
Significant Safety Issue	TGA	Urgent Safety Measure (USMs): Without undue delay and no later than 72 hours of the measure being taken. Reasons for the urgent safety measure, Measures taken, Further actions planned Contact the TGA within 24 hours of the measure being taken. Other significant safety measures: Without undue delay and no later than 15 calendar days of the sponsor being aware of the issue. Details of significant safety issue, Further actions planned Temporary halt of a trial for safety reasons: Without undue delay and no later than 15 calendar days of the sponsor's decision to halt the trial. Reasons for the halt, The scope of the halt, Measures taken, Further actions planned Early termination of a trial for safety reasons: Without undue delay and no later than 15 calendar days of the sponsor's decision to termination the trial. Reasons for the termination, Measures taken, Further actions planned *(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 part 2 section C.1.k)*
Other New information	TGA	Rapidly communicate information that has an important bearing on the benefit-risk assessment of the investigational product or that would be sufficient to consider changes to the overall conduct of the clinical study. Such information may arise as a result of the sponsor's monitoring of the study, including an internal statistical analysis of data. *(Access to unapproved therapeutic goods- clinical studies in Australia October 2004, and other applicable local laws and regulations)*

Table 15. Sponsor reports applicable to Australia and New Zealand (continued)

Significant safety issue	Any Australian Investigator and HREC	Urgent Safety Measure (USMs): Without undue delay and no later than 72 hours of the measure being taken. Reasons for the urgent safety measure, Measures taken, Further actions planned Other significant safety measures: Without undue delay and no later than 15 calendar days of the sponsor being aware of the issue. Details of significant safety issue, Further actions planned Temporary halt of a trial for safety reasons: Without undue delay and no later than 15 calendar days of the sponsor's decision to halt the trial. Reasons for the halt, The scope of the halt, Measures taken, Further actions planned Early termination of a trial for safety reasons: Without undue delay and no later than 15 calendar days of the sponsor's decision to termination the trial. Reasons for the termination, Measures taken, Further actions planned *(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 part 2 section C.1.k)*
USADEs for Australia and international / Safety Report / updated IB / approved Product Information	HREC and Investigator	Per EC requirements, but at least annually: Annual safety report including; a summary of the evolving safety profile of the trial, a brief description and analysis of new/relevant findings, implications of safety data to the risk-benefit ratio for the trial, a description of any measures taken or proposed to minimize risks *(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 part 2 section C.1.i)* An updated/addenda of IB, or IFU, if appropriate (eg, in a study for a product approved in Australia or where an IB is no longer maintained). *(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 part 2 section C.1.h)*
Unanticipated Serious Adverse Device Effect (USADE)	Medsafe	The New Zealand sponsor is required to report all fatal or life-threatening suspected unexpected serious adverse reactions occurring in New Zealand trial participants where the treatment is known. Reports must be sent to Medsafe within 7 days of the sponsor receiving an investigator or life-threatening Adverse reactions occurring in a clinical trial participants are considered to be unexpected if they are not outlined in the protocol and investigatorial participants where the trned study end-points (eg, death or hospitalisation). *(Guideline on the Regulation of Therapeutic Products in New Zealand – Part 11- Edition 1.2 section 5.4.2)*
Reporting Other Adverse Events	Medsafe	The New Zealand sponsor is required to hold reports of all (worldwide) USADEs. These reports should not be routinely sent to Medsafe, but must be held in an accessible form and made available to Medsafe on request. *(Guideline on the Regulation of Therapeutic Products in New Zealand – Part 11- Edition 1.2 section 5.4.3)*

Note: When determining whether a USADE has occurred, where the sponsor's causality assessment conflicts with the assessment made by the site investigator, the site investigator's assessment cannot be downgraded by the sponsor (ie, altered from 'related' to 'not related'). In this case, if an investigator's judgment triggers the reporting of a USADE, the opinion of both the investigator and the sponsor should be provided with any report sent to the TGA.

Note: It is the responsibility of the sponsor to provide the investigator with reportable events for HREC reporting purposes.

3.3.31.3 Record Retention

The investigator must retain the Investigator Site File, source documents, and the records listed in Section 3.3.30.1, until informed by Medtronic they no longer need to be retained. At a minimum, the investigator must retain records for at least 2 years (or for 15 years if required by local law) after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least two years have elapsed since the formal discontinuation of clinical development of the investigational devices. The investigator should take measures to prevent accidental or early destruction of the trial related materials.

3.3.31.4 Additional Contact Information

The following contact information will be provided to the clinical site under a separate cover:

- The name, address, and telephone number of the monitor
- The name, title, address, and telephone numbers of the study Co-Principal Invesigators
- The name, title, address, and telephone number of the sponsor's medical expert for the study.

4.0 RISK/BENEFIT ANALYSIS

4.1 Description of Risk Analysis

Medtronic has determined the Medtronic TAVR system to be a significant risk medical device. Therefore, Medtronic is sponsoring this clinical trial to support approvals for an expanded indication for the Medtronic TAVR system to patients with aortic stenosis at low risk for 30-day mortality for SAVR.

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 authorities in Europe, Canada, Australia, New Zealand, and Japan.

Risk Analysis procedures were completed in accordance with ISO 14971:2012, and the results are provided in the Investigators Brochure.

4.2 Risks

As with any TAVR or SAVR procedure, there are risks associated with participation in this trial. However, the risks to a patient for participation in this trial are not materially different than those a patient would incur if they underwent TAVR or SAVR outside of this trial.

TAVR has been associated with serious complications, including death. In addition, complications may occur at varying intervals necessitating re-intervention or surgical replacement of the TAV. Known complications that may result from TAVR include but are not limited to the following:

- Death
- Cardiac arrest
- Coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)
- Urgent surgery (eg, coronary artery bypass, heart valve replacement, valve explant)
- Multi-organ failure
- Heart failure or low cardiac output
- Myocardial infarction
- Cardiogenic stroke
- Respiratory insufficiency or respiratory failure
- Cardiovascular injury (including rupture, perforation, or dissection of vessels, ventricles, myocardium, or valvular structures that may require intervention)
- Perforation of the myocardium or a vessel
- Stroke or other neurological deficits
- Transient ischemic attack
- Permanent disability
- Urgent need for balloon valvuloplasty (note that BAV during implantation is expected)
- Urgent need for Percutaneous Coronary Intervention (PCI)
- Major or minor bleeding that may or may not require transfusion or intervention (including life-threatening or disabling bleeding)
- Respiratory insufficiency or respiratory failure
- Cardiac tamponade
- Ascending aorta trauma
- Disturbances in the electrical system of the heart that may result in the permanent placement of a device (pacemaker)

  - Atrio-ventricular node block
  - Bundle branch block
  - Asystole
- Cardiac arrhythmias
- Thrombosis (including valve thrombosis)
- Valve migration/embolization
- Ancillary device embolization
- Prosthetic valve dysfunction including but not limited to:
  - Fracture
  - Bending (out-of-round configuration) of the valve frame
  - Under-expansion of the valve frame
  - Calcification
  - Pannus
  - Wear, tear, prolapse or retraction in the valve leaflet
  - Poor valve coaptation
  - Suture breaks or disruption
  - Leak
  - Mal-sizing (prosthesis-patient mismatch)
  - Malposition (either too high or too low)
  - Valve regurgitation (paravalvular or transvalvular)
  - Valve stenosis
- Mitral valve regurgitation or injury
- Hypotension or hypertension
- Renal insufficiency or renal failure (including acute kidney injury)
- Allergic reaction to antiplatelet agents, contrast medium, or anesthesia
- Infection (including septicemia or endocarditis)
- Vascular access site or access related complications, including but not limited to:
  - Dissection
  - Perforation
  - Pain
  - Bleeding
  - Hematoma
  - Pseudoaneurysm
  - Irreversible nerve injury
  - Compartment syndrome
  - Arteriovenous fistula
  - Stenosis
- Tissue erosion
- Encephalopathy
- Pulmonary edema
- Pericardial effusion
- Pleural effusion
- Myocardial ischemia
- Peripheral ischemia
- Bowel ischemia
- Heart murmur
- Hemolysis

- Cerebral infarction-asymptomatic
- Non-emergent reoperation
- Inflammation
- Fever
- Syncope
- Dyspnea
- Anemia
- Angina
- Abnormal lab values (including electrolyte imbalance)
- Exposure to radiation through fluoroscopy and angiography
- Delivery catheter malfunction resulting in need for additional re-crossing of the aortic valve and prolonged procedural time.

Each of these complications has the potential to be life-threatening, and some could lead to the need for open heart surgery.

4.3 Measures to Mitigate Risks to Trial Subjects

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

- Implanting physicians will have considerable experience with TAVR
- Study sites will have significant experience with surgical SAVR and TAVR
- Patients will undergo thorough imaging assessment during their pre-implant workup
- Patients will be rigorously followed over the course of the trial
- An independent DSMB will review adverse events and interim results in order to advise Medtronic regarding trial conduct, should safety concerns be identified.

4.4 Benefits

The primary potential benefit to subjects participating in the trial is restored function of their diseased (stenotic) aortic valve. TAVR with the Medtronic TAVR system has been shown to be a safe and effective treatment for patients with symptomatic severe aortic stenosis who are at high risk through extreme risk for operative mortality with SAVR.

4.5 Alternatives

Presently, therapeutic alternatives for patients with the expanded clinical indication targeted for the Medtronic TAVR System include the following:

- Medical therapy
- Balloon aortic valvuloplasty
- Surgical aortic valve replacement
- TAVR with another device

4.6 Results from the Risk Analysis and Justification for the Trial

TAVR is now established as a safe and effective treatment option for patients with symptomatic severe aortic stenosis who are at high or extremely high risk for surgical aortic valve replacement. The Medtronic CoreValve bioprosthesis has been in widespread use since receiving the CE Mark in 2007, and there is now extensive published experience demonstrating the CoreValve system is fulfilling its intended role with a

favorable risk/benefit ratio.[21-24] Rigorous clinical trials have established its safety and effectiveness, with improved mortality and quality of life compared with medical therapy in extreme risk patients,[2] and even superiority to SAVR among high operative risk patients.[4, 25]

A comprehensive protocol of bench and animal testing has indicated the Evolut R system is equivalent to the CoreValve system in terms of structural integrity, hydrodynamic performance, and valve durability. Clinical studies of the Evolut R system have confirmed the safety and efficacy of the Evolut R system to be equivalent to the CoreValve system, with no new clinical risks associated with the use of the resheath/recapture feature. Further, no new Class III risks were identified through Risk Analysis.[60]

This trial is designed to evaluate the safety and effectiveness of the Medtronic TAVR system in patients who are at low predicated risk of mortality at 30 days. Although there are risks to the subjects for participation in the trial, they are anticipated to be similar to the risks of undergoing TAVR or SAVR outside of the trial. The trial endpoints are clinically relevant for the patient population targeted for the indication expansion, and consistent with the trial objectives. Therefore the trial as described is justified.

5.0 DESCRIPTION OF INVESTIGATIONAL DEVICES

5.1 Evolut R System

The Evolut R System is a transcatheter aortic valve implantation system comprised of the following three components:

1. Evolut R Transcatheter Aortic Valve (TAV)
2. EnVeo R Delivery Catheter System (DCS) with EnVeo R InLine Sheath or EnVeo PRO Delivery Catheter System (DCS)
3. EnVeo R Loading System (LS) or EnVeo PRO Loading System (LS)

All of the Evolut R system components are considered investigational in each of the study geographies for the low risk patient population . These components are provided separately for the procedure. All components are provided sterile and are intended for single use only. The Evolut R TAV is loaded into the EnVeo R or EnVeo PRO delivery catheter system using the EnVeo R or EnVeo PRO loading system immediately prior to implantation.

The Evolut R TAV is intended as a permanent implant throughout the patient's life, unless there is clinical indication to replace it with another prosthetic valve. The delivery catheter system is in contact with the body only during the device introduction and deployment phase of the implant procedure, typically less than 90 minutes.

The system components and associated model numbers for the clinical trial are shown in Table 15. A detailed description of the system components is provided in Sections 5.1.1 through 5.1.5.

Table 16. Evolut R System Components

Component	US Model Number	OUS Model Number	ANZ Model Number	TAV Size (mm)	Aortic Annulus Diameter (mm)
Evolut R TAV	EvolutR-23-C	EVOLUTR-23	EVOLUTR-23	23	18 – 20
	EvolutR-26-C	EVOLUTR-26	EVOLUTR-26	26	20 – 23
	EvolutR-29-C	EVOLUTR-29	EVOLUTR-29	29	23 – 26
	EvolutR-34-C	EVOLUTR-34	EVOLUTR-34	34	26 – 30
EnVeo R Catheter Delivery System with EnVeo InLine Sheath (18 Fr)	EnVeoR-L-C	ENVEOR-L-GC	ENVEOR-L	23, 26, and 29	Not applicable
EnVeo R Catheter Delivery System with EnVeo InLine Sheath (20 Fr)	EnVeoR-N-C	ENVEOR-N-GC	ENVEOR-N	34	Not applicable
EnVeo PRO Catheter Delivery System (14eFr)[i]	ENVPRO-14-C	Not applicable	Not applicable	23,26, and 29	Not applicable
EnVeo PRO Catheter Delivery System (16eFr)[i]	ENVPRO-16-C	Not applicable	Not applicable	34	Not applicable
EnVeo R Loading System	LS-EnVeoR-23-C	LS-ENVEOR-23-GC	LS-ENVEOR-23	23	Not applicable
EnVeo R Loading System	LS-EnVeoR2629-C	LS-ENVEOR2629GC	LS-ENVEOR-2629	26 and 29	Not applicable
EnVeo R Loading System	LS-EnVeoR-34-C	LS-ENVEOR-34-GC	LS-ENVEOR-34	34	Not applicable
EnVeo PRO Loading System (14eFr) [i]	LS-ENVPRO-14-C	Not applicable	Not applicable	23,26, and 29	Not applicable
EnVeo PRO Loading System (16eFr) [i]	LS-ENVPRO-16-C	Not applicable	Not applicable	34	Not applicable

[i] [i]The EnVeo PRO Delivery Catheter System and EnVeo PRO Loading System are limited to clinical investigation only with sites located in the United States in scope of this Clinical Investigation Plan.

5.1.1 Evolut R TAV

The Evolut R TAV is available in four sizes (23, 26, 29, and 34 mm) for this trial, covering an aortic annulus diameter of 18 to 30 mm. The TAV is comprised of three leaflets and a sealing skirt constructed from gluteraldehyde-fixated porcine pericardium, sewn to a compressible and self-expandable Nitinol support frame (Figure 2A). The TAV is processed with an anti-mineralization treatment of alpha-amino oleic acid (AOA), a compound derived from oleic acid, a naturally occurring long-chain fatty acid.

5.1.2 EnVeo R Catheter Delivery System with EnVeo InLine Sheath

The EnVeo R catheter delivery system facilitates the placement of the TAV within the annulus of the aortic valve (Figure 2B). The catheter assembly is flexible and compatible with a 0.035 in (0.889 mm) guidewire. The distal (deployment) end of the system features an atraumatic, radiopaque catheter tip and a capsule that covers and maintains the bioprosthesis in a crimped position. The capsule includes a distal flare to enable full recapture of the bioprosthesis after partial deployment. A stability layer is fixed at the handle and extends down the outside of the catheter shaft. It provides a barrier between the retractable catheter and the introducer sheath and vessel walls, thus enabling the catheter to retract freely.

The EnVeo R InLine Sheath is assembled over the stability layer, which functions as a hemostatic introducer sheath and minimizes the access site size to the capsule diameter. The EnVeo R InLine Sheath is also compatible with an 18 Fr introducer.

The delivery catheter system consists of a catheter with an integrated handle to provide the user with accurate and controlled deployment. The handle is on the proximal end of the catheter and is used to load, deploy, recapture, and reposition the bioprosthesis. The handle features a gray front grip used to stabilize the system. The blue actuator turns to deploy the bioprosthesis precisely. Arrows on the actuator indicate the direction of rotation required to deploy the bioprosthesis. If desired, the blue actuator can be turned in the opposite direction to recapture the bioprosthesis if the radiopaque capsule marker band has not yet reached the distal end of the spindle. The blue actuator also features a trigger, which can be engaged to make macro adjustments to the capsule position. A blue hand rest connects to the blue actuator. The end of the handle features a tip-retrieval mechanism, which can be used to withdraw the catheter tip to meet the capsule after the device has been fully deployed.

The catheter packaging contains an integrated loading bath and a removable tray with 3 rinsing bowls for loading and rinsing the bioprosthesis. The integrated loading bath features a mirror, which aids in accurate placement of the bioprosthesis frame paddles during loading. In addition, the device packaging is swiveled and secured to facilitate the bioprosthesis loading procedure.

5.1.3 EnVeo PRO Catheter Delivery System

The EnVeo PRO DCS is a single use, intravascular “over the wire” delivery catheter that is sterilized using a validated Ethylene Oxide (EO) sterilization process. The EnVeo PRO DCS is available in two sizes; the EnVeo

PRO 14eFr DCS and EnVeo PRO 16eFr DCS (

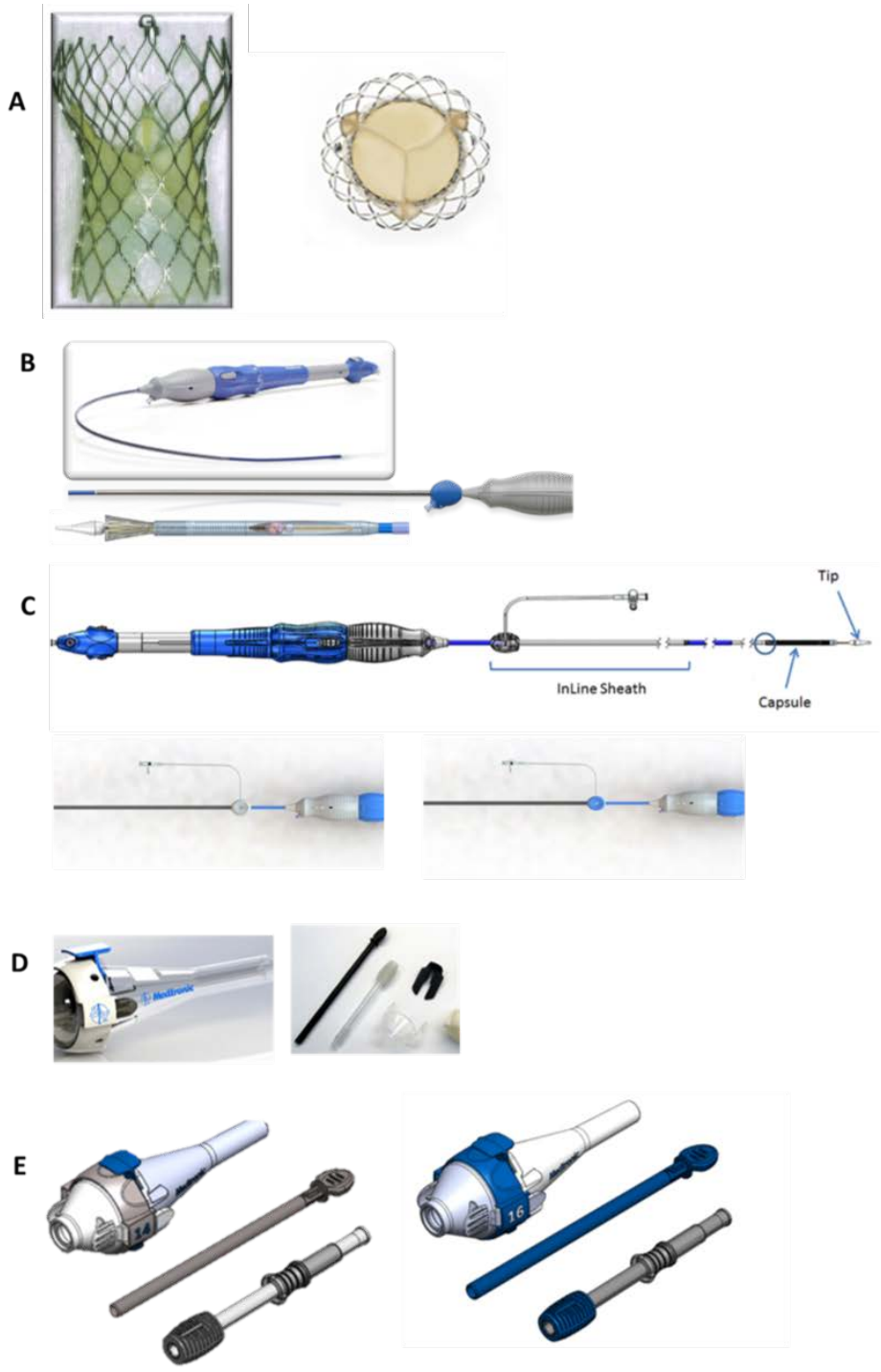
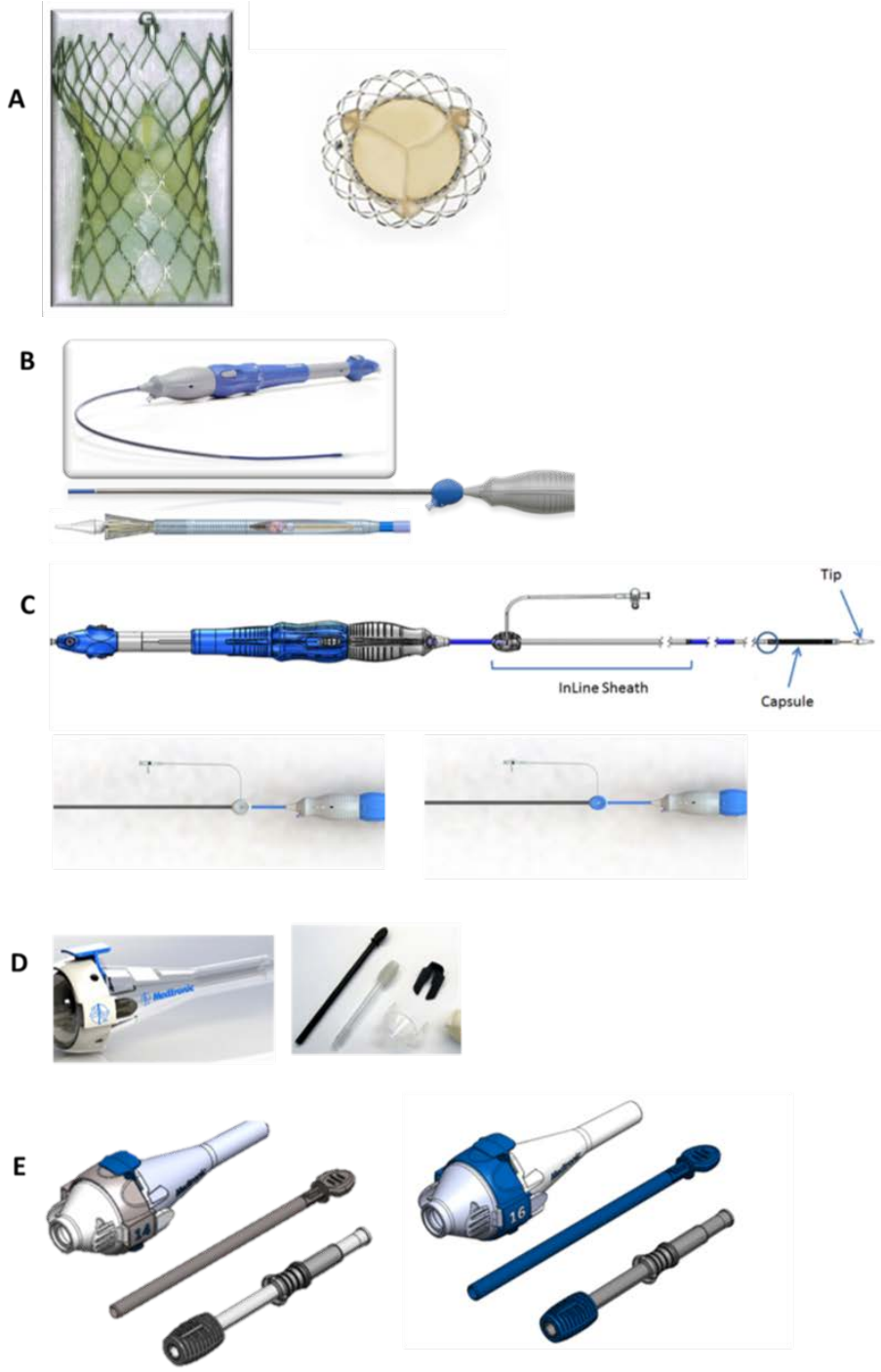


Figure 2C). The EnVeo PRO 14eFr DCS has an 18 Fr crossing profile and is designed to be compatible with commercially available 0.035" intravascular wires and 18 Fr introducers. The EnVeo PRO 16eFr DCS has a 20 Fr crossing profile and is designed to be compatible with commercially available 0.035" intravascular wires and 20 Fr introducers. Changes to the EnVeo PRO DCS include manufacturing process changes to form the capsule frame as a single piece nitinol capsule, introducing the option for either a single piece or two-piece

capsule to be used. Additionally, the distal tip of the DCS required dimensional changes to increase the amount of material on the proximal end of the tip which then decreases the open space between the tip and the distal end of the TAV when encapsulated in the DCS. This minor tip redesign optimizes the bending stiffness of the device as it tracks through the patient anatomy. Furthermore, the snap component of the inline sheath (ILS) hub was updated on the pad printing and color of the sizing nomenclature (14eFr or 16eFr) of the DCS to improve product differentiation.

5.1.4 EnVeo R Loading System

The EnVeo R loading system facilitates manual loading of the TAV into the deployment sheath capsule of the catheter delivery system by gradually reducing the diameter of the bioprosthesis radially to an optimal



diameter (Figure 2D). The manual loading is performed during the procedure prior to implantation. The loading procedure is performed while immersing the loading system, the TAV, and the distal end of the catheter delivery system in cold sterile saline.

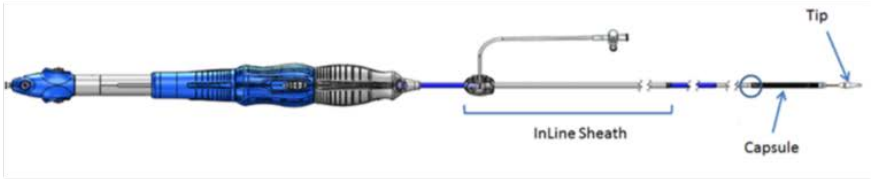
5.1.5 EnVeo PRO Loading System

The EnVeo PRO LS is a system of reduction cones and tubing designed to gradually reduce the diameter of the TAV radially to an optimal diameter to facilitate manual loading of the Evolut R TAV or Evolut PRO TAV into the deployment sheath capsule of the EnVeo R DCS or EnVeo PRO DCS. The EnVEo PRO loading system was modified to consolidate the number of loading systems from five to three (

A

B

C



D

E

Figure 2E). Minor modifications include a change to the capsule guide tube (CGT) to include a locking collar which reduces the ability of the user to load the TAV with a paddle in the incorrect position by preventing movement of the frame paddles once positioned in the spindle pockets. Additionally, there was a more robust manufacturing process and a minor design and material change, including the color differentiation between the two loading system sizes, implemented on the tip guide tube (TGT) components. A third modification is to the inner diameter of the inflow ring designed to allow multiple TAVs to seat securely into the inflow ring.

Note: In the United States, in the event that product delivery timelines (per sponsor process) cannot support supplying investigational labeled Evolut XL system components (TAV, DCS, and LS) in time for a scheduled case and using medical judgment, the site investigator and screening committee determine that the Evolut R 34 mm TAV is the most viable option for the subject, the study subject may receive commercial devices distributed by Medtronic. In this case, no site-specific protocol deviation would be required.

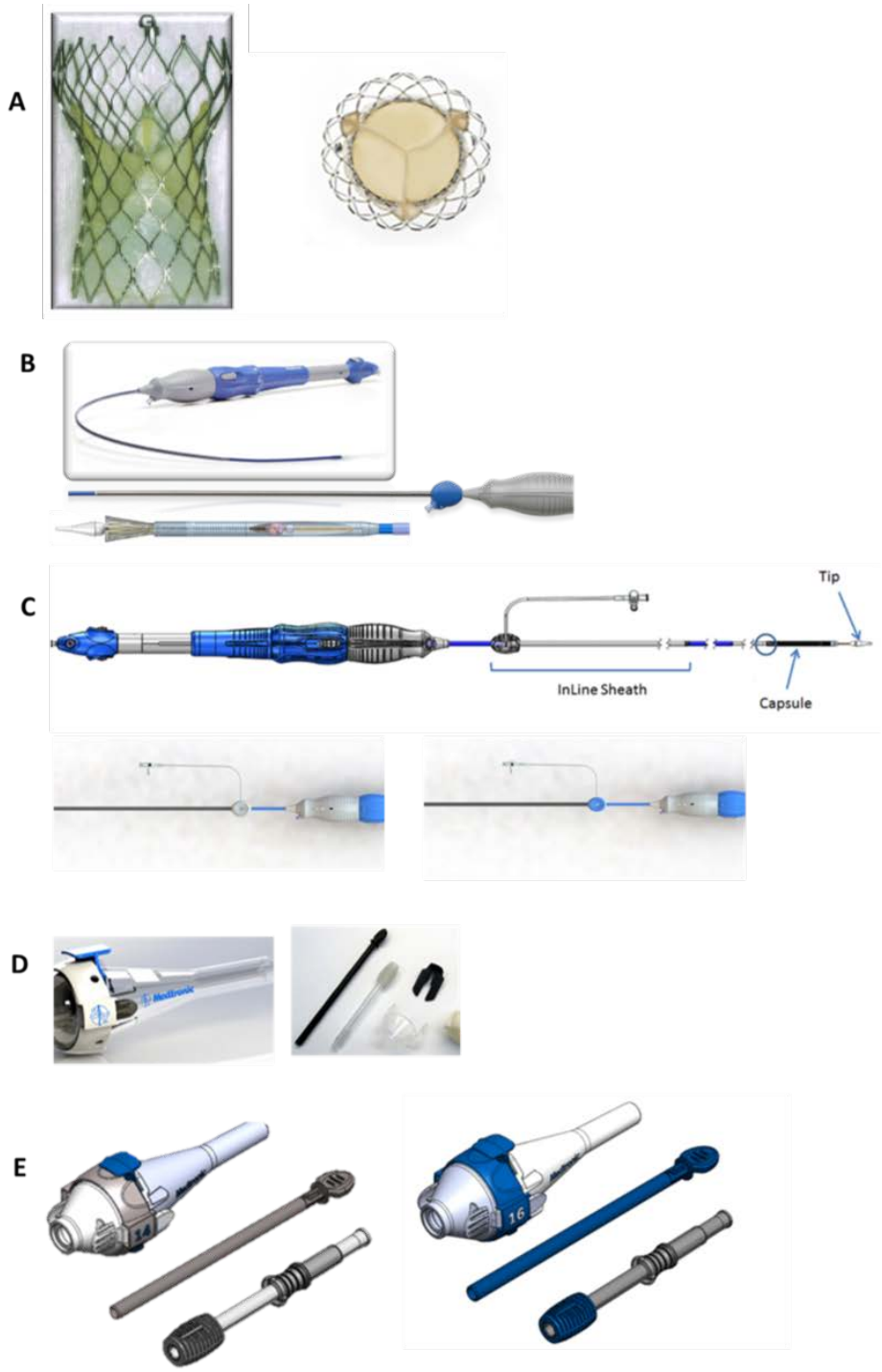


Figure 2 (A) Evolut R TAV **(B)** EnVeo R catheter delivery system and EnVeo R InLine sheath **(C)** EnVeo PRO delivery catheter system **(D)** EnVeo R loading system **(E)** EnVeo PRO loading system

5.2 Medtronic Evolut PRO System

The Medtronic Evolut PRO System (commercially referred to as the Medtronic Evolut PRO System) is a TAVR implantation system comprised of the following three components (Table 16):

1. Medtronic Evolut PRO TAV
2. Medtronic Evolut PRO DCS with InLine Sheath or EnVeo R Delivery Catheter System (DCS) with EnVeo R InLine Sheath or EnVeo PRO Delivery Catheter System (DCS)
3. Medtronic Evolut PRO LS or EnVeo PRO Loading System (LS)

All of the Evolut PRO system components are considered investigational in each of the study geographies for the low risk patient population. The system components for the clinical study are shown in Figure 3 A detailed description of the system components is provided in Sections 5.2.1 through 5.2.6.

Table 16. Evolut PRO System Components

Component	US Model Number	OUS Model Number	ANZ Model Number	Size (mm)	Aortic Annulus Diameter (mm)
Medtronic Evolut PRO TAV	TAV-MDT2-23-C	TAV-MDT2-23-C	EVOLUTPRO-23	23	18 – 20
	TAV-MDT2-26-C	TAV-MDT2-26-C	EVOLUTPRO-26	26	20 – 23
	TAV-MDT2-29-C	TAV-MDT2-29-C	EVOLUTPRO-29	29	23 – 26
Medtronic Evolut PRO DCS with InLine Sheath	DS-MDT2-C	DS-MDT2-GC	ENVEOR-N	23, 26, and 29	Not applicable
EnVeo R Catheter Delivery System with EnVeo InLine Sheath (20 Fr)	EnVeoR-N-C	ENVEOR-N-GC	ENVEOR-N	23, 26, and 29	Not applicable
EnVeo PRO Catheter Delivery System (16eFr)[i]	ENVPRO-16-C	Not applicable	Not applicable	23,26, and 29	Not applicable
Medtronic Evolut PRO LS	LS-MDT2-23-C	LS-MDT2-23-GC	LS-MDT2-23	23	Not applicable
	LS-MDT2-2629-C	LS-MDT2-2629-GC	LS-MDT2-2629	26 and 29	Not applicable
EnVeo PRO Loading System (16eFr)[i]	LS-ENVPRO1623C	Not applicable	Not applicable	23	Not applicable
	LS-ENVPRO-16-C	Not applicable	Not applicable	26 and 29	Not applicable

[i] [i]The EnVeo PRO Delivery Catheter System and EnVeo PRO Loading System are limited to clinical investigation only with sites located in the United States in scope of this Clinical Investigation Plan.

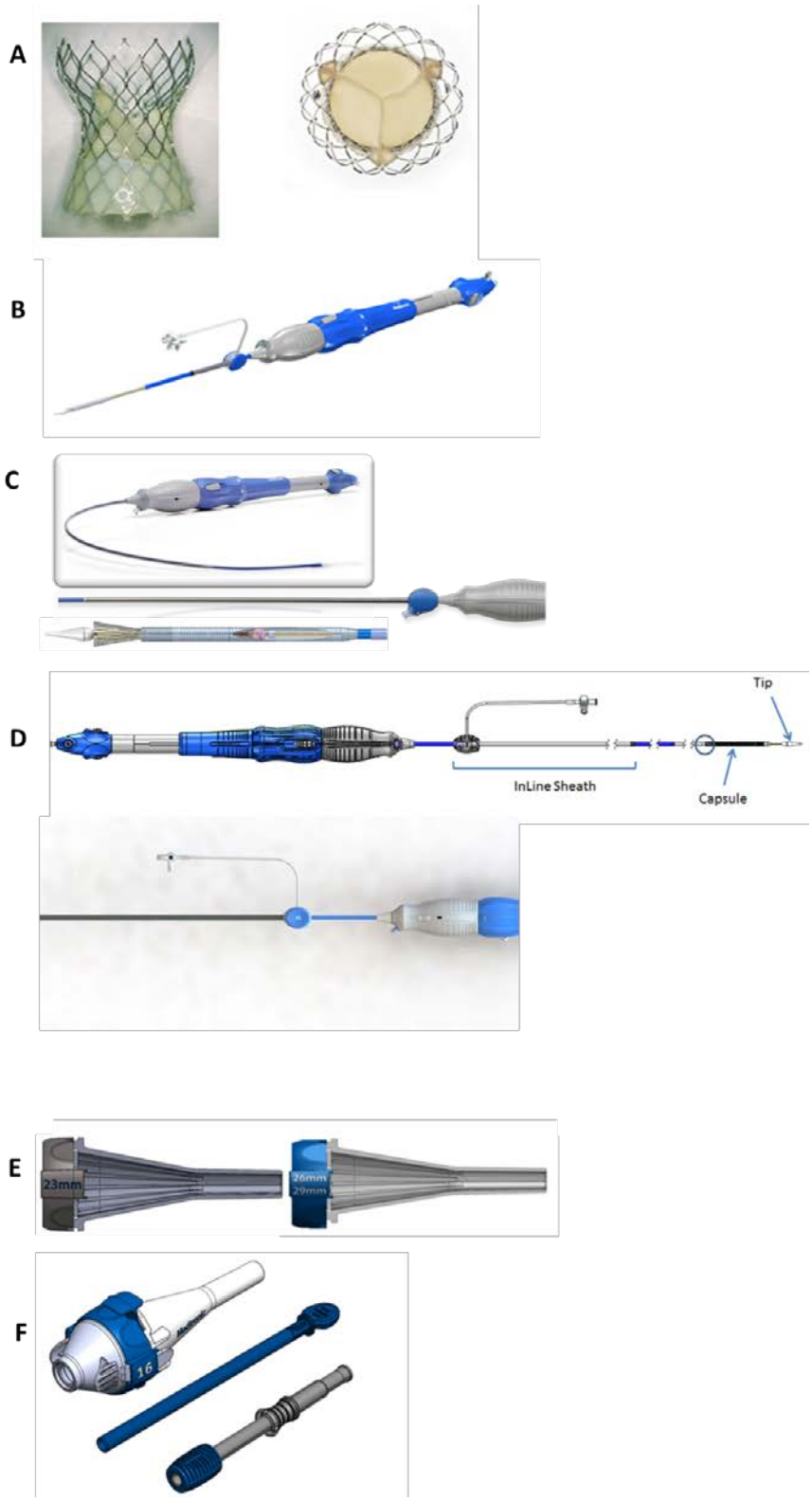


Figure 3. (A) Evolut PRO TAV**; (B)** Evolut PRO DCS and inline sheath; **(C)** EnVeo R catheter delivery system and EnVeo R InLine sheath **(D)** EnVeo PRO delivery catheter system **(E)** Evolut PRO loading system **(F)** EnVeo PRO loading system

5.2.1 Medtronic Evolut PRO Transcatheter Aortic Valve

The Evolut PRO TAV is available in 3 sizes (23, 26, 29 mm), covering an aortic annulus diameter of 18 to 26 mm. If the patient's annulus diameter is within 0.5 mm of the upper or lower bound of the range, use of the larger valve size can be considered, provided additional dimensional criteria as outlined in the CIP are met. The TAV is comprised of 3 leaflets, a sealing skirt, and outer tissue wrap constructed from gluteraldehyde-fixated porcine pericardium, sewn to a compressible and self-expandable Nitinol support frame. The TAV is processed with an anti-mineralization treatment of AOA, a compound derived from oleic acid, a naturally occurring long-chain fatty acid.

5.2.2 Medtronic Evolut PRO Delivery Catheter System

The Evolut PRO DCS facilitates the placement of the TAV within the annulus of the aortic valve. The catheter assembly is flexible and compatible with a 0.035 in (0.889 mm) guidewire. The distal (deployment) end of the system features an atraumatic, radiopaque catheter tip and a capsule that covers and maintains the bioprosthesis in a crimped position. The capsule includes a distal flare to enable full recapture of the bioprosthesis after partial deployment. A stability layer is fixed at the handle and extends down the outside of the catheter shaft. It provides a barrier between the retractable catheter and the introducer sheath and vessel walls, thus enabling the catheter to retract freely.

The InLine Sheath is assembled over the stability layer, which functions as a hemostatic introducer sheath and minimizes the access site size to the capsule diameter. The InLine Sheath for the 23 mm, 26 mm, and 29 mm system is compatible with a 20 Fr introducer.

The DCS consists of a catheter with an integrated handle to provide the user with accurate and controlled deployment. The handle is on the proximal end of the catheter and is used to load, deploy, recapture, and reposition the bioprosthesis. The handle features a gray front grip used to stabilize the system. The blue actuator turns to deploy the bioprosthesis precisely. Arrows on the actuator indicate the direction of rotation required to deploy the bioprosthesis. If desired, the blue actuator can be turned in the opposite direction to recapture the bioprosthesis if the radiopaque capsule marker band has not yet reached the distal end of the spindle. The blue actuator also features a trigger, which can be engaged to make macro adjustments to the capsule position. A blue hand rest connects to the blue actuator. The end of the handle features a tip-retrieval mechanism, which can be used to withdraw the catheter tip to meet the capsule after the device has been fully deployed.

The catheter packaging contains an integrated loading bath and a removable tray with 3 rinsing bowls for loading and rinsing the bioprosthesis. The integrated loading bath features a mirror, which aids in accurate placement of the bioprosthesis frame paddles during loading. In addition, the device packaging is swiveled and secured to facilitate the bioprosthesis loading procedure.

5.2.3 EnVeo R Catheter Delivery System with EnVeo InLine Sheath

The EnVeo R catheter delivery system facilitates the placement of the TAV within the annulus of the aortic valve (Figure 3C). The catheter assembly is flexible and compatible with a 0.035 in (0.889 mm) guidewire. The distal (deployment) end of the system features an atraumatic, radiopaque catheter tip and a capsule that covers and maintains the bioprosthesis in a crimped position. The capsule includes a distal flare to enable full recapture of the bioprosthesis after partial deployment. A stability layer is fixed at the handle

and extends down the outside of the catheter shaft. It provides a barrier between the retractable catheter and the introducer sheath and vessel walls, thus enabling the catheter to retract freely.

The EnVeo R InLine Sheath is assembled over the stability layer, which functions as a hemostatic introducer sheath and minimizes the access site size to the capsule diameter. The EnVeo R InLine Sheath is also compatible with an 18 Fr introducer.

The delivery catheter system consists of a catheter with an integrated handle to provide the user with accurate and controlled deployment. The handle is on the proximal end of the catheter and is used to load, deploy, recapture, and reposition the bioprosthesis. The handle features a gray front grip used to stabilize the system. The blue actuator turns to deploy the bioprosthesis precisely. Arrows on the actuator indicate the direction of rotation required to deploy the bioprosthesis. If desired, the blue actuator can be turned in the opposite direction to recapture the bioprosthesis if the radiopaque capsule marker band has not yet reached the distal end of the spindle. The blue actuator also features a trigger, which can be engaged to make macro adjustments to the capsule position. A blue hand rest connects to the blue actuator. The end of the handle features a tip-retrieval mechanism, which can be used to withdraw the catheter tip to meet the capsule after the device has been fully deployed.

The catheter packaging contains an integrated loading bath and a removable tray with 3 rinsing bowls for loading and rinsing the bioprosthesis. The integrated loading bath features a mirror, which aids in accurate placement of the bioprosthesis frame paddles during loading. In addition, the device packaging is swiveled and secured to facilitate the bioprosthesis loading procedure.

5.2.4 EnVeo PRO Delivery Catheter System

The EnVeo PRO DCS is a single use, intravascular "over the wire" delivery catheter that is sterilized using a validated Ethylene Oxide (EO) sterilization process. The EnVeo PRO DCS is available in two sizes; the EnVeo PRO 14eFr DCS and EnVeo PRO 16eFr DCS. The EnVeo PRO 14eFr DCS has an 18 Fr crossing profile and is designed to be compatible with commercially available 0.035" intravascular wires and 18 Fr introducers. The EnVeo PRO 16eFr DCS has a 20 Fr crossing profile and is designed to be compatible with commercially available 0.035" intravascular wires and 20 Fr introducers. Changes to the EnVeo PRO DCS include manufacturing process changes to form the capsule frame as a single piece nitinol capsule, introducing the option for either a single piece or two-piece capsule to be used. Additionally, the distal tip of the DCS required dimensional changes to increase the amount of material on the proximal end of the tip which then decreases the open space between the tip and the distal end of the TAV when encapsulated in the DCS. This minor tip redesign optimizes the bending stiffness of the device as it tracks through the patient anatomy. Furthermore, the snap component of the inline sheath (ILS) hub was updated on the pad printing and color of the sizing nomenclature (14eFr or 16eFr) of the DCS to improve product differentiation.

5.2.5 Medtronic Evolut PRO Loading System

The Evolut PRO LS facilitates manual loading of the TAV into the deployment sheath capsule of the DCS by gradually reducing the diameter of the bioprosthesis radially to an optimal diameter. The manual loading is performed during the procedure prior to implantation. The loading procedure is performed while immersing the LS, the TAV, and the distal end of the DCS in cold sterile saline.

The Evolut PRO LS was designed with ribs on the interior surface of the cone designed to decrease the friction between the TAV tissue wrap on the inflow cone during loading. There are two loading system models; one for the 23 mm TAV and another for the 26 mm and 29 mm TAV sizes.

5.2.6 EnVeo PRO Loading System

Similar to the EnVeo R LS, the EnVeo PRO LS is a system of reduction cones and tubing designed to gradually reduce the diameter of the TAV radially to an optimal diameter to facilitate manual loading of the Evolut R TAV or Evolut PRO TAV into the deployment sheath capsule of the EnVeo R DCS or EnVeo PRO DCS. The EnVEo PRO loading system was modified to consolidate the number of loading systems from five to three. Minor modifications include a change to the capsule guide tube (CGT) to include a locking collar which reduces the ability of the user to load the TAV with a paddle in the incorrect position by preventing movement of the frame paddles once positioned in the spindle pockets. Additionally, there was a more robust manufacturing process and a minor design and material change, including the color differentiation between the two loading system sizes, implemented on the tip guide tube (TGT) components. A third modification is to the inner diameter of the inflow ring designed to allow multiple TAVs to seat securely into the inflow ring.

5.3 Manufacturer of the Investigational Devices

The manufacturer and design site of the Evolut R and Evolut PRO systems is as follows:
Medtronic CoreValve LLC
1851 E Deere Avenue
Santa Ana, CA 92705
USA

5.4 Comparator Devices

The comparator devices used in the SAVR control arm are any surgical aortic valve bioprostheses (stented or stentless) that are approved for commercial use in both the United States and the geography in which the study center is located. As such, the comparator devices are not investigational in this trial.

6.0 MONITORING AND AUDITING

6.1 Monitoring

Investigational sites will be monitored to ensure compliance with the trial protocol, adherence to applicable regulations, and accuracy of trial data. Monitoring visits will be conducted primarily to ensure the safety and well-being of the subjects is preserved. Monitoring visits will also be used to verify that trial data submitted on case report forms are complete and accurate with respect to the subject clinical records and to verify device accountability. Sites should provide appropriate access to the source data. Site personnel will complete eCRFs following each subject visit. Trial data submitted will be reviewed against subject charts and other sources containing original records of subject data. Source document verification will occur in accordance to a Monitoring Plan.

The progress of the trial will be monitored by:

- On-site review, as deemed appropriate by Medtronic
- Telephone communications between the site personnel (eg, investigator, trial coordinator) and trial monitors
- Review of eCRFs and the associated clinical records
- Review of regulatory documents

Monitoring and monitoring oversight will be provided by Medtronic (8200 Coral Sea St NE, Mounds View, MN 55112). Representatives of Medtronic (ie, contractors and designees) may also act as trial monitors.

Under the Japan GCP Ordinance, the sponsor or a designee will conduct regular monitoring. This monitoring includes one or more pre-study visits prior to enrollment. During interim visits, the monitor will check for compliance of the study with the "3.1.1 Statement(s) of Compliance", and will compare the eCRF with the source data (source data verification). The monitor will also check the device storage/management conditions at appropriate timing.

All monitoring activities shall be documented and include a summary of what the monitor reviewed and the observations with regard to the completion of previous action items, significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure compliance. Additionally, the monitor will confirm periodic testing, calibration and maintenance of equipment used for study assessments according to local standard of practice.

6.2 Auditing

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, independent 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.

6.3 Trial Closure

Upon completion of the trial, 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.

7.0 LABELING

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

The Instructions for Use for the Medtronic TAVR System used in this trial will be provided as a separate document. If changes are made to the labeling, they will be provided under separate cover to the appropriate authorities per local requirements.

8.0 CONSENT MATERIALS

A sample informed consent form for the trial is attached in APPENDIX VI: SAMPLE INFORMED CONSENT FORM.

9.0 INVESTIGATOR BROCHURE AND REPORT OF PRIOR INVESTIGATIONS

An Investigator Brochure for this trial will be provided under separate cover to the relevant sites and regulatory agencies. Medtronic will update the Investigator Brochure in accordance with ISO14155:2011, and provide those updates to sites and regulatory agencies. For geographies under ISO14155:2011, documentation of receipt of the Investigator Brochure by each site's Ethics Board is required for all versions of the Investigator Brochure. Report of Prior Investigations requirements (21 CFR 812.27) are included in the Investigator Brochure.

10.0 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE INFORMATION

Information on each participating Institutional Review Board/Ethics Committee will be maintained in a separate document. A definitive list of all participating IRB/ECs will be maintained and provided in clinical reports.

11.0 OTHER INSTITUTIONS AND PROFESSIONAL SERVICES

This trial will utilize an Echo Core Lab, an MDCT Core Lab, an Explant Pathology Core Lab, a Clinical Events Committee, and a Data Safety Monitoring Board. Information and contact details for each of these parties will be maintained in a separate document and provided to the study sites. A definitive list of all participating parties will be provided in clinical reports. In addition, a list of the names and addresses of participating institutions will maintained and provided to the sites.

12.0 PUBLICATION POLICY

Medtronic is committed to the widespread dissemination of all primary and secondary endpoint results. A Publication Plan will be implemented and followed. At the conclusion of the trial, a multisite abstract reporting the primary results will be prepared by the Principal Investigators (in collaboration with others including but not limited to the echo core lab physicians, and the CEC/DSMB). 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 participating investigators, CEC/DSMB committee members, and core laboratory personnel will be solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications regarding the primary endpoint and secondary endpoints from the trial requires approval by the Principal Investigators after review by the Publications Committee.

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

13.0 SPONSOR TRIAL PERSONNEL

A list of sponsor personnel (including monitors, safety representatives, and the medical expert) and their contact details will be maintained in a separate document and provided to the trial centers.

14.0 INSURANCE/SUBJECT INDEMNIFICATION

Medtronic (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 IRB/EC if required.

APPENDIX I: ECHOCARDIOGRAPHY PROCEDURES

1.0 Required Exams

Transthoracic echocardiography is required at the following intervals:

Interval	Time Window
Baseline (Pre-implant)	Within 12 weeks prior to submission to Screening Committee
Device Success	Between 18 hours and 7 days post-procedure
30 days	Between 30 and 45 days post procedure
6 months	Between 183 and 213 days post procedure
1 year	Between 365 and 395 days post procedure
2 Year	Between 730 and 760 days post procedure
3, 4, 5, 7 and 10 years	Between implant anniversary date and +/-60 days after

2.0 General Imaging and Recording Procedures

- A list of recommended images is provided in Section 2.1, List of Recommended Images.
- The subject's ID number and exam interval should be annotated on the image.
- A simultaneous ECG with a clearly defined R-wave should be displayed on all clips.
- Digital cine clips should be a minimum of two cardiac cycles in length (preferably three cycles)
- Color Doppler images should be obtained at a minimum frame rate of 20 Hz through optimization of sector width and depth settings.
- Still frames of measured variables (eg, LVOT diameter, velocities) should be captured. In addition, still frames of spectral Doppler tracings without the measurements should be captured to facilitate analysis by the Echo Core Lab. Still frames of spectral Doppler tracings should contain a minimum of 3 cardiac cycles for subjects in sinus rhythm, and a minimum of 5 cardiac cycles for subjects in atrial fibrillation (two sequential frames per variable may be necessary).
- Spectral Doppler waveforms should be recorded at a minimum sweep speed of 50 mm/sec.
- Echocardiograms should be recorded and archived on a DICOM digital format for transmission to the Echo Core Lab.
- Exams will be transmitted to the Echo Core Lab via compact disc (CD-R) or Web-based picture archiving and communication system. Details of the image transmission process for each site will be established during site initiation process.
- Exams sent to the Echo Core Lab via CD-R should be DICOM files in a true or pure DICOM format.
- The following information should be documented on any CD-R disks sent to the Echo Core Lab:
  - Trial site ID number
  - Subject ID number
  - Exam date
  - Trial interval

2.1 List of Recommended Images

Parasternal long-axis window

1. 2D gray scale standard view (LV in a sagittal section)
2. 2D color Doppler for mitral regurgitation (MR)
3. 2D color Doppler of aortic (native or prosthetic) regurgitation (AR)
4. If AR is present, ZOOM & narrow sector with focus on vena contracta of regurgitant jet
5. 2D gray scale ZOOM for LV outflow tract diameter (LVOT)
6. Frozen image of measured LVOT diameter
7. 2D gray scale; ZOOM at an intercostal space higher for aortic root/aortic prosthesis

Parasternal short-axis window

8. 2D grayscale LV at mitral valve level
9. 2D grayscale LV at papillary muscle level
10. Frozen image of measured LV dimensions (without measurements)
11. 2D grayscale LV at apical level
12. 2D grayscale aortic valve level
13. 2D color Doppler of AR: post-implant start scanning from highest position and record first visible AR jet, scan more downwards and look for additional jets – confirm origin of AR jets from PLAX

Parasternal long-axis view (RV inflow)

14. 2D color Doppler of tricuspid regurgitation (TR)
15. If TR is present, CW Doppler of TR jet (frozen image without measurements)
16. Frozen image of TR jet velocity with measurements

Apical 4-Chamber window

17. 2D grayscale standard view
18. 2D color Doppler of MR
19. If MR is present, ZOOM & narrow sector
20. If MR is present, CW Doppler of MR jet (frozen image)
21. 2D color Doppler of TR
22. If TR is present, CW Doppler of TR jet (frozen image without measurement)
23. Frozen image of TR jet velocity with measurements
24. 2D grayscale focussed on LV with decreased depth
25. PW Doppler of transmitral flow at mitral valve tips (frozen image)
26. Tissue Doppler of the septal mitral annulus (frozen image)
27. Tissue Doppler of the lateral mitral annulus (frozen image)

Apical long–axis view

28. 2D grayscale standard view
29. 2D color Doppler of AR
30. If AR is present, ZOOM & narrow sector, shift Nyquist 35-40 for PISA measurements
31. If AR is present, CW Doppler of AR jet (frozen image without measurement)
32. Frozen image of CW Doppler of AR jet (with measurements)
33. CW Doppler of aortic/prosthetic valve (frozen image without measurement)
34. Frozen image of measured aortic/prosthetic valve velocity

35. PW Doppler LVOT (native aortic valve): within 0.5 – 1 cm below native aortic valve (frozen image without measurements
36. PW Doppler LVOT (post –implant) immediately proximal to inflow of stent or valve (frozen image without measurements)
37. Frozen image: measured LVOT velocity

Apical 2-Chamber view

38. 2D grayscale standard view
39. 2D grayscale focused on LV with decreased depth

Sub-costal Position

40. 2D grayscale; long-axis view
41. 2D grayscale; short-axis view
42. 2D grayscale: IVC and hepatic vein
43. If TR moderate by color Doppler, PW Doppler of hepatic vein (frozen image)
44. IF AR mild by color Doppler, PW Doppler from descending aorta (frozen image)

Supra-Sternal Position

45. CW Doppler of aortic valve velocity non-imaging probe (frozen image without measurements)
46. Frozen image: measured aortic valve velocity
47. If AR mild by color Doppler, PW Doppler from descending aorta (frozen image)

Right Parasternal Position

48. CW Doppler of aortic valve velocity; non-imaging probe (frozen image without measurements)
49. Frozen image: measured aortic valve velocity

Results Reporting

50. Screen prints of all results pages

3.0 Data Requirements

Sites should obtain the appropriate images and Doppler recordings in order for the Echo Core Lab to assess and report the variables listed below. Procedures for acquiring key variables are described in Section 4, Acquisition of Key Variables.

- Height (cm) and Weight (kg)
- Heart rate
- Left ventricular outflow tract (LVOT) diameter in mid systole
- Max aortic/prosthetic valve velocity (V_2) by CW Doppler
- Aortic valve velocity time integral (VTI) by CW Doppler
- Mean gradient across aortic valve (MGV_2) by CW Doppler
- LVOT VTI by PW Doppler
- Grade of aortic/prosthetic transvalvular regurgitation (post-implant only)
- Grade of aortic/prosthetic paravalvular regurgitation (post-implant only)
- Grade of prosthetic total (transvalvular plus paravalvular) regurgitation (post-implant only)
- Grade of mitral regurgitation
- Grade of tricuspid regurgitation
- Max tricuspid regurgitant (TR) jet velocity (if TR is present)
- Left ventricular internal dimension at end diastole
- Left ventricular internal dimension at end systole
- Interventricular septal thickness at end diastole
- Left ventricular posterior wall thickness at end diastole
- Left atrial diameter (anterior-posterior linear dimension) at systole
- Left ventricular ejection fraction by visual estimate
- Grade of diastolic dysfunction (if present)

In addition, the following variables will be derived by the central database from the appropriate measurements reported on the site eCRF.

- Body surface area (Dubois and Dubois)[55]
- Peak aortic pressure gradient
- Aortic valve area (AVA)/effective orifice area (EOA) by continuity equation
- Aortic valve area/effective orifice area index (EOAI)
- Doppler Velocity Index
- Estimated right ventricular systolic pressure (RVSP)

Derived variables will be displayed on the eCRF upon entry of the appropriate raw measurements. The pre-implant qualifying AVA must be based on the site reported variables for LVOT diameter, LVOT VTI, aortic valve VTI, height, and weight.

4.0 Acquisition of Key Variables

4.1 LVOT Diameter

Pre-implant LVOT diameter is measured from the inner edge to inner edge of the septal endocardium, and the anterior mitral leaflet in mid-systole (Figure A and B).[61, 62.] Following implantation of the TAV, LVOT diameter is measured from the parasternal long-axis view, immediately proximal to the inflow aspect of the stent, and in mid systole (Figure C and D).[61-63] Post surgical valve implantation, LVOT diameter is measured from the junction of the anterior sewing ring and the ventricular septum to the junction of the sewing ring and the anterior mitral valve leaflet (Figure 4E and F).[61]

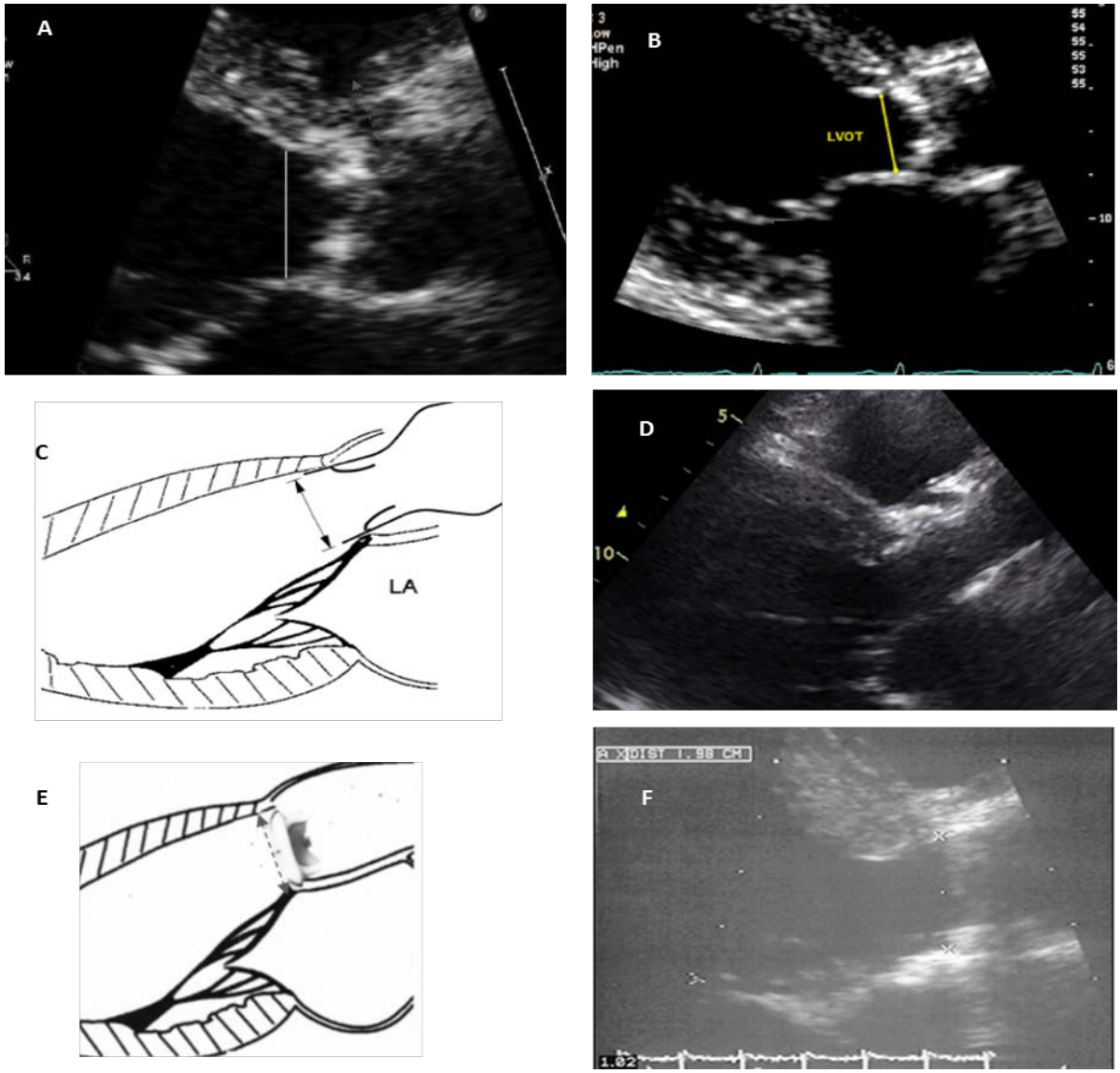


Figure 4. (A) and **(B)** Examples of measurement of pre-implant LVOT diameter. LVOT diameter is measured from the white-black interface of the septal endocardium to the anterior mitral leaflet, parallel to the aortic valve plane, approximately 0.5 cm below the level of the aortic annulus, and in mid systole **(C)** and **(D)** Post TAV implantation, LVOT diameter measurement is from outer edge to outer edge of the inflow aspect of the stent **(E)** and **(F)** post surgical valve implantation, LVOT diameter is measured from the junction of the anterior sewing ring and the ventricular septum to the junction of the sewing ring and the anterior mitral valve leaflet.

4.2 LVOT Velocity

LVOT velocity is recorded with PW Doppler from the apical position, in either the apical long-axis view or in the anteriorly angulated four-chamber view (or "5-chamber view"). For pre-implant exams, the PW sample volume should be positioned just proximal to the aortic valve, with care to avoid the zone of pre-valve acceleration (usually 0.5 to 1.0 cm proximal to the cusps, Figure A).[61]

Post TAV implantation, the sample volume should be placed proximal to the inflow aspect of the stent.[64] Full-screen imaging of the TAV should be used to verify positioning of the sample volume below the stent before switching to spectral Doppler mode (Figure C and D).[64, 65] Post surgical valve implantation, the sample volume should be placed proximal to the inflow aspect of the sewing ring.

The LVOT VTI is measured by tracing the modal velocity (middle of the dense signal) for use in the continuity equation.[61]

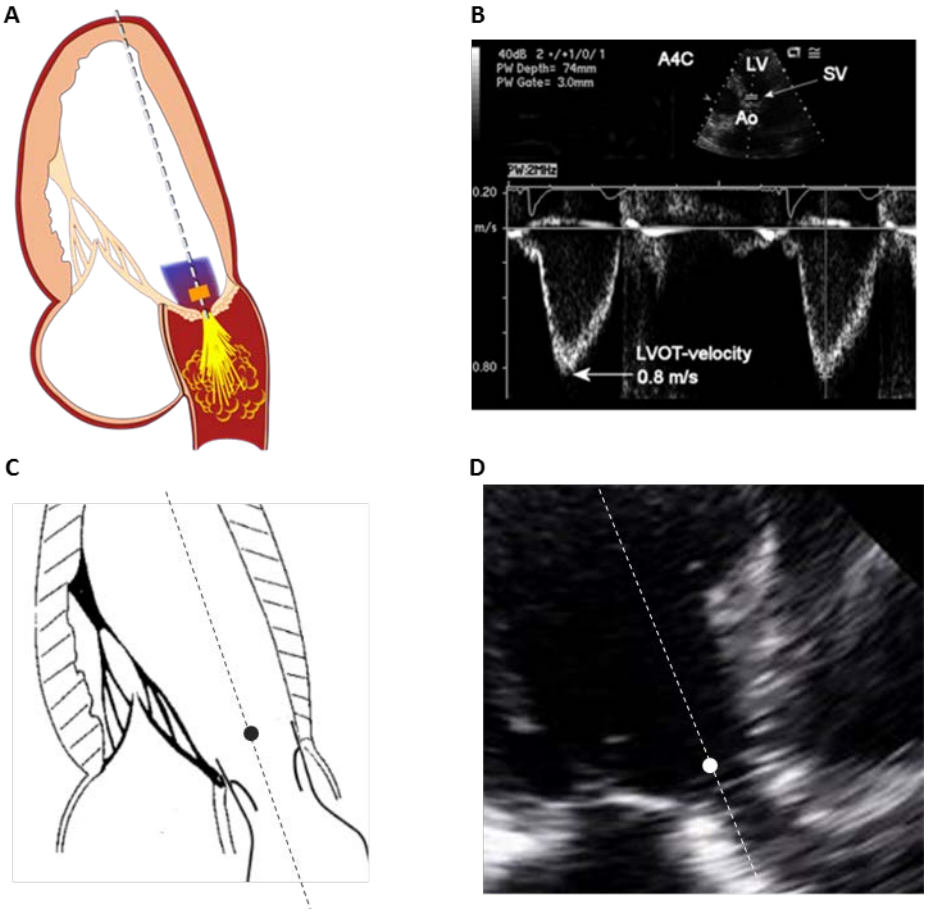


Figure 5 (A) Sample volume placement just proximal to zone of pre-valve acceleration (*illustration by Mayo Clinic, used with permission)* **(B)** Optimal LVOT velocity signal showing a smooth spectral Doppler recording with a narrow velocity range at each time point **(C)** Illustration showing correct sample volume placement just proximal to inflow of TAV stent **(D)** Full-screen imaging of stent to ensure positioning of sample volume below the TAV stent.

4.3 Aortic Valve Velocities

Aortic valve velocity should be interrogated with CW Doppler from a minimum of 2 transducer positions (apical and either a parasternal or suprasternal position). The position that provides the highest velocity is used for measurements. A smooth velocity curve with a clear outer edge and maximal velocity should be recorded. The maximal velocity is measured at the outer edge of the dark signal; fine linear signals at the peak should not be included in measurements. The outer edge of the dark "envelope" of the velocity curve is traced to provide both the VTI for the continuity equation and the mean gradient (Figure).[61]

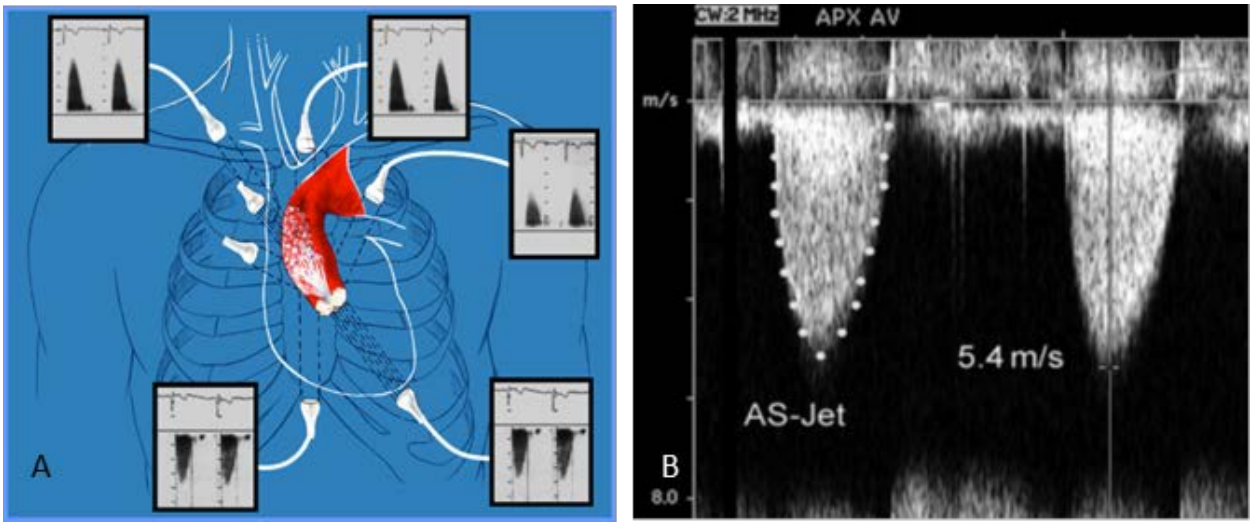


Figure 6. (A) Aortic valve velocities interrogated from multiple transducer positions *(illustration by Mayo Clinic, used with permission)* **(B)** CW Doppler of severe aortic stenosis showing tracing of the velocity curve from mean gradient and VTI, and measurement of max velocity.

4.4 Assessment of Prosthetic Aortic Regurgitation

An integrated exam approach using color flow, pulsed-wave (PW), and continuous-wave (CW) Doppler is used to assess the severity of transvalvular and paravalvular aortic regurgitation (AR). Color flow Doppler imaging should be performed from the parasternal long and short-axis views, and the apical long-axis and/or 5-chamber views. In the short axis view, color imaging should be performed at multiple levels (from level of the leaflets to below the skirt and frame to assess paravalvular regurgitation, and at the coaptation point of the leaflets for transvalvular (central) regurgitation.[66, 67]

If AR is seen by color Doppler, a CW Doppler recording of the regurgitant signal should be obtained for measurement of pressure half-time and assessment of jet density. If the degree of AR by color Doppler appears more than mild by visual estimate, the velocity in the proximal descending aorta should be recorded with PW Doppler.

The degree of transvalvular, paravalvular, and total (transvalvular plus paravalvular) AR will be graded as none, trace, mild, mild to moderate, moderate, moderate to severe, and severe based on the synthesis of the Doppler parameters shown in Table 17.[67] The category of "trace" should be used in cases where regurgitation is barely detectable by color Doppler. Regurgitant signals observed to originate within the stent will be considered transvalvular, and regurgitant signals observed to originate outside the stent will be considered paravalvular.

Table 17. Parameters for evaluation of the severity of aortic regurgitation

3-class Grading Scheme	**Trace**	**Mild**	**Mild**	**Moderate**	**Moderate**	**Severe**
Unifying 5-Class Grading Scheme	**Trace**	**Mild**	**Mild-to-Moderate**	**Moderate**	**Moderate-to-severe**	**Severe**
Doppler parameters (qualitative or semiquantitiative)						
Jet Features						
Extensive/wide jet origin	Absent	Absent	Absent	Present	Present	Present
Multiple jets	Possible	Possible	Often present	Often present	Usually present	Usually present
Jet path visible along stent	Absent	Absent	Possible	Often present	Usually present	Usually present
Proximal flow convergence visible	Absent	Absent	Absent	Possible	Often present	Often present
Vena contracta width (mm)	<2	<2	2-4	4-5	5-6	>6
Vena contracta area (mm^2)	<5	5-10	10-20	20-30	30-40	>40
Jet width at origin (% LVOT diameter)	Narrow (<5)	Narrow (5-15)	Intermediate (15-30)	Intermediate (30-45)	Large (45-60)	Large (>60)
Jet density: CW Doppler	Incomplete or faint	Incomplete or faint	Variable	Dense	Dense	Dense
Pressure half-time (ms): CW Doppler	Slow (>500)	Slow (>500)	Slow (>500)	Variable (200-500)	Variable (200-500)	Steep (<200)
Diastolic flow reversal in descending aorta	Absent	Absent or brief early diastolic	Intermediate	Intermediate	Holodiastolic (end-diast. Vel. >20 cm/s)	Holodiastolic (end-diast. Vel. >25 cm/s)
Circumferential extent of PVR (%)	<10	<10	10-20	20-30	>30	>30
Doppler parameters (quantitiative)						
Regurgitant volume (ml/beat)	<15	<15	15-30	30-45	45-60	>60
Regurgitant fraction (%)	<15	<15	5-10	10-20	20-30	>30
Effective regurgitant orifice area (mm^2)	<5	<5	5-10	10-20	20-30	>30

4.5 Assessment of Mitral Regurgitation

Color flow Doppler imaging of the left atrium should be performed from the parasternal long-axis view, and from the apical 4, 2, and long axis views.

Mitral regurgitant (MR) jets should be recorded with CW Doppler using a velocity scale that allows assessment of the density, shape, duration, and peak velocity of the MR jet. If the severity appears moderate or greater by visual assessment, pulmonary vein velocities should be recorded with PW Doppler to assess for the presence of systolic flow reversal. Grading of the severity of mitral regurgitation should be integrative using the parameters in Table 18.[68]

Table 18. Parameters for evaluation of the severity of mitral regurgitation

Parameter	Mild	Moderate	Severe
Color flow jet area	Small, central jet (usually <4 cm^2 or <20% of LA area)	Variable	Large central jet (usually >10 cm^2 or >40% of LA area), or variable wall-impinging jet swirling in the LA
Jet density (CW)	Incomplete or faint	Dense	Dense
Jet contour (CW)	Parabolic	Usually parabolic	Early peaking, triangular
Pulmonary vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal

4.6 Assessment of Tricuspid Regurgitation

Color flow imaging of the right atrium should be performed from the apical 4-chamber view, the parasternal long-axis view of the RVOT, and the parasternal short-axis view at the level of the aortic valve.

Tricuspid regurgitant (TR) jets should be recorded with CW Doppler using a velocity scale that allows assessment of the density, shape, duration, and peak velocity of the TR jet. If the severity appears moderate or greater by visual assessment, hepatic vein velocities should be recorded with PW Doppler to assess for the presence of systolic flow reversal. Grading of the severity of tricuspid regurgitation should be integrative using the parameters in Table 19.[68]

Table 19. Parameters for evaluation of the severity of tricuspid regurgitation

Parameter	Mild	Moderate	Severe
Jet area (cm^2)	<5	5 – 10	>10
VC width (cm)	Not defined	Not defined, but <0.7	≥0.7
PISA Radius (cm)	≤0.5	0.6 – 0.9	>0.9
Jet density & contour	Soft & parabolic	Dense, variable contour	Dense, triangular, with early peaking
Hepatic vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal

4.7 Assessment of Left Ventricular Function and Left Atrial Size

Dimensions of the left ventricle and left atrium should be obtained by either 2-D linear measurements or using 2-D guided m-mode from either the parasternal long or short axis views (Figure 3). Left ventricular chamber dimensions, septal thickness, and posterior wall thickness are measured using the American Society of Echocardiography (ASE) measurement convention[69] (blood-tissue interface). In addition, standard 2-D views of the left ventricle should be obtained from parasternal and apical transducer positions for visual estimation and quantitative assessment of left ventricular ejection fraction using the modified Simpson's rule, and for assessment of regional wall motion.

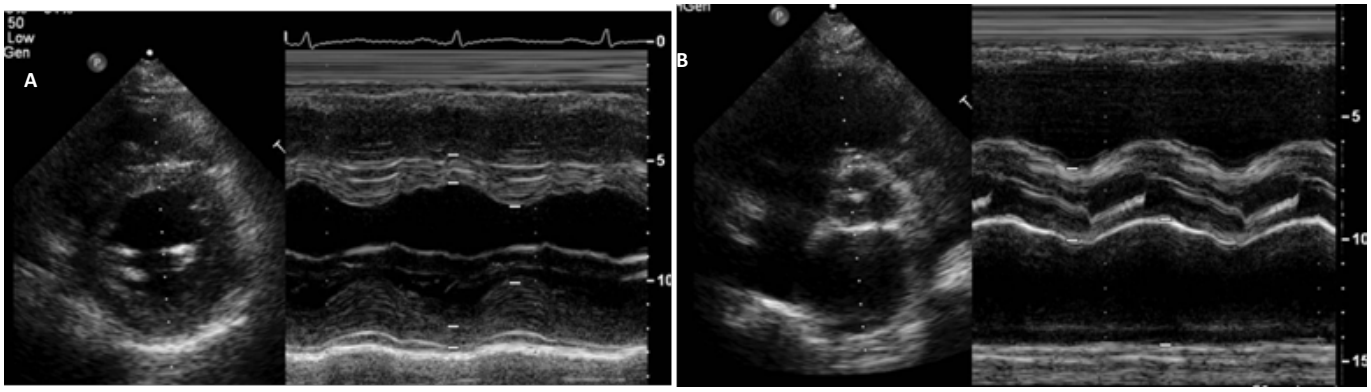


Figure 3. Measurements of the left ventride **(A)** and left atrium **(B)** using 2-D guided m-mode.

4.8 Assessment of Left Ventricular Diastolic Function

A spectral Doppler recording of mitral inflow should be obtained with PW Doppler in the apical 4-chamber view, using a 1 to 3 mm sample volume placed between the mitral leaflet tips during diastole (Figure 4). The spectral gain and wall filter settings should be optimized to clearly display the onset and cessation of left ventricular inflow. The following variables should be measured:

- Mitral inflow "A" velocity
- Mitral inflow "E" velocity
- Mitral inflow E-wave deceleration time

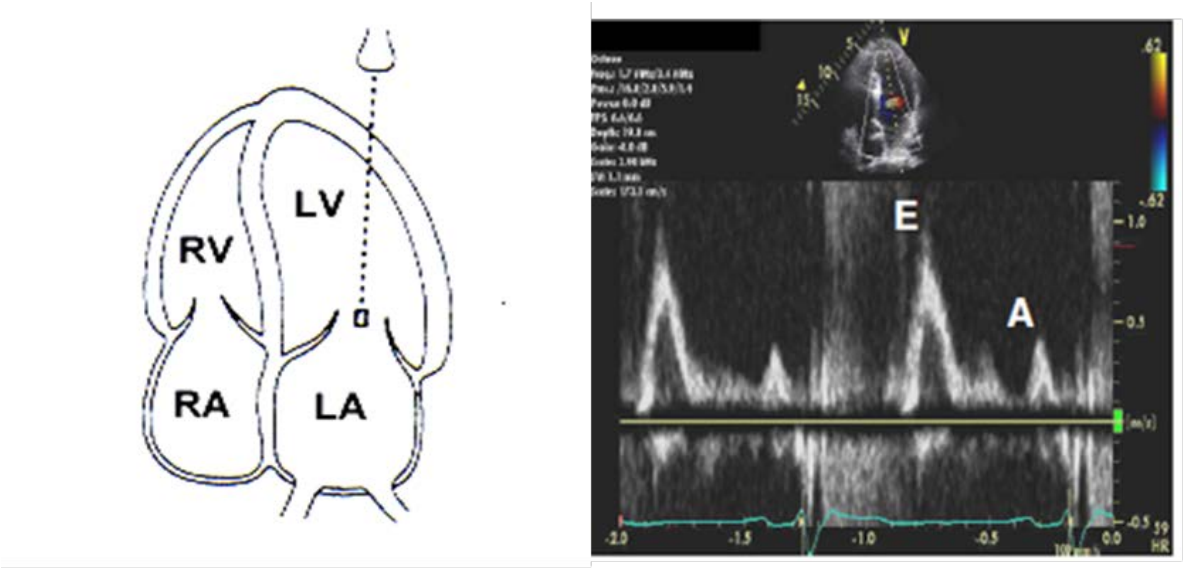


Figure 4. Positioning of the sample volume for recording of mitral inflow velocities.

Mitral annular velocities should be obtained from the lateral and septal aspects of the mitral annulus using PW tissue Doppler (DTI) performed in the apical 4-chamber view. The sample volume should be positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5 to 10 mm) to cover the longitudinal excursion of the mitral annulus in both systole and diastole. Minimal angulation (<20 degrees) should be present between the ultrasound beam and the plane of cardiac motion. The following variables should be measured:

- Mitral annular tissue Doppler systolic velocity (septal and lateral)
- Mitral annular tissue Doppler early diastolic velocity (septal and lateral)
- Mitral annular tissue Doppler late diastolic velocity (septal and lateral)

Diastolic function should be categorized as normal, mild dysfunction (impaired relaxation pattern), moderate dysfunction (pseudonormal filling), or severe dysfunction (restrictive filling) per the 2009 American Society of Echocardiography recommendations.[70]

5.0 Core Lab Analysis

Protocol-required echocardiograms will be sent to the Echo Core lab for assessment: the data generated by the Echo Core Lab will be the primary data used for analysis and reporting. Received echocardiograms will be logged in and analyzed by the Echo Core Lab according to their procedures determined for this trial.

The Echo Core Lab will report the following variables:

- Heart rate
- Left ventricular outflow tract (LVOT) diameter in mid systole
- Max aortic/prosthetic valve velocity (V_2) by CW Doppler
- Aortic valve velocity time integral (VTI) by CW Doppler
- Mean gradient across aortic valve (MGV_2) by CW Doppler
- LVOT VTI by PW Doppler

- Grade of aortic/prosthetic transvalvular regurgitation (post-implant only)
- Grade of aortic/prosthetic paravalvular regurgitation (post-implant only)
- Grade of prosthetic total (transvalvular plus paravalvular) regurgitation (post-implant only)
- Grade of mitral regurgitation
- Grade of tricuspid regurgitation
- Max tricuspid regurgitant (TR) jet velocity (if TR is present)
- Left ventricular internal dimension at end diastole
- Left ventricular internal dimension at end systole
- Interventricular septal thickness at end diastole
- Left ventricular posterior wall thickness at end diastole
- Left atrial diameter (anterior-posterior linear dimension) at systole
- Left ventricular ejection fraction by visual estimate
- Grade of diastolic dysfunction (if present)

Qualitative grading of valvular regurgitation will be performed using the criteria described in Sections 4.4 through 4.7. For reporting the degree of prosthetic regurgitation, the grading classes may be collapsed according to the 3-class grading scheme recommended by the American Society or Echocardiography (ASE)-European Association of Cardiovascular Imaging Guidelines (Table 16).[68, 71]

In addition, the following variables will be derived by the central database from the appropriate measurements reported by the Echo Core Lab:

- Peak Pressure Gradient (Peak Δ P) Across the Aortic Valve in mmHg
  Peak Δ P = 4 x (V_2^2)
  Where: V_2 is the peak velocity across the prosthesis in m/sec
- Aortic Valve Area (AVA) in cm^2
  AVA = LVOT diameter in cm^2 x 0.785 x (VTI_{V1}/VTI_{V2})
  Where: VTI_{V1} is the velocity time integral of the left ventricular outflow tract in cm, and VTI_{V2} is the velocity time integral of the native aortic valve in cm
- Aortic Valve Area Index (AVAI) in cm^2/m^2
  AVAI = AVA/BSA
  Where: AVA is the native aortic valve area in cm^2, and BSA is the body surface area in m^2 [x]
- Effective Orifice Area (EOA) in cm^2
  EOA = LVOT diameter^2 x 0.785 x (VTI_{V1}/VTI_{V2})
  Where: VTI_{V1} is the velocity time integral of the left ventricular outflow tract in cm, and VTI_{V2} is the velocity time integral of the aortic prosthesis in cm
- Effective Orifice Area Index (EOAI) in cm^2/m^2
  EOAI = EOA/BSA
  Where: EOA is the effective orifice area in cm^2, and BSA is the body surface area in m^2
- Doppler Velocity Index (DVI)
  DVI= VTI_{V1}/VTI_{V2}
  Where: VTI_{V1} is the velocity time integral of the left ventricular outflow tract in cm, and VTI_{V2} is the time velocity integral of the prosthetic aortic valve in cm
- Left Ventricular Mass (LVM) in grams
  LVM = 0.83 x [(LVIDD + LVPW + IVS)3 - (LVIDD)3] +0.6
  Where: LVIDD is the left ventricular internal dimension at end diastole in cm, LVPW is the left ventricular posterior wall thickness at end diastole in cm, and IVS is the interventricular wall thickness at end diastole in cm.
- Left Ventricular Mass Index (LVMI) in g/m^2 body surface area
  LVMI = LVM/BSA
  Where: LVM is left ventricular mass in g, and BSA is body surface area in m^2
- Estimated Right Ventricular Systolic Pressure (RVSP) in mmHg
  RVSP = (4 x MVTR jet^2) + 10
  Where: MV TR jet is the max velocity of the tricuspid regurgitant jet, and 10 = the assumed mean right atrial pressure in mmHg
- Body Surface Area (BSA) in m^2
  BSA = 0.007184 x (height in $cm^{0.725}$ x weight in $kg^{0.425}$)

[x] BSA derived from height and weight reported on the site eCRF

APPENDIX II: MDCT ACQUISTION GUIDELINES: PRE-TAVR PLANNING

1.0 Introduction

Multi-Detector Computed Tomography (MDCT) is used to evaluate aortic valve anatomy, determine aortic root dimensions for device sizing, and to evaluate peripheral vessel dimensions and anatomy. The following sections are intended as guidelines for acquiring the images for assessing anatomical suitability for implantation with the Medtronic TAVR systems.

2.0 General Requirements

- Multi-detector CT scanner (64-slice minimum) with ECG-gating capability.
- ECG-gated contrast enhanced aortic root (slice thickness of ≤1.0 mm)
- Temporal resolution should be optimized to reduce motion artifact.
- Spatial resolution should be as high as possible (goal is smallest isotropic voxel size)

3.0 ECG-gated Contrast Enhanced Scan of Aortic Root

Retrospective ECG-gated scans are recommended, which allows for reconstruction in various phases of the cardiac cycle and optimal evaluation of anatomic dimensions and valve morphology. Recommended scan parameters are listed in Table 20.

Prospective ECG-gated sequential scans (step-and-shoot) and high-pitch spiral scans with ECG-gating (flash spiral) are also acceptable. The following parameters are important to the optimum scan:

- Detector collimation 0.4-0.625 mm.
- Slice thickness ≤1.0 mm.
- The recommended coverage area is from superior to the aortic arch to inferior to the cardiac apex. The minimum required coverage area is from 50 mm above the aortic annulus to 10 mm below the aortic annulus.
- The recommended slice overlap is 0.4 mm (will result in isotropic voxels with a 20 cm field of view).

3.1 Post-processing

- Retrospective ECG-gated scans
  - Verify heart rate ECG triggers are at consistent place in cardiac cycle, edit if necessary. Additional editing/removal of arrhythmias may be performed.
  - Reconstruct at multiple phases (10 increments of 10%), with ≤1.0 mm slice thickness. If the system has the capability, also reconstruct a “best systolic” and “best diastolic” phase.
- Prospective ECG-gated scans (including flash spiral)
  - Reconstruct with medium soft kernel and slice thickness ≤1.0 mm (slice overlap of 0.4 mm recommended)

Table 20. Recommended MDCT parameters for pre TAVR planning

Parameter	Recommendation
IV injection with iodine contrast	80-100 (320mg/ml or higher), modify per patient as appropriate
Injection rate	4-6 mL/sec
Bolus tracking, delay	Delay time calculated using protocol for current scanner (bolus tracking or similar) with peak of contrast concentration in the ascending aorta during acquisition.
ECG-gating	Retrospective
Scan direction	Cranial-caudal
Scan coverage	From above the aortic arch to past the cardiac apex
Detector collimation	0.4 – 0.625 mm
Pitch	0.2–0.43 adapted to the heart rate
Dose modulation	Modulation and full current between 30 and 80% of the cardiac cycle
Slice thickness	0.8 mm
Slice overlap	0.4 mm
Reconstruction kernel	Medium Smooth
Post-processing	Retrospective ECG gating reconstruction algorithm that minimizes motion artifact. Reconstruct at multiple phases (10 minimum). Reconstructed slice thickness ≤0.8 mm.

3.2 Required Aortic Root Measurements

The following measurements of the aortic root are obtained for assessing anatomical suitability for the Evolut R TAV:

- Annulus perimeter (measured at systole if retrospective gating is used)
- Sinus of Valsalva diameters (measured at diastole)
- Sinus of Valsalva heights (measured at diastole)

For the Evolut PRO TAV, the following measurements of the aortic root are obtained for assessing anatomical suitability:

- Major aortic annulus (measured at systole if retrospective gating is used)
- Orthogonal minor aortic annulus diameter (measured at systole if retrospective gating is used)
- Annulus perimeter (measured at systole if retrospective gating is used)
- Sinus of Valsalva diameters (measured at diastole)
- Sinus of Valsalva heights (measured at diastole)

Dimensional sizing criteria for the Evolut R and Evolut PRO are provided in Tables 20 and 21.

3.2.1 Reformatting of Images

Reformatting of the images is as follows: [72]

- Site image cross-hairs on aortic root in all windows where it is visible. Lock cross-hairs so they remain orthogonal for all steps.
- In the coronal window, rotate cross-hairs (horizontal line) counter-clockwise to align with virtual basal plane, (Figure 95, upper left panel).
- In the sagittal window, the horizontal line is rotated clockwise or counter-clockwise to align with virtual basal plane (Figure 95, lower left panel).
- On the newly defined double-oblique axial image, scroll up and down through the aortic root until the most caudal attachment points of the three native leaflets come into view (indicated by arrowheads in Figure 6). If one of the leaflets comes into view at a more cranial or caudal slice, adjust the coronal or sagittal cross-hairs until all three leaflets come into view on the same axial slice.
- For confirmation of the correct aortic annulus plane, scroll through the double oblique axial images starting in the mid sinus and ending at the level of the aortic annulus. The sinuses should appear to be relatively the same size at the level of the mid-sinus and the leaflets should all disappear equally at the level of the annulus.

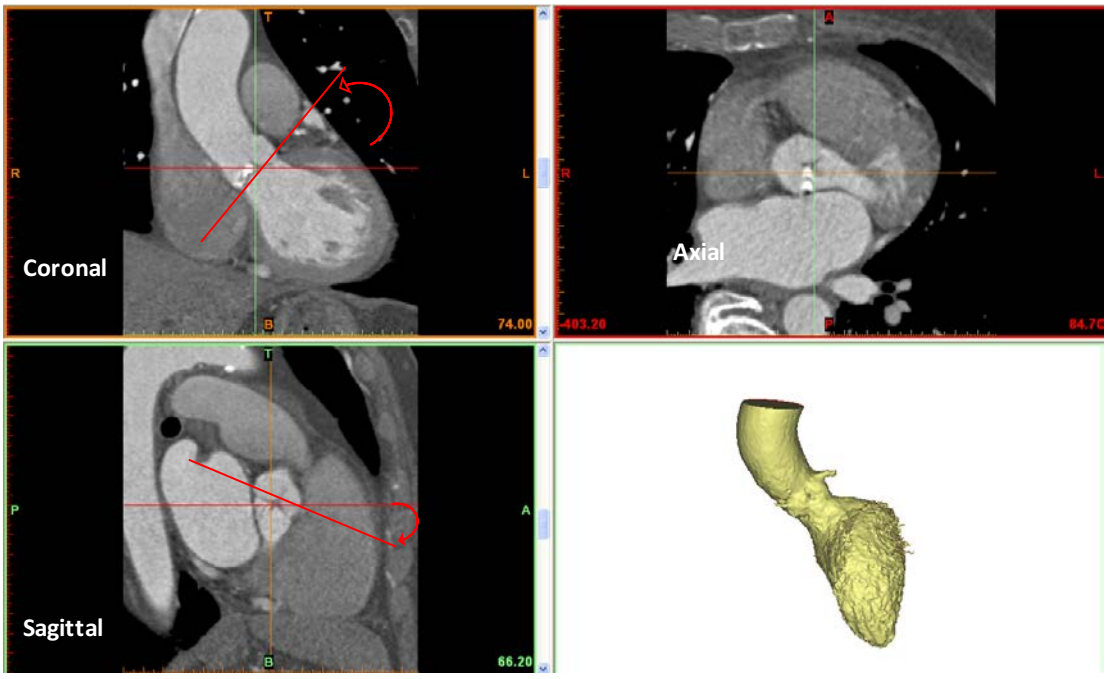


Figure 95. Example images in original orientation (axial, coronal, and sagittal). Red curved arrow and line indicate adjustment of coronal and sagittal planes to align with aortic basal annulus.

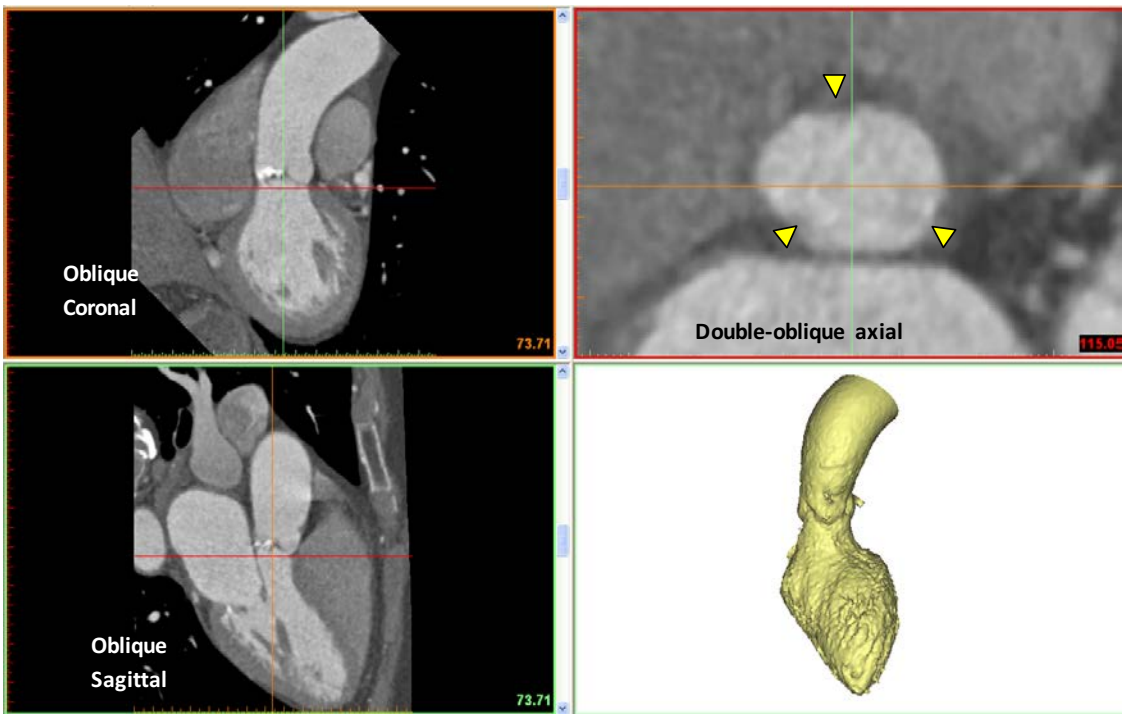


Figure 6. Example images of reformatted oblique coronal (upper left), oblique sagittal (lower left), double oblique axial (upper right), and 3D reconstruction (lower right). Yellow arrowheads indicate most caudal attachment of three leaflets of the aortic valve).

3.2.2 Aortic Annulus Measurements

- Choose the cleanest systolic images for the aortic annulus measurements, either automatically (eg, best systolic) or by manually identifying. Measurement on a diastolic image is also acceptable.
- Aortic annulus measurements should be completed on the properly reformatted double-oblique axial image at aortic annulus level, as described in Section 3.2.1, Reformatting of Images.
- Trace the perimeter of the basal annulus (Figure 7, left). Place cross-hairs at site of basal annulus, create major diameter through the site, create minor diameter defined as perpendicular to major and through site (Figure 7, right).

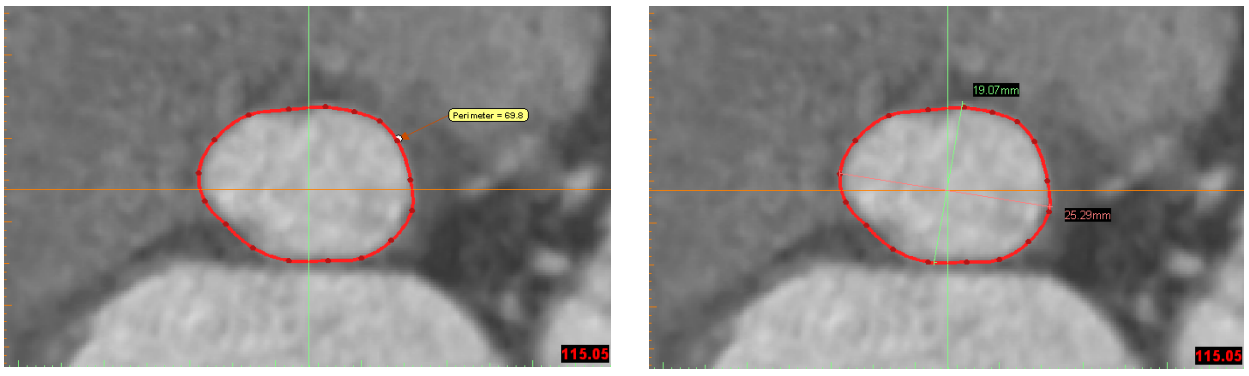


Figure 7. Example of perimeter measurement (left) and major and minor diameter measurements (right).

3.2.3 Sinus of Valsalva Measurements

Choose the best diastolic images for measurement of sinus of Valsalva diameters and heights from images using the same reformatting technique as described in Section 3.2.1.

Sinus of Valsalva Diameters

- Select the double oblique axial image where the widest portion of the three sinuses is visible.
- Measure a diameter from each commissure through the site of the root to the opposite sinus. Complete for all three sinuses (Figure 8).

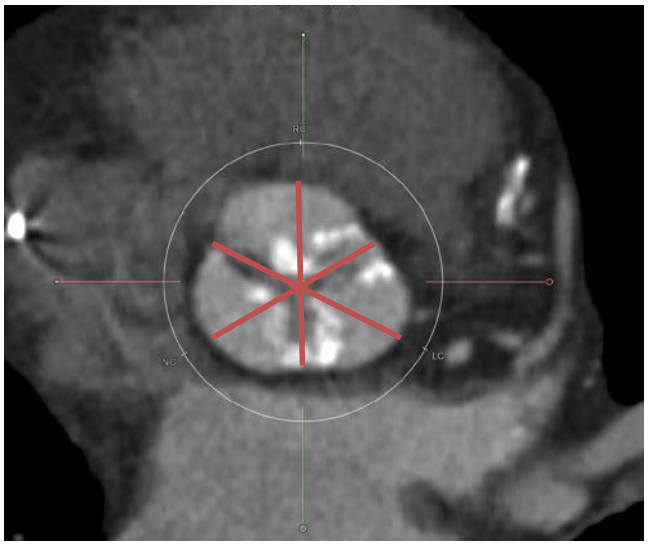


Figure 8. Example of sinus of Valsalva diameters

Sinus of Valsalva Heights

- The sinotubular junction is typically not co-planar with the aortic annulus. Therefore, a sinus of Valsalva height must be measured for each of the three sinuses. This height is defined as the distance between the aortic annular plane and the tallest point in the sinus.
- Choose the double oblique axial image so that it is located at the level of the aortic annulus. The reformatting line representing the double oblique axial image should now be visible in the oblique coronal and oblique sagittal images at the level of the aortic annulus.
- For the left coronary and non coronary heights, use the oblique coronal image. For the right coronary height, use the oblique sagittal image.
- To complete the measurement, scroll through the oblique coronal or sagittal image (depending on which sinus you are measuring) and locate the heights location of the sinotubular junction. On that image, measure the distance along the path of the aortic root from the aortic annular plane, marked by the reformatting line, to the sinotubular junction (Figure 9).

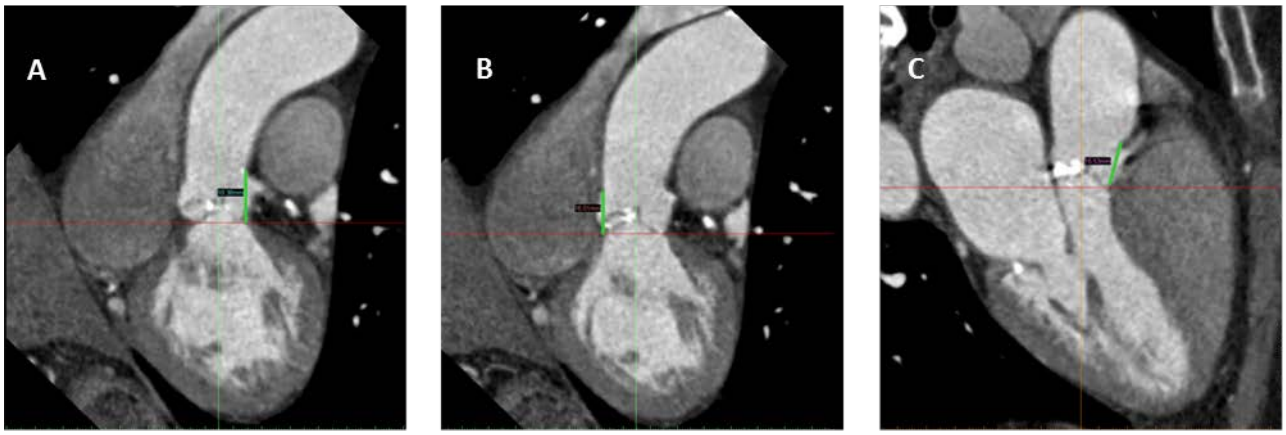


Figure 9. Examples of sinus of Valsalva heights **(A)** left coronary **(B)** non coronary **(C)** right coronary

4.0 Evolut R and Evolut PRO TAV Sizing Matrix

Table 21. Dimensional sizing criteria for Evolut R TAV

Device Size	Aortic Annulus		Sinus of Valsalva	
	Perimeter (mm)	Mean Diameter (mm)	Mean Diameter (mm)	Mean Height (mm)
23 mm	56.5 – 62.8	18 – 20	≥25	≥15
26 mm	62.8 – 72.3	20 – 23	≥27	≥15
29 mm	72.3 – 81.6	23 – 26	≥29	≥15
34 mm	81.7 – 94.2	26 - 30	≥31	≥16

Table 22. Dimensional sizing criteria for Evolut PRO TAV

Device Size	Aortic Annulus		Sinus of Valsalva	
	Perimeter (mm)	Mean Diameter (mm)	Mean Diameter (mm)	Mean Height (mm)
23 mm	56.5 – 62.8	18 – 20	≥25	≥15
26 mm	62.8 – 72.3	20 – 23	≥27	≥15
29 mm	72.3 – 81.6	23 – 26	≥29	≥15

APPENDIX III: DEFINITIONS OF STS FACTORS AND OTHER CO-MORBIDITIES

1.0 STS Factors

http://riskcalc.sts.org/stswebriskcalc/#/calculate, Risk Model and Variables - STS Adult Cardiac Surgery Database Version 2.81

Factor	Definition
Heart Failure	Physician documentation or report that the patient has been in a state of heart failure within the past 2 weeks. Heart failure is defined as physician documentation or report of any of the following clinical symptoms of heart failure described as unusual dyspnea on light exertion, recurrent dyspnea occurring in the supine position, fluid retention; or the description of rales, jugular venous Distension, pulmonary edema on physical exam, or pulmonary edema on chest x-ray presumed to be cardiac dysfunction. A low ejection fraction alone, without clinical evidence of heart failure does not qualify as heart failure. An elevated BNP without other supporting documentation should not be coded as CHF.
Diabetes	History of diabetes diagnosed and/or treated by a healthcare provider. The American Diabetes Association criteria include documentation of the following: 1. Hemoglobin A1c ≥6.5%; or 2. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L); or 3. 2-h Plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test; or 4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L) This does not include gestational diabetes.
Dialysis	Subject currently (prior to surgery) undergoing dialysis
Hypertension	Any of the following: • documented history of hypertension diagnosed and treated with medication, diet and/or exercise, • prior documentation of blood pressure >140 mmHg systolic or 90 mmHg diastolic for patients without diabetes or chronic kidney disease, or prior documentation of blood pressure >130 mmHg systolic or 80 mmHg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease • currently on pharmacologic therapy to control hypertension
Immunocompromise	Indicate whether immunocompromise is present due to immunosuppressive medication therapy within 30 days preceding the operative procedure or existing medical condition. This includes, but is not limited to systemic steroid therapy, anti-rejection medications and chemotherapy. This does not include topical steroid applications, one time systemic therapy, inhaled steroid therapy or preprocedure protocol.
Arrhythmia	History or preoperative arrhythmia (sustained ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial flutter, third degree heart block, second degree heart block, sick sinus syndrome) that has been treated with any of the following modalities: • ablation therapy • AICD • pacemaker • pharmacologic treatment • electrocardioversion, defibrillation

1.0 STS Factors (continued)

Factor	Definition
Atrial fibrillation/atrial flutter	Presence of atrial fibrillation or flutter within 30 days of the procedure
Myocardial infarction	History of at least one documented myocardial infarction at any time prior this surgery
Endocarditis	Indicate whether the patient has a history of endocarditis. Endocarditis must meet at least 1 of the following criteria: 1. Patient has organisms cultured from valve or vegetation. 2. Patient has 2 or more of the following signs or symptoms: fever (>38°C or >100.4°F), new or changing murmur*, embolic phenomena*, skin manifestations* (ie, petechiae, splinter hemorrhages, painful subcutaneous nodules), congestive heart failure*, or cardiac conduction abnormality. *with no other recognized cause and at least 1 of the following: a. organisms cultured from 2 or more blood cultures b. organisms seen on Gram's stain of valve when culture is negative or not done c. valvular vegetation seen during an invasive procedure or autopsy d. positive laboratory test on blood or urine (eg, antigen tests for H mmunocom, S mmunocom, N mmunocompro, or Group B Streptococcus) e. evidence of new vegetation seen on echocardiogram and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.
Chronic lung disease	Presence of lung disease and severity level as follows: None Mild: FEV1 60% to 75% of predicted, and/or on chronic inhaled or oral bronchodilator therapy. Moderate: FEV1 50% to 59% of predicted, and/or on chronic steroid therapy aimed at lung disease. Severe: FEV1 <60 or Room Air pCO2 >50. CLD present, severity not documented Unknown A history of chronic inhalation reactive disease (asbestosis, mesothelioma, black lung disease or pneumoconiosis) may qualify as chronic lung disease. Radiation induced pneumonitis or radiation fibrosis also qualifies as chronic lung disease. (if above criteria is met) A history of atelectasis is a transient condition and does not qualify. Chronic lung disease can include patients with chronic obstructive pulmonary disease, chronic bronchitis, or emphysema. It can also include a patient who is currently being chronically treated with inhaled or oral pharmacological therapy (eg, beta-adrenergic agonist, anti-inflammatory agent, leukotriene receptor antagonist, or steroid). Patients with asthma or seasonal allergies are not considered to have chronic lung disease.

1.0 STS Factors (continued)

Factor	Definition
Peripheral vascular disease	History of peripheral arterial disease (includes upper and lower extremity, renal, mesenteric, and abdominal aortic systems). This can include: • claudication, either with exertion or at rest • amputation for arterial vascular insufficiency • vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (excluding dialysis fistulas and vein stripping) • documented aortic aneurysm with or without repair • positive noninvasive test (eg, ankle brachial index ≤0.9, ultrasound, magnetic resonance or computed tomography imaging of >50% diameter stenosis in any peripheral artery, ie, renal, subclavian, femoral, iliac), or angiographic imaging **Excludes disease in the carotid cerebrovascular arteries, or thoracic aorta. PVD does not include deep vein thrombosis*
Cerebrovascular disease	Indicate whether the patient has a current or previous history of any of the following: a. Stroke: Stroke is an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, where the neurological dysfunction lasts for greater than 24 hours. b. TIA: is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction, where the neurological dysfunction resolves within 24 hours. c. Noninvasive or invasive arterial imaging test demonstrating ≥50% stenosis of any of the major extracranial or intracranial vessels to the brain d. Previous cervical or cerebral artery revascularization surgery or percutaneous intervention. This does not include chronic (nonvascular) neurological diseases or other acute neurological insults such as metabolic and anoxic ischemic encephalopathy.
Cerebrovascular accident	History of stroke. Stroke is an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, where the neurological dysfunction lasts for greater than 24 hours.
Previous cardiac interventions	Any previous cardiovascular intervention, either surgical or non-surgical, which may include those done during the current admission.
Number of diseased vessels	The number of diseased major native coronary vessel systems: LAD system, Circumflex system, and/or Right system with ≥50% narrowing of any vessel preoperatively. NOTE: Left main disease (≥50%) is counted as TWO vessels (LAD and Circumflex, which may include a Ramus Intermedius). For example, left main and RCA would count as three total. A vessel that has ever been considered diseased, should always be considered diseased.
Inotropes	Subject received IV inotropic agents within 48 hours preceding surgery.

1.0 STS Factors (continued)

Factor	Definition
Cardiogenic shock	A sustained (>30 min) episode of hypoperfusion evidenced by systolic blood pressure <90 mm Hg and/or, if available, cardiac index <2.2 L/min per square meter determined to be secondary to cardiac dysfunction and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support (eg, IABP, extracorporeal circulation, VADs) to maintain blood pressure and cardiac index above those specified levels. Note: Transient episodes of hypotension reversed with IV fluid or atropine do not constitute cardiogenic shock. The hemodynamic compromise (with or without extraordinary supportive therapy) must persist for at least 30 min.
Resuscitation	Patient required cardiopulmonary resuscitation before the start of the operative procedure which includes the institution of anesthetic management. Capture resuscitation timeframe: within 1 hour or 1-24 hours pre-op
Incidence	Indicate if this is the patient's: • first surgery • first re-op surgery • second re-op surgery • third re-op surgery • fourth or more re-op surgery. Surgery is defined as cardiothoracic operations (heart or great vessels) surgical procedures performed with or without cardiopulmonary bypass (CPB). Also include lung procedures utilizing CPB or tracheal procedures utilizing CPB. Reoperation increases risk due to the presence of scar tissue and adhesions.

1.0 STS Factors (continued)

Factor	Definition
Cardiac presentation on admission	Indicate the patient's cardiac symptoms at the time of this admission. No Symptoms: No Symptoms, no angina. Stable Angina: Angina without a change in frequency or pattern for the prior 6 weeks. Angina is controlled by rest and/or oral or transcutaneous medications. Unstable Angina: There are three principal presentations of unstable angina: 1. Rest angina (occurring at rest and prolonged, usually >20 minutes); 2. New-onset angina (within the past 2 months, of at least Canadian Cardiovascular Society Class III severity); or 3. Increasing angina (previously diagnosed angina that has become distinctly more frequent, longer in duration, or increased by 1 or more Canadian Cardiovascular Society class to at least CCS III severity). –Non-ST Elevation MI (Non- STEMI): The patient was hospitalized for a non-ST elevation myocardial infarction (STEMI) as documented in the medical record. Non-STEMIs are characterized by the presence of both criteria: a. Cardiac biomarkers (creatinine kinase-myocardial band, Troponin T or I) exceed the upper limit of normal according to the individual hospital's laboratory parameters with a clinical presentation which is consistent or suggestive of ischemia. ECG changes and/or ischemic symptoms may or may not be present. b. Absence of ECG changes diagnostic of a STEMI –ST Elevation MI (STEMI): The patient 'presented with a ST elevation myocardial infarction (STEMI) or its equivalent as documented in the medical record. STEMIs are characterized by the presence of both criteria: a. ECG evidence of STEMI: New or presumed new ST segment elevation or new left bundle branch block not documented to be resolved within 20 minutes. ST segment elevation is defined by new or presumed new sustained ST-segment elevation at the J-point in two contiguous electrocardiogram (ECG) leads with the cutoff points: ≥0.2 mV in men or ≥0.15mV in women in leads V2-V3 and/or ≥0.1 mV in other leads and lasting greater than or equal to 20 minutes. If no exact ST-elevation measurement is recorded in the medical chart, physician's written documentation of ST elevation or Q waves is acceptable. If only one ECG is performed, then the assumption that the ST elevation persisted at least the required 20 minutes is acceptable. Left bundle branch block (LBBB) refers to new or presumed new LBBB on the initial ECG. b. Cardiac biomarkers (creatinine kinase-myocardial band, Troponin T or I) exceed the upper limit of normal according to the individual hospital's laboratory parameters a clinical presentation which is consistent or suggestive of ischemia. Angina equivalent Other: Presentation/symptom not listed above.

1.0 STS Factors (continued)

Factor	Definition
Status of the procedure	Elective: The patient's cardiac function has been stable in the days or weeks prior to the operation. The procedure could be deferred without increased risk of compromised cardiac outcome. Urgent: Procedure required during same hospitalization in order to minimize chance of further clinical deterioration. Examples include but are not limited to: Worsening, sudden chest pain, CHF, acute myocardial infarction (AMI), anatomy, IABP, unstable angina (USA) with intravenous (IV) nitroglycerin (NTG) or rest angina. Emergent: Patients requiring emergency operations will have ongoing, refractory (difficult, complicated, and/or unmanageable) unrelenting cardiac compromise, with or without hemodynamic instability, and not responsive to any form of therapy except cardiac surgery. An emergency procedure is one in which there should be no delay in providing operative intervention. The patient's clinical status includes any of the following: a. Ischemic dysfunction (any of the following): (1) Ongoing ischemia including rest angina despite maximal medical therapy (medical and/or IABP)); (2) Acute Evolving Myocardial Infarction within 24 hours before surgery; or (3) pulmonary edema requiring intubation. b. Mechanical dysfunction (either of the following): (1) shock with circulatory support; or (2) shock without circulatory support. Emergent Salvage: The patient is undergoing CPR en route to the OR or prior to anesthesia induction or has ongoing ECMO to maintain life.

2.0 Other Factors Not Captured by Traditional Risk Score[49]

Co-morbidity	Definition/Criteria
Porcelain aorta or severely atherosclerotic aorta	Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible.
Frailty	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence Criteria: • 5 meter walking time • Grip strength • BMI <20 kg/m^2 and/or weight loss 5 kg/yr • Serum albumin <3.5 g/dL • Cognitive impairment or dementia
Sever liver disease/cirrhosis	Any of the following: • Child-Pugh class C • MELD score ≥10 • Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt • Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction
Hostile chest	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications from prior surgery • Evidence of severe radiation damage (eg, skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) • History of multiple recurrent pleural effusions causing internal adhesions
IMA or other critical conduit(s) crossing midline and/or adherent to posterior table of sternum	A patent IMA graft that is adherent to the sternum such that injuring it during re-operation is likely. A patient may be considered extreme risk if any of the following are present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. • The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3 mm of the posterior table.
Severe pulmonary hypertension Severe right ventricular dysfunction	Primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure Criteria as defined by the guidelines (eg, TAPSE <15mm, RV end-systolic area >20 cm^2)

APPENDIX IV: RESHEATH AND RECAPTURE DEFINITIONS

The following definitions are applicable to the data elements on the Implant eCRF that address the use of the resheath and recapture feature.

Resheath attempt	An attempt to intentionally resheath only a portion of the TAV (including the frame) into the capsule of the delivery catheter (eg, with the intent to reposition of the valve during deployment).
Recapture attempt	An attempt to intentionally fully resheath the entire TAV (including the frame) into the capsule of the delivery catheter until there is no gap between capsule and the tip (eg, with the intent to enable re-crossing of the aortic valve or retrieval of the system, Figure 14D).
Reposition	Repositioning of the TAV proximally or distally before final deployment
Retrieve	Retrieval of a partially deployed TAV

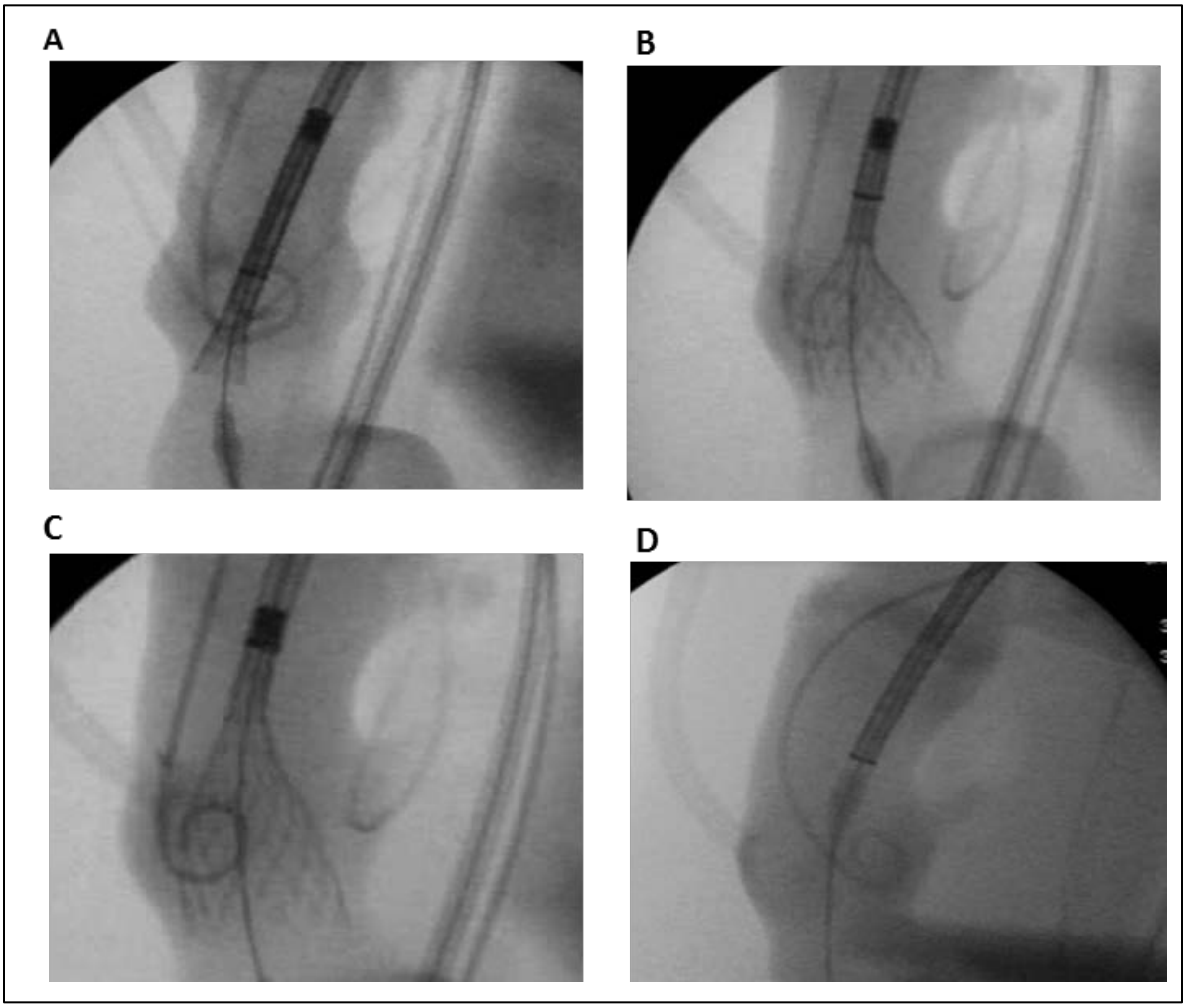


Figure 10. (A) Between 0 and 1/3 of the valve length outside of the capsule **(B)** between 1/3 and 2/3 of the valve length outside of the capsule **(C)** Point of no return: capsule marker in alignment with the spindle marker **(D)** Full recapture: entire valve resheathed into the capsule until there is no gap between capsule and the tip.

APPENDIX V: DEFINITIONS: SAFETY ENDPOINTS AND EFFICACY EVENTS

Definitions of adverse events to be evaluated as clinical safety endpoints, other related complications, and efficacy events are provided in Sections 1.0, 2.0, and 3.0, respectively. [49] The CEC and site investigators will code safety endpoint events according to these definitions, using the associated code list provided on Section 4.0, Event Code List.

1.0 Safety Endpoint Definitions

Mortality	
Cardiovascular mortality	Any of the following criteria: 1) Death due to proximate cardiac cause (eg, myocardial infarction, cardiac tamponade, worsening heart failure) 2) Death caused by non coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease 3) All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure 4) All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events 5) Sudden or unwitnessed death 6) Death of unknown cause
Non-cardiovascular mortality	Any death in which the primary cause of death is clearly related to another condition (eg, trauma, cancer, suicide).

1.0 Safety Endpoints (continued)

Myocardial Infarction	
Periprocedural MI (≤72 h after the index procedure)	New ischemic symptoms (eg, chest pain or shortness of breath), or new ischemic signs (eg, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least 2 contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least 1 sample post procedure with a peak value exceeding 15x as the upper reference limit for troponin or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase in at least 50% post procedure is required AND the peak value must exceed the previously stated limit.
Spontaneous MI (>72 h after the index procedure)	Any of the following criteria: 1) Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least 1 of the following: • Symptoms of ischemia • ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block (LBBB)) • New pathological Q-waves in at least 2 contiguous leads • Imaging evidence of a new loss of viable myocardium or new wall motion abnormality 2) Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. 3) Pathological findings of an acute myocardial infarction

1.0 Safety Endpoints (continued)

Stroke and TIA

Diagnostic criteria

1) Acute episode of a focal or global neurological deficit with at least 1 of the following:
   - change in the level of consciousness
   - hemiplegia, hemiparesis
   - numbness or sensory loss affecting 1 side of the body
   - dysphasia or aphasia
   - hemianopia
   - amaurosis fugax
   - other neurological signs or symptoms consistent with stroke

   Stroke: duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death

   TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
2) No other readily identifiable non-stroke cause for the clinical presentation (eg, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the neurologist
3) Confirmation of the diagnosis by at least 1 of the following:
   - Neurologist or neurosurgical specialist
   - Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

Stroke Definitions

Disabling stroke: an mRS score of 2 or more at 90 days and an increase in at least 1 mRS category from an individual's pre-stroke baseline

Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least 1 mRS category from an individual's pre-stroke baseline

Stroke Classifications

Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue

Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage

Undetermined: insufficient information to allow categorization as ischemic or hemorrhagic

1.0 Safety Endpoints (continued)

Bleeding Complications	
Life-threatening or disabling bleeding	1) Fatal bleeding *(BARC type 5)* OR 2) Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome *(BARC type 3b and 3c)* OR 3) Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* OR 4) Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* *(BARC type 3b)*
Major bleeding *(BARC type 3a)*	1) Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND 2) Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding *(BARC type 2 or 3a, depending on the severity)*	Any bleeding worthy of clinical mention (eg, access site hematoma) that does not qualify as life-threatening, disabling, or major
*Given one unit of packed RBC typically will raise hemoglobin concentration by 1 g/dL, an estimated decrease in haemoglobin will be calculated; BARC: Bleeding Academic Research Consortium29; RBC: red blood cell	

Note: With respect to blood transfusions, it is critical to acknowledge that a bleeding complication has to be the result of overt bleeding and cannot be adjudicated based on blood transfusions alone.

Acute Kidney Injury (up to 7 days post procedure)	
Stage 1	1) Increase in serum creatinine to 150%-199% (1.5-1.99 x increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR 2) Urine output <0.5 mL/kg/h for >6 but <12 h
Stage 2	1) Increase in serum creatinine to 200%-299% (2.0-2.99 x increase compared with baseline) OR 2) Urine output <0.5 mL/kg/h for >12 but <24 h
Stage 3	1) Increase in serum creatinine to ≥300% (>3 x increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR 2) Urine output <0.3 ml/kg/h for ≥24 h OR 3) Anuria for ≥12 h

1.0 Safety Endpoints (continued)

Vascular Access Site and Access Related Complications	
Major vascular complication	1) Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm OR 2) Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) *leading to* death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR 3) Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR 4) The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR 5) Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR 6) Surgery for access site-related nerve injury OR 7) Permanent access site-related nerve injury
Minor vascular complication	1) Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) *not leading to* death, life-threatening or major bleeding*, visceral ischemia, or neurological impairment OR 2) Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR 3) Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR 4) Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)
Percutaneous closure device failure	Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

*Refer to VARCII bleeding definitions[49]

VALVE DYSFUNCTION REQUIRING REPEAT PROCEDURE
Any valve dysfunction that requires repeat procedure (eg, balloon valvuloplasty, TAVR, snare repositioning, placement of vascular plug paravalvular leak, or surgical AVR)

Note: Repeat procedures are reported on the appropriate eCRF (Surgical Intervention or Catheter Reintervention)

2.0 Other Related Complications

Complication	Definition
Conversion to open surgery	Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications
Unplanned use of cardiopulmonary bypass	Unplanned use of CPB for hemodynamic support at any time during the TAVI procedure
Coronary artery obstruction	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the TAV prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVR procedure.
Ventricular septal perforation	Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVR procedure
Mitral valve apparatus damage or dysfunction	Angiographic or echocardiographic evidence of new damage (chordae, papillary muscle, or leaflet) to the mitral valve apparatus or dysfunction (eg, restrictions due to the TAV of the mitral valve during or after the TAVR procedure
Cardiac tamponade	Evidence of new pericardial effusion associated with hemodynamic instability and clearly related to the TAVI procedure
Prosthetic valve thrombosis	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. *Valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve related should not be reported as valve thrombosis*.
Valve migration	After initial correct positioning, any observed movement (upward or downward) of the TAV within the aortic annulus from its initial position, with or without consequences.
Valve embolization	The TAV moves during or after deployment such that it loses contact within the aortic annulus
Ectopic valve deployment	Permanent deployment of the TAV in a location other than the aortic root
TAV in TAV deployment	Additional valve prosthesis is implanted within a previously implanted TAV because of sub-optimal device position and/or function, during or after the index procedure.
Hemolysis	Red cell destruction confirmed by lab data **Minor hemolysis:** No intervention required **Major hemolysis:** Requires intervention (eg, iron supplements, transfusion, invasive intervention).
Frame fracture	Visual evidence on radiography or at explant of loss of contact between elements (cells) of the stent. **Minor frame fracture:** Does not require intervention, or is not associated with prosthetic valve dysfunction. **Major frame fracture:** Intervention required (eg, reoperation, catheter re-intervention) or is associated with prosthetic valve dysfunction

2.0 Other TAVR-Related Complications (continued)

PROSTHETIC VALVE ENDOCARDITIS

Any of the following:

1) Fulfillment of the following Duke criteria for definite endocarditis: [74]
   - Histologic and/or microbiologic evidence of infection at surgery or autopsy, or
   - 2 major criteria, or
   - 1 major criteria or 3 minor criteria, or
   - 5 minor criteria

   Major and minor criteria are as follows:

   Major Criteria:
   - Blood cultures positive for Infective Endocarditis (IE)
     - Typical microorganisms consistent with IE isolated from two separate blood cultures, as noted below
       - Viridans streptococci, *Streptococcus bovis*, *Staphylcoccus aureus*, or HACEK group
       - Community-acquired enterococci in the presence of a primary focus
     - Microorganisms consistent with IE isolated from persistently positive blood cultures defined as:
       - At least two positive cultures or blood samples obtained >12 hours apart, or
       - All of three, or a majority of four or more separate cultures of blood, the first and last sample obtained > one hour apart
     - Single blood culture positive for Coxiella burnetti or an antiphase I IG antibody titer >1:800
   - **Evidence of endocardial involvement**
     - Positive results of echocardiography for IE defined as:
       - Oscillating intracardiac mass on a valve or supporting structures in the path of regurgitant jets or on implanted material in the absence of an anatomic explantation, or
       - Abscess, or
       - New partial dehiscence of a valvular prosthesis
     - New valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)

   Minor Criteria:
   - **Predisposition:** predisposing heart condition or intravenous drug use
   - **Fever:** temperature >38°C
   - **Vascular phenomena:** major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
   - **Immunological phenomena:** glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
   - **Microbiological evidence:** positive blood culture but does not meet a major criterion (as noted above) or serological evidence of active infection with organism consistent with infectious endocarditis.
   - **Echocardiographic findings:** consistent with IE but do not meet a major criterion as noted above

   If only 1 major and 1-2 minor criteria are fulfilled, or if only 3-4 minor criteria are fulfilled, the event will be coded as "possible endocarditis"
2) Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation
3) Findings of abscess, pus, or vegetation involving the TAV or surgical bioprosthesis at autopsy

3.0 Efficacy Event Definitions

PROSTHETIC VALVE DYSFUNCTION	
Stenosis: moderate/severe	Any of the following 1) Peak aortic velocity >4 m/s OR mean aortic gradient >40 mmHg, AND EOA <0.8 cm^2. 2) Peak aortic velocity >4 m/s OR mean aortic gradient >40 mmHg, AND EOA ≥0.8 cm^2, and DVI <0.25, 3) Peak aortic velocity ≤4 m/s and mean aortic gradient ≤ 40 mmHg, AND EOA <0.8 cm^2, and DVI <0.25
Paravalvular regurgitation: moderate	Moderate paravalvular regurgitation (per echo criteria in Table 17, 3 grade scheme)
Paravalvular regurgitation: severe	Severe paravalvular regurgitation (per echo criteria in Table 17, 3 grade scheme) per echo criteria in CIP)
Transvalvular regurgitation: moderate	Moderate paravalvular regurgitation (per echo criteria in Table 17, 3 grade scheme)
Transvalvular regurgitation: severe	Severe transvalvular regurgitation (per echo criteria in Table 17, 3 grade scheme)
Total regurgitation: moderate	Moderate total regurgitation (per echo criteria in Table 16, 3 grade scheme)
Total regurgitation: severe	Severe total regurgitation (per echo criteria in Table 16, 3 grade scheme)

Notes:

1. DVI = Doppler Velocity Index (LVOT VTI/valve VTI)
2. For subjects with BSA <1.6 m^2, the EOA criteria for significant (moderate or severe) stenosis is <0.6 cm^2
3. For subjects with LVOT diameter >2.5 cm, the DVI criteria for significant (moderate or severe) stenosis is <0.2 cm^2
4. Reporting of prosthetic valve dysfunction will be based on core lab results.
5. Prosthetic valve dysfunction events are not reported as adverse events, unless the dysfunction is accompanied with clinical sequelae at the time of event detection, and the clinical sequelae are chronologically and physiologically associated with the dysfunction. However, prosthetic dysfunctions that are associated with adverse events, and that meet the definition of a serious adverse event, should be reported as such.

4.0 Event Code List

Myocardial Infarction

100 Peri-procedural myocardial infarction
101 Spontaneous myocardial infarction

Stroke and TIA

102 Disabling stroke: ischemic
103 Disabling stroke: hemorrhagic
104 Disabling stroke: undetermined origin
105 Non-disabling stroke: ischemic
106 Non-disabling stroke: hemorrhagic
107 Non-disabling stroke: undetermined origin
108 Transient ischemic attack

Bleeding Complications

110 Life threatening or disabling bleed event
111 Major bleeding event
112 Minor bleeding event

Acute Kidney Injury

113 Acute kidney injury: stage 1
114 Acute kidney injury: stage 2
115 Acute kidney injury: stage 3

Vascular Access and Access Site Complications

Major

120 Major vascular complication: aortic dissection, aortic rupture, LV perforation, or new apical aneurysm/pseudoaneurysm
121 Major vascular complication: access site or access site-related vascular injury (dissection, stenosis, perforation, etc)
122 Major vascular complication: distal embolization from vascular source
123 Unplanned endovascular or surgical intervention
124 New ipsilateral lower extremity ischemia
125 Surgery for access site-related nerve injury
126 Permanent access site-related nerve injury
127 Other major vascular complication

Minor

130 Minor vascular complication: access site or access site-related vascular injury
131 Minor vascular complication: distal embolization from vascular source
132 Unplanned endovascular stenting or unplanned surgical intervention not meeting criteria for major complication
133 Vascular repair or need for vascular repair
134 Other minor vascular access site complication
140 Failure of closure device leading to alternative treatment

Other TAVR-Related Complications

150 Conversion to open surgery
151 Unplanned used of CPB
152 Coronary artery obstruction
153 Ventricular septal perforation
154 Mitral valve apparatus damage
155 Cardiac tamponade
156 Prosthetic valve thrombosis
157 Valve migration
158 Valve embolization
159 Ectopic valve deployment
160 TAV in TAV deployment
161 Major hemolysis
162 Minor hemolysis
163 Prosthetic valve endocarditis: definite
164 Prosthetic valve endocarditis: possible
165 Major frame fracture
166 Minor frame fracture
167 Other TAVR-related complication

Conduction Disturbances and Arrhythmias

170 Atrio-ventricular block, 1°
171 Atrio-ventricular block, 2°
172 Atria-ventricular block, 3°
173 LBBB
174 RBBB
175 Left anterior fascicular block
176 Left posterior fascicular block
180 Atrial fibrillation
181 Atrial flutter
182 Junctional rhythm (<100 bpm)
183 Junctional rhythm (≥100 bpm)
184 Sinus bradycardia (<50 bpm)
185 Supraventricular tachycardia
186 Ventricular fibrillation
187 Ventricular premature beats
188 Ventricular tachycardia
189 Other arrhythmia

Prosthetic Valve Dysfunction

191 Moderate/severe stenosis
192 Moderate paravalvular regurgitation
193 Severe paravalvular regurgitation
194 Moderate transvalvular regurgitation
195 Severe transvalvular regurgitation
196 Moderate total regurgitation
197 Severe total regurgitation

Other Implantation/Catheterization Procedure-Related Adverse Events

200 Brachial plexus injury
201 Hypovolemia
202 Hypotension requiring intervention
203 Air embolism
204 Venous thrombosis, definite
205 Venous thrombosis, suspected
206 Metabolic acidosis
207 Catheter induced arrhythmia
208 Hemothorax
209 Radiation-induced erythema
210 Other implantation/catheterization

Other Cardiac Adverse Events

300 Cardiac arrest
301 Congestive heart failure
302 Cardiogenic shock
303 Valvular regurgitation, mitral
304 Valvular regurgitation, tricuspid
307 Syncope
308 Palpitations
309 Cyanosis
310 Chest pain
311 Pericardial effusion, hemorrhagic
312 Pericardial effusion, non-hemorrhagic
313 Intracardiac mass
399 Other cardiac event

Respiratory/Pulmonary Adverse Events

400 Respiratory arrest
401 Pneumothorax
402 Chronic pulmonary disease
403 Bronchospasm/asthma
404 Pleural effusion
405 Hemoptysis
406 Respiratory failure
407 Atelectasis
408 Hemothorax
409 Respiratory insufficiency
410 Apnea/hypoventilation
499 Other respiratory/pulmonary

Other Neurologic Adverse Events

500 Seizure(s)
502 Meningitis, infectious
504 Headaches
505 Dizziness
599 Other central nervous system

Gastrointestinal Adverse Events

600 Vomiting
601 Diarrhea
602 Protein losing enteropathy
603 Liver disease
604 Liver failure
699 Other gastrointestinal

Hematologic/Oncologic Adverse Events

700 Cancer/malignancy
701 Coagulopathy
702 Anemia (Hgb <10g or Hct <30%)
703 Thrombocytopenia
704 Transfusion reaction
799 Other hematologic/oncologic

Infection Adverse Events

801 Fever
802 Sepsis, confirmed (positive blood culture)
803 Sepsis, suspected (by clinical findings)
804 Endocarditis, other than the TAV or surgical valve
805 Urinary tract infection
806 Pneumonia
807 Gastroenteritis
808 Hepatitis
809 Upper respiratory tract infection
899 Other infection

Other Renal Adverse Events (Exclusive of AKI)

900 Renal insufficiency
902 Chronic renal failure
903 Proteinuria
904 Urinary retention
999 Other renal

Allergic Reactions

1000 Anaphylaxis
1001 Pruritus
1002 Rash
1003 Contrast reaction/allergy
1004 Medication reaction/allergy
1099 Other allergic reaction

Other

1200 Multi organ failure
1299 Other

5.0 Classification of Causal Relationships

The following definitions are intended as guidelines for classifying causal relationships between the event and the TAV or surgical valve, the catheter delivery system, and the TAVR or SAVR implant procedure.

Causal relationships between event and the TAV or surgical valve

Not related to the TAV or surgical valve	The relationship to TAV or surgical valve can be excluded when: • the event is not a known side effect of the TAV or surgical valve product category the device belongs to or of similar devices; • The event has no temporal relationship with the TAV or surgical valve • The event does not follow a known response pattern to the TAV or surgical valve and is biologically implausible; • The event involves a body-site or an organ not expected In order to establish non-relatedness, not all the criteria listed above might be met at the same time.
Unlikely to be related to the TAV or surgical valve	The relationship with the TAV or surgical valve seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly related to the TAV or surgical valve	The relationship with the TAV or surgical valve is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably related to the TAV or surgical valve	The relationship with TAV or surgical valve seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship "Related" to the TAV or surgical valve	The event is associated with the TAV or surgical valve beyond reasonable doubt when:
	• the event is a known side effect of the TAV or surgical valve product category the device belongs to or of similar devices;
	• the event has a temporal relationship with investigational device use/application or procedures;
	• the event involves a body-site or organ that
	  o the TAV or surgical valve is applied to;
	  o the TAV of surgical valve has an effect on;
	• the event follows a known response pattern to the TAV or surgical valve;
	• other possible causes (eg, an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out
	• harm to the subject is due to error in use
	
	In order to establish relatedness, not all the criteria listed above might be met at the same time.

Timeframe for assessing implant procedure relationships begin when subject is being prepared for the TAVR or SAVR implant (or re-implant) procedure.

Causal relationships between event and the TAVR delivery system

Not related to the TAVR delivery system	The relationship with the TAVR delivery system can be excluded when: • the event is not a known side effect of the TAVR delivery system product category the device belongs to or of similar devices; • The event has no temporal relationship with the use of the TAVR delivery system • The event does not follow a known response pattern to the TAVR delivery sysem and is biologically implausible; • The event involves a body-site or an organ not expected In order to establish non-relatedness, not all the criteria listed above might be met at the same time
Unlikely to be related to the TAVR delivery system	The relationship with the TAVR delivery sysem seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly related to the TAVR delivery system	The relationship with the TAVR delivery system is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably related to the TAVR delivery system	The relationship with the TAVR delivery system seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship "Related" to the TAVR delivery system	The event is associated with the TAVR delivery system reasonable beyond doubt when:
	• the event is a known side effect of the product category the device belongs to or of similar devices;
	• the event has a temporal relationship with the TAVR delivery system use/application;
	• the event involves a body-site or organ that
	  ○ the TAVR delivery system is applied to;
	  ○ the TAVR delivery system has an effect on;
	• the event follows a known response pattern to the TAVR delivery system;
	• other possible causes (eg, an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out
	• harm to the subject is due to error in use
	
	In order to establish relatedness, not all the criteria listed above might be met at the same time.

Causal relationships between event and the TAVR or SAVR implant procedure

Not related to the TAVR or SAVR implant procedure	The relationship with the TAVR or SAVR implant procedure can be excluded when: • the event is not a known side effect of the TAV or SAVR implant procedure; • The event has no temporal relationship with the TAVR or SAVR implant relationship • The event does not follow a known response pattern to the TAVR or SAVR implant procedure and is biologically implausible; • The event involves a body-site or an organ not expected In order to establish non-relatedness, not all the criteria listed above might be met at the same time.
Unlikely to be related to the TAVR or SAVR implant procedure	The relationship with the TAVR or SAVR implant procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly related to the TAVR or SAVR implant procedure	The relationship with the TAVR or SAVR implant procedure is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably related to the TAVR or SAVR implant procedure	The relationship with TAVR or SAVR implant procedure seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship "Related" to the TAVR delivery system	The event is associated with the TAVR or SAVR implant procedure beyond reasonable doubt when:
	• the event is a known side effect of the TAVR or SAVR implant procedure;
	• the event has a temporal relationship with the TAVR or SAVR implant procedure;
	• the event involves a body-site or organ that
	  o the TAVR or SAVR is applied to;
	  o the TAVR or SAVR implant procedure has an effect on;
	• the event follows a known response pattern to the TAVR or SAVR implant procedure;
	• other possible causes (eg, an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out
	• harm to the subject is due to error in use
	
	In order to establish relatedness, not all the criteria listed above might be met at the same time.

Note: Procedure related events refers to the procedure related to the initial application of the investigational medical device only and therefore not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) adverse events.

APPENDIX VI: SAMPLE INFORMED CONSENT FORM: MAIN TRIAL

An informed consent form template will be provided under separate cover.

APPENDIX VII: LEAFLET THICKENING/IMMOBILITY SUB-STUDY PROTOCOL

1.0 Synopsis

Title	Frequency of Leaflet Thickening/Immobility Detected By Multidetector CT Scanning Following Aortic Valve Replacement Sub-Study
Purpose	Evaluate leaflet thickening/immobility (LTI) after transcatheter and surgical aortic valve replacement in subjects enrolled in the Medtronic Transcatheter Aortic Valve (Medtronic TAVR) Low Risk Trial
Design	Subjects participating in the LTI Sub-Study will undergo post-procedure MDCT scanning. An independent MDCT Core Laboratory will evaluate scans for the presence of LTI.
Study Objective	Establish the prevalence of the LTI detected by MDCT angiography following TAVR and SAVR
Investigational Sites	Up to 100 Low Risk sites worldwide. All LTI sites will be participating in the Low Risk Trial
Sample Size	At least 150 evaluable TAVR subjects and at least 150 evaluable SAVR subjects will followed up through one year as part of the sub-study
Subject Selection Criteria	• Enrollment in the Medtronic TAVR Low-Risk Trial • Absence of Chronic Kidney Disease Stage IV or V (eGFR <30 ml/min)
Study Evaluations and Procedures	• Patients who consent to sub study participation will undergo MDCT angiography at 30 days and one year
Professional Services	MDCT Core Laboratory

2.0 Background

Recent publications[75-77] have reported Multidetector Computed Tomography (MDCT) imaging findings in asymptomatic patients following transcatheter and surgical aortic valve replacement (TAVR and SAVR) referred to as leaflet thickening or immobility (LTI). The incidence of LTI in these reports ranged widely from 4%[77] to 40%,[75] and frequencies across device platforms could not be established due to the small number of subjects studied. Similarly, no definitive correlation between LTI and patient characteristics, procedural factors, or clinical events could be made although it was shown that LTI can be resolved with anticoagulation therapy using Vitamin K Antagonists (VKAs).

These preliminary findings highlight the need for further investigation; principally, determining the incidence of LTI in transcatheter and surgical aortic bioprostheses. Foundational work to understand the impact of LTI in terms of late clinical events is also warranted.

3.0 Sub-Study Objective

The objective of the LTI Sub-Study is to establish the prevalence of the LTI detected by MDCT angiography following transcatheter and surgical aortic valve replacement. Additionally, the relationship between LTI and late clinical events will be explored.

4.0 Methodology

Patients enrolled in the LTI Sub-Study will follow all methods and procedures according to the main protocol. This section will provide information on methods and requirements specific to the LTI Sub-Study.

4.1 Sub-Study Design

Subjects will undergo MDCT scanning at 30 days and one year post-implantation. MDCT scans will be acquired by study-trained staff with oversight by a designated cardiovascular imaging specialist to ensure MDCT images are in accordance with the LTI Sub-Study protocol. An independent MDCT Core Laboratory will evaluate site images and determine if LTI is present or absent according to protocol definitions.

4.2 Investigational Sites

The LTI Sub-Study will be conducted at up to 100 investigational sites. Investigational sites must meet the following criteria for LTI Sub-Study participation:

- Demonstrated ability to perform high quality retrospective ECG gated MDCT scans with validated CT equipment meeting minimum requirements for temporal resolution
- Dedicated cardiac CT imaging specialist with experience acquiring and reviewing CT imaging of TAVR patients
- Completion of MDCT Core Lab training for compliance with study imaging protocol
- Participation in ongoing assessment of imaging quality

4.3 Number of Subjects

At least 150 evaluable patients treated with the Medtronic TAVR system bioprostheses and at least 150 evaluable patients treated with surgical valves will be enrolled in the LTI Sub-Study. The MDCT Core Laboratory will determine if patients are evaluable by review of the 30 day MDCT scan.

4.4 Subject Selection Criteria

4.4.1 Inclusion Criteria

Prospective subjects for the LTI Sub-Study must meet all subject selection criteria for enrollment in the Medtronic TAVR Low Risk Trial (see Section 3.3.5 of the main protocol) and undergo device implantation.

4.4.2 Exclusion Criteria

Subjects with history of Chronic Kidney Disease Stage IV or V (eGFR <30 ml/min) are excluded from participation in the LTI Sub-Study.

Additionally if any of the following clinical findings are present at the time of MDCT, the subject is not eligible for image acquisition:

1. Chronic Kidney Disease Stage IV or V (eGFR <30 ml/min)

2. Atrial fibrillation that cannot be rate controlled to ventricular response rate <60 bpm

4.5 Informed Consent

Prior to enrolling in the study, patients should be fully informed of the details of study participation as required by applicable regulations, the site's IRB and by Medtronic. An informed consent addendum specific to the LTI Sub-Study will be reviewed and signed by patients participating in the LTI Sub-Study.

4.6 Screening and Enrollment

See section 3.3.8 and Figure 1 of main protocol for screening and enrollment information.

4.7 Post Procedure Anti-thrombotic Therapy

The recommended post procedure anti-thrombotic regiment for TAVR will be 30 days or more of DAPT followed by aspirin through 12 months. Recommended pharmacology post procedure for SAVR will be a VKA or aspirin in accordance with current guidelines.[13] As the clinical significance of any LTI findings has not been established, treatment of subjects should be based on current standard of care practices. The local clinical site investigator should avoid empiric anticoagulation unless any of the following clinical findings are demonstrated:

- Any neurological event
- Any potential embolic event
- ST segment elevation or Non ST elevation myocardial infarction
- Increase in aortic regurgitation to moderate to severe
- An increase by more than 50% of discharge mean aortic valve gradient or a decrease in the Doppler Velocity Index (DVI) by more than 50%

4.8 Required Evaluations

LTI Sub-Study protocol evaluations should be performed at the investigational site. The protocol required sub-study evaluations are as follows:

30 days (between 30 and 45 days post procedure)

- ECG if history or symptoms of atrial fibrillation are present
- MDCT image acquisition

One year (between 365 and 395 days post procedure)

- ECG if history or symptoms of atrial fibrillation are present
- MDCT image acquisition

4.9 Unblinding of MDCT Core Laboratory Findings

Images will be read in a standard fashion for cardiac and non-cardiac findings by clinical site CT imaging specialist. If deterioration of subject health due to suspected thrombosis occurs, the clinical site may request an unblinding of the MDCT Core Laboratory findings.

4.10 Adverse Events, Clinical Events Committee, Data Safety Monitoring Board

Investigational sites will report events related to sub-study participation as described in the main protocol (Section 3.3.25). The Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB) procedures are found in the main protocol (Section 3.3.26 and Section 3.3.27).

4.11 Statistical Analysis

Primary analysis for the LTI Sub-study will be performed after subjects have completed one year evaluations. Descriptive statistics will be used to identify the presence of LTI at 30 days and 1 year in subjects undergoing aortic valve replacement, with frequencies provided for transcatheter and surgical aortic valves.

5.0 MDCT Image Acquisition

5.1 General requirements

5.1.1 General requirements for CT hardware

- Single source CT scanner
  - With 8 cm detector coverage (Toshiba Aquilion Premium, Philips iCT256)
  - Volume CT scanner with 16 cm detector coverage (Aquilion One/Vision; GE Revolution)
- Dual Source CT scanners (Siemens Somatom Definition, Flash, Force)

5.1.2 General requirements for CT data acquisition

- Contrast enhancement
  - 4-6 ml/s contrast media injection rate
- ECG-assisted/synchronized data acquisition
  - Helical/spiral data acquisition with retrospective ECG-gating
  - ECG-gated volume acquisition (one beat, one slab, 8 cm or 16 cm acquisition)
  - CAVEAT: sequential/axial data acquisition with prospective ECG-triggering or high-pitch helical data acquisition is not acceptable
- Data acquisition covering the entire cardiac cycle
- Sufficient z-axis coverage to allow for coverage of the transcatheter heart valve or surgical heart valve

5.1.3 General requirements for CT data reconstruction

- Multiphasic, thin sliced, overlapping axial image reconstructions
  - ≤0.625 mm slice thickness with overlap
  - 5% or 10% increments (relative reconstruction), or 50ms increments (absolute reconstruction)
  - Coverage of the entire cardiac cycle
- ECG-editing in case of increased heart rate variability and premature contractions when using retrospective ECG-gating.

5.2 Specific recommendations

5.2.1 Heart rate control

- Use oral or intra-venous beta-blockade for heart rate control, in particular when using single-source/volume scanners.

- Indications/contraindications for administration of beta-blockade should follow institutional standards/guidelines

5.2.2 Acquisition technique

The following table lists recommended techniques for ECG-assisted data acquisition stratified by scanner type:

Scanner	Recommendation
GE	
GE Revolution (Volume scanner)	ECG-gated, 'one-beat, one-slab' volume acquisition (detector has 16cm coverage)
Philips	
Philips iCT 256	ECG-gated, 'one-beat, one-slab' volume acquisition (detector has 8cm coverage)
Siemens	
Siemens Dual-Source (Somatom Definition, Flash, Force)	Helical/spiral acquisition with retrospective ECG-gating (do not use high-helical pitch acquisition or step-and shoot mode)
Toshiba	
Toshiba Aquilion One/Vision or Aquilion Premium	ECG-gated, 'one-beat, one-slab' volume acquisition (detectors have 16 cm or 8 cm coverage)

5.2.3 Acquisition settings

The following table lists recommended settings for the ECG-assisted data acquisition:

Parameter	Recommendation
Tube current	Absolute or reference tube current settings similar to institutional settings for routine coronary cardiac CT
Dose modulation	Dose modulation is not recommended in order to allow for images of equal, diagnostic image quality throughout the entire cardiac cycle
Tube voltage	120 kVp, alternatively 140 kVp to reduce beam hardening artifacts of stent frame (in particular with volume-scanners); use of 100kVp or 80kVp is not recommended; automated algorithms for tube voltage selection may need to be overridden
Collimation	Thinnest possible, eg, 0.625 mm with GE and Philips hardware, 0.6 mm with Siemens Hardware, 0.5 mm/0.25 mm with Toshiba hardware

5.2.4 Contrast administration

The following table lists recommendations for contrast administration:

Parameter	Recommendation
Iodine concentration	Iodinated contrast agent as per institutional standards
Flow rate	4-6 ml/sec
Volume	As per institutional standard for routine coronary cardiac CT, commonly 50-80 cc
IV-access	Antecubital vein is recommended
Timing	Bolus tracking to allow for peak contrast in the ascending aorta

5.2.5 Image reconstruction

The following table lists recommendations for image reconstruction settings:

Parameter	Recommendation
Technique	Both, reconstructions with filtered back projection or iterative reconstruction are acceptable. If iterative reconstruction is used, the strength/weighting should be intermediate (eg, ADMIRE/SAPHIRE/IRIS strength 3, ASIR 40%)
Slice thickness	Thinnest possible, eg, 0.625 mm with GE and Philips hardware, 0.6 mm with Siemens Hardware, 0.5 mm/0.25 mm with Toshiba hardware
Slice overlap	Slice overlap is recommended to improve MPR quality; eg, 0.4 mm increment with 0.6 mm slice thickness when using Siemens equipment
Reconstruction field of view and matrix	Small field of view (FOV) limited to the heart; 512 x 512 matrix
Reconstruction kernel	Same kernel as used for coronary CTA per institutional standard; alternatively use edge-pronounced kernel ('stent' kernel, eg, I46f) in particular with pronounced blooming
Multiphasic reconstruction	• Coverage of the entire cardiac cycle Volume scanner (GE Revolution, Toshiba Aquilion One/Vision): • 5% or 10% increments Other scanner: • 5% or 10% increments (relative reconstruction), or 50 ms increments (absolute reconstruction, not available on Philips Hardware)

6.0 MDCT Core Laboratory Data Analysis

MDCT analysis is performed on dedicated post-processing work-stations using multiplanar reformats. Analysis steps resulting in either binary values or semi-quantitative, grading scale values are performed by two physician readers independently. In case of disagreement, arbitration will be performed by a third reader. Quantitative analysis resulting in continuous variables (such as caliper measurements) are performed by one expert physician reader.

6.1 Assessment and documentation of image quality based on pre-defined standards

- Verification that a multiphasic dataset has been provided and assessment of which parts of the cardiac cycle are covered by the multiphasic reconstruction.
- Assessment of slice thickness and slice overlap.
- Assessment of presence of sufficient contrast attenuation.
- Assessment of image quality throughout cardiac cycle, with focus on presence of reconstruction with diagnostic image quality in mid-systole and diastole

6.2 Leaflet thickening and immobility (LTI) assessments

The location of the affected cusp(s) will be defined with regard to the bioprosthetic valve commissure that is aligned with one of the outflow tabs. This tab also has an x-ray marker 'c' which may be visible on the reformatted CT images. For surgical valves, the location of the affected cusp(s) will be defined with regard to the former native cusp position as right, left, or non-coronary.

6.2.1 Leaflet thickening

Leaflet thickening will be assessed as follows:

- Presence of hypoattentuating leaflet thickening or focal hypoattenuating abnormality attached to one or more prosthetic leaflets identifiable on at least two reconstructed planes
- Maximum thickness of the affected cusp will be measured on the long axis of the device

6.2.2 Leaflet immobility

Quantification of leaflet immobility/restriction requires systolic reconstruction phases of diagnostic image quality and will be evaluated using multiplane reformats (MPRs) and graded in regard to the involvement along the curvilinear leaflet at its center

- Partial immobility limited to basal restriction (<25%)
- Partial immobility, 25-75%
- Immobile or largely immobile (>75%)

6.2.3 Prosthesis position and expansion

For the TAV stent frame expansion will be planimetrically assessed at the inflow, mid-level, and outflow regions of device.

7.0 Sample Informed Consent Addendum for LTI Sub-Study

A sample informed consent addendum will be provided under separate cover.

APPENDIX VIII: Quality of Life Questionairres

A sample Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol (EQ-5D) will be provide under separate cover

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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan Title	Transcatheter Aortic Valve Replacement (TAVR) in Patients with the Medtronic Transcatheter Aortic Valve Replacement System (TAVR) in Patients at Low Risk for Surgical Aortic Valve Replacement (SAVR) Continued Access Trial
Addendum To	Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement Trial Number 10234430DOC
Study Product Name	Medtronic Evolut R Transcatheter Aortic Valve (TAV) System Medtronic Evolut PRO TAV System
Sponsor/Local Sponsor	Medtronic Coronary and Structural Heart Clinical 8200 Coral Sea St. NE, MVS 66 Mounds View, MN 55112 United States
Document Version, Date	1A
Document Date	25-JUL-2018
Document Reference Number	10831957DOC

Table of Contents

1. Glossary

Term	Definition
TAVR	Transcatheter Aortic Valve Replacement
SAVR	Surgical Aortic Valve Replacement
TAV	Transcatheter Aortic Valve
TVT-R	Transcatheter Valve Therapies Registry
CMS	Centers for Medicare & Medicaid Services
KCCQ	Kansas City Cardiomyopathy Questionnaire
RDC	Remote Data Capture
TTE	Transthoracic Echocardiography
ICF	Informed Consent Form
MDCT	Multi-Detector Computed Tomography
PCI	Percutaneous Coronary Intervention
DTL	Delegated Task List
eCRFs	Electronic Case Report Forms
SID Number	Subject Identification Number

2. Synopsis

Title	Transcatheter Aortic Valve Replacement (TAVR) in Patients with the Medtronic Transcatheter Aortic Valve Replacement System (TAVR) in Patients at Low Risk for Surgical Aortic Valve Replacement (SAVR) Continued Access Trial
Clinical Trial Type	Continued Access
Product Name	Investigational Devices • Evolut R 23, 26, 29, and 34 mm Transcatheter Aortic Valve (TAV) • Medtronic Evolut PRO TAV 23, 26, and 29 mm • EnVeo R Delivery Catheter System with EnVeo Inline Sheath and EnVeo R Loading System • EnVeo PRO Delivery Catheter System and EnVeo PRO Loading System
Sponsor	Medtronic
Local Sponsor	Coronary and Structural Heart Clinical 8200 Coral Sea St. NE, MVS 66 Mounds View, MN 55112 United States
Investigation Purpose	Evaluate the safety and effectiveness of the Medtronic TAVR System in patients with severe aortic stenosis at low risk for SAVR
Primary Objective	Evaluate the safety and effectiveness of the Medtronic TAVR system as measured by the rate of all-cause mortality or all stroke at 1 year in subjects who have a low predicted risk of operative mortality for SAVR. Annual clinical summaries will report long term follow-up and adverse events (as collected through the TVT-R and Centers for Medicare & Medicaid Services (CMS) claims data) through 10 years post implant.
Study Design	Multi-center, prospective, non-randomized continued access trial. All heart team approved subjects will be assigned to TAVR with the Medtronic TAVR system
Primary Endpoint	All-cause mortality or all stroke at 1 year
Secondary Endpoint	Safety

	• Composite of death, all stroke, life-threatening bleed, or major vascular complication at 30 days • New permanent pacemaker implantation at 30 days • Prosthetic valve endocarditis at one year • Prosthetic valve thrombosis at one year • All stroke at one year • Life-threatening bleed at one year • Valve-related dysfunction requiring repeat procedure at one year (surgical or interventional therapy) Effectiveness • Quality of Life as assessed by Kansas City Cardiomyopathy (KCCQ) at one year • Device Success (intra-procedure)
Sample Size	The sample size of the continued access phase of the TAVR in Low Risk Patients Trial will be determined based on FDA approval. Maximum sample size is not expected to exceed 3660 attempted implant subjects in the United States.
Patient Population	Subjects with severe aortic stenosis with an indication for SAVR with a bioprosthesis whose predicted risk of mortality at 30 days is <3% per multidisciplinary local heart team assessment
Key Inclusion Criteria	• Patient is considered low risk for SAVR, where low risk is defined as predicted risk of mortality for SAVR <3% at 30 days per multidisciplinary local heart team assessment • Severe aortic stenosis, defined as: ▪ Symptomatic aortic stenosis Aortic valve area ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **OR** mean gradient ≥40 mmHg, **OR** maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest ▪ Asymptomatic aortic stenosis: - Very severe aortic stenosis with an aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** maximal aortic velocity ≥5.0 m/sec, or mean gradient ≥60 mmHg by transthoracic echocardiography at rest, **OR**

	- Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** a mean gradient ≥40 mmHg, or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** an exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia **OR** - Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** mean gradient ≥40 mmHg, or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** a left ventricular ejection fraction <50%. • Indicated for SAVR with a bioprosthesis
Key Exclusion Criteria	• Bicuspid aortic valve identified by echocardiography, MDCT, or Magnetic Resonance Imaging • Significant ascending aortopathy
Study Procedures and Assessments	• Subjects will be enrolled, and if approved, and an implant is attempted, they will be followed via TVT-R through 1 year with assessments at pre-, peri- and post-procedure, discharge, 30 days and 1 year • Additional clinical data available from CMS claims data will be reported out to 10 years
Co-Principal Investigators	Jeffrey Popma, MD, Interventional Cardiologist Beth Israel Deaconess Medical Center, Boston MA Michael Reardon, MD, Cardiothoracic Surgeon Houston Methodist Hospital, Houston TX
Vendors	• ACC/STS Transcatheter Valve Therapies Registry™ • Centers for Medicare & Medicaid Services • Independent Explant Pathology Core Laboratory

3. Introduction

3.1. Background

The Medtronic TAVR in Low Risk Patients Trial is a multi-center, prospective, randomized, interventional pre-market trial. The purpose of this trial is to evaluate the safety and effectiveness of the Medtronic TAVR System in patients with severe aortic stenosis at low risk for SAVR.

The purpose of this addendum to the Medtronic TAVR in Low Risk Patients Trial protocol is to conclude the randomized phase of the trial and initiate the single-arm, non-randomized, continued access phase of the trial.

3.2. Purpose

The purpose of this trial is to evaluate the safety and effectiveness of the Medtronic TAVR System in patients with severe aortic stenosis at low risk for SAVR.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective

The primary objective is to characterize the composite event rate of all-cause mortality and all stroke at 1 year post procedure.

4.1.2. Secondary Safety Endpoints

- Composite of death, all stroke, life-threatening bleed, or major vascular complication at 30 days
- New permanent pacemaker implantation at 30 days
- Prosthetic valve endocarditis at one year
- Prosthetic valve thrombosis at one year
- All stroke at one year
- Life-threatening bleed at one year
- Valve-related dysfunction requiring repeat procedure at one year (surgical or interventional therapy)

4.1.3 Secondary Effectiveness Endpoints

- Quality of Life as assessed by Kansas City Cardiomyopathy (KCCQ) change from baseline at one year.
- Device Success (intra-procedure)

5. Study Design

The continued access trial is a multi-center, prospective, non-randomized, interventional trial conducted in the United States. The maximum sample size is not expected to exceed 3660 subjects with an attempted implant, this maximum is based on enrollment during the randomized phase of the trial and will be distributed in semi-annual allocations of 732 attempted implants per 6 months. No site will enroll more than 15% of the semi-annual allocation (ie, no site will implant > 110 subjects during any given allocation period) without prior authorization from Medtronic. Subjects who exit from the trial after implantation will not be replaced.

All enrolled, qualified, and heart team approved low risk subjects will be implanted with the Medtronic Evolut R or Evolut PRO system. Subjects that undergo an attempted implant or are implanted will be followed via TVT-R through 1 year with assessments at pre-, peri- and post-procedure, discharge, 30 days and 1 year. Additional clinical data available from CMS data claims will be reported out to 10 years.

5.1. Duration

Subjects will be consented for follow-up through 10 years. The enrollment period for this continued access study will be through completion of FDA review for the PMA supplement for the TAVR Low indication; therefore, the estimated total duration of the trial (first subject enrolled to last subject completing his/her last follow-up exam) is estimated to be 12 years.

5.2. Rationale

This trial will evaluate the safety and effectiveness of the Medtronic Transcatheter Aortic Valve Replacement system (Evolut R and Evolut PRO systems) in patients with aortic stenosis who are at low predicted risk for mortality at 30 days with SAVR. Data from this trial will be used to additionally support regulatory reports for the TAVR in Low Risk Patients Trial.

6. Product Description

6.1 Trial Materials

Medtronic will control the supply of investigational devices and trial materials (eg, Investigator Site File, eCRF access). Investigational devices will not be sent to the site until the site is activated. Commercial product may be used in situations where investigational is not available.

Medtronic will not provide any trial-specific equipment to the sites. Equipment used for assessing study variables (eg, echocardiographic systems) should be maintained per the site's standard procedures.

6.2 Device Accountability

The Evolut R and Evolut PRO systems are not approved for use in low risk patients, and therefore are considered investigational devices. As such, they should be stored as labeled and in a secure location. The method of storage should prevent the use of these investigational devices for applications other than mentioned in this CIP. The investigator shall maintain adequate records of the receipt and disposition of all investigational devices.

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

- Investigational device name
- TAV serial number

- Lot number (for delivery catheter system and loading system only)
- Date of receipt of device
- Name of person receiving the device
- Name of person using the device
- Date of implant or use
- ID number of subject receiving or using the device
- Disposition (implanted, disposed of, or returned to Medtronic)

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

- TAV serial numbers
- Lot numbers (for delivery catheter system and loading system only)
- The quantity and reason for the device being returned to Medtronic or disposed of
- Name of the person who returned or disposed of each device
- Date of shipment back to Medtronic

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

6.3. Device Malfunction or Explant

In the event of a device malfunction of the Medtronic TAVR system prior to implant, or in the event a TAV or surgical bioprosthesis is explanted after implant (due to reintervention or autopsy), the TAV or surgical bioprosthesis, and/or affected components Medtronic TAVR system should be sent to Medtronic at the following address:

Medtronic
Attn: Explant Lab [PE#]
1851 E. Deere Avenue
Santa Ana, CA 92705-5720

Additional details surrounding the device return process are contained within the Medtronic explant kit that will be provided upon notification of a device malfunction or explant.

This trial will utilize the CV Pathology Explant Core Lab for any explants performed during the duration of the trial.

7. Selection of Subjects

7.1. Study Population

The population includes males and females with severe aortic stenosis with a clinical indication for surgical aortic valve replacement with a bioprosthesis who are at low predicted risk of mortality at 30 days for surgical aortic valve replacement.

7.2. Subject Enrollment

Subjects are considered enrolled at time of consent.

7.3. Inclusion Criteria

Prospective subjects must meet all following inclusion criteria to be eligible for the trial:

1. Severe aortic stenosis, defined as follows:
   a) For symptomatic patients:
   Aortic valve area ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **OR** mean gradient ≥40 mmHg, **OR** Maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest
   b) For asymptomatic patients:
      - Very severe aortic stenosis with an aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** maximal aortic velocity ≥5.0 m/sec , or mean gradient ≥60 mmHg by transthoracic echocardiography at rest, **OR**
      - Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** a mean gradient ≥40 mmHg or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** an exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia **OR**
      - Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** mean gradient ≥40 mmHg, or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** a left ventricular ejection fraction <50%.
2. Patient is considered low risk for SAVR, where low risk is defined as predicted risk of mortality for SAVR <3% at 30 days per multidisciplinary local heart team assessment.
3. The subject and the treating physician agree that the subject will return for all post-procedure follow-up visits.

7.4. Exclusion Criteria

If any of the following exclusion criteria are present, the prospective subject is not eligible for implantation:

1. Subject has refused surgical aortic valve replacement (SAVR) as a treatment option – **Not Applicable for Continued Access**
2. Any condition considered a contraindication for placement of a bioprosthetic valve (eg, subject is indicated for mechanical prosthetic valve).
3. A known hypersensitivity or contraindication to any of the following that cannot be adequately pre-medicated:
   a. aspirin or heparin (HIT/HITTS) and bivalirudin
   b. ticlopidine and clopidogrel
   c. Nitinol (titanium or nickel)
   d. contrast media
4. Blood dyscrasias as defined: leukopenia (WBC <1000 mm^3), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states.
5. Ongoing sepsis, including active endocarditis.
6. Any percutaneous coronary or peripheral interventional procedure with a bare metal stent within 30 days prior to Heart Team approval, or drug eluting stent performed within 180 days prior to Heart Team approval.
7. Multivessel coronary artery disease with a Syntax score >22 and/or unprotected left main coronary artery.
8. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 10 weeks of Heart Team assessment.
9. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.
10. Recent (within 2 months of Heart Team assessment) cerebrovascular accident (CVA) or transient ischemic attack (TIA).
11. Gastrointestinal (GI) bleeding that would preclude anticoagulation.
12. Subject refuses a blood transfusion.
13. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits).
14. Estimated life expectancy of less than 24 months due to associated non-cardiac co-morbid conditions.
15. Other medical, social, or psychological conditions that in the opinion of the investigator precludes the subject from appropriate consent or adherence to the protocol follow-up exams.
16. Currently participating in an investigational drug or another device trial (excluding registries).
17. Evidence of an acute myocardial infarction ≤30 days before the trial procedure due to unstable coronary artery disease (WHO criteria).
18. Need for emergency surgery for any reason.
19. Subject is pregnant or breast feeding.

20. Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable

Anatomical exclusion criteria:

21. Pre-existing prosthetic heart valve in any position.
22. Severe mitral regurgitation amenable to surgical replacement or repair.
23. Severe tricuspid regurgitation amenable to surgical replacement or repair.
24. Moderate or severe mitral stenosis amenable to surgical replacement or repair.
25. Hypertrophic obstructive cardiomyopathy with left ventricular outflow gradient.
26. Bicuspid aortic valve verified by echocardiography, MDCT, or MRI.
27. Prohibitive left ventricular outflow tract calcification.
28. Sinus of Valsalva diameter unsuitable for placement of the self-expanding bioprosthesis.
29. Aortic annulus diameter of <18 or >30 mm.
30. Significant aortopathy requiring ascending aortic replacement.

For transfemoral or transaxillary (subclavian) access:

31. Access vessel mean diameter <5.0 mm for Evolut 23R, 26R, or 29R mm TAV, or access vessel mean diameter <5.5 mm for Evolut 34R mm or TAVR PRO TAV. However, for transaxillary (subclavian) access in patients with a patent LIMA, access vessel mean diameter <5.5mm for Evolut 23R, 26R, or 29R mm TAV, or access vessel mean diameter <6.0 mm for the Evolut 34R or TAVR PRO TAV[i].

[i]For subjects with a patent LIMA undergoing tranaxillary (subclavian) access, the minimal access vessel mean diameter is 5.5 mm for the Evolut 23R, 26R, and 29R TAV, and 6.0 mm for the Evolut 34R and TAVR PRO TAV.

8. Study Procedures

Trial procedures will continue to be followed as outlined in the primary TAVR in Low Risk Patients protocol, unless otherwise noted below.

8.1. Schedule of Events

Follow-up protocol evaluations should be performed at the trial site. The protocol recommended evaluations for each trial interval are listed as follows.

Baseline/Pre-implant (within 12 weeks prior to submission to the Heart Team; except for MDCT and coronary arteriography) [ii]

Baseline data will be collected for subjects prior to procedure to capture data points included in the TVT-R data collection forms including:

- Subject demographics
- History and Risk Factors, including cardiac history and other history and risk factors[iii]
- Pre-Procedure Status, including NYHA class, cardiac medications
- 5 Meter Walk Test
- KCCQ-12
- STS Risk Factor
- Labs
- Coronary Arteriography
- TTE
- MDCT
- Heart Team Assessment

[ii] Pre-implant MDCT and Coronary arteriography should be performed within 365 days of Heart Team approval.
[iii] Definitions of STS risk factors and other co-morbidities are provided in Appendix I.

Peri- and Post- Procedure

The following peri- and post-procedure data will be collected for subjects to capture data points included in the TVT-R data collection forms, including:

- Procedure information
- Device information
- Hemodynamics (pre-implant and post-implant)
- Post Procedure Labs
- 12-lead ECG
- Echocardiogram
- Adverse events, interventions and surgical procedure assessment

Discharge (7 days post procedure or discharge, whichever comes first)

The following data will be collected for subjects prior to discharge to capture data points included in the TVT-R data collection forms, including:

- RBC/whole blood transfusion
- Number of hours in ICU
- Discharge date and status
- Discharge medications
- Adverse event assessment

30 days (between 30 to 45 days post implant)

The following data will be collected for subjects at 30 days to capture data points included in the TVT-R data collection forms including:

- Clinical Assessment
- Five meter walk
- KCCQ-12
- 12-lead ECG
- Echocardiogram
- Medications
- NYHA Classification
- Adverse event assessment

One Year (between 335 and 395 days post implant)

The following data will be collected for subjects at 1 year to capture data points included in the TVT-R data collection forms including:

- Clinical Assessment
- Five meter walk
- KCCQ-12
- 12-lead ECG
- Echocardiogram
- Medications
- NYHA Classification
- Adverse event assessment

Evaluations 2 - through 10 - years

Subject evaluations will occur via standard of care treatment. Data collected through CMS claims data will be reported to the sponsor out to 10 years post implant. These clinical summaries will report long term follow-up and monitor adverse events [all-cause mortality, all stroke, and repeat procedure for valve-related dysfunction (surgical or interventional therapy)].

8.1.1 Echocardiography

Transthoracic echocardiography (TTE) will be performed at the following intervals: pre-implant, peri- and post- procedure, 30 days, and 1 year. Exams will not be sent to an Echo Core Lab for central assessment.

8.2. Subject Consent

Prior to enrolling in the trial, patients are required to be fully informed of the details of trial participation as required by applicable regulations, the site's IRB and by Medtronic. Informed consent must be obtained from each patient prior to conducting any protocol-induced activities beyond standard of care, by using the informed consent form (ICF) approved by that site's IRB and by Medtronic. The ICF must be signed and dated by the patient and by the person obtaining the consent. Any additional persons required by the site's IRB to sign the informed consent form must also comply.

8.3. Subject Screening

The process of patient screening and subject enrollment is as follows:

- Patients identified by or presented to the trial site with aortic stenosis will be screened by the investigative team for the criteria described in 7.3 and 7.4, Inclusion and Exclusion Criteria, using available medical records, including relevant imaging studies previously performed for diagnostic purposes.
- If the patient is deemed a potential candidate for the trial, the investigational status of the Medtronic TAVR System and all aspects of the trial will be explained to the patient. The patient will then be invited to participate in the Low Risk Continued Access Trial.
- If the patient agrees to participate, written informed consent will be obtained. This will be considered the point of enrollment and the subject will be assigned a Subject ID number.
- The subject will undergo transthoracic echocardiography (TTE) to assess his/her degree of aortic stenosis.
- Subjects who meet the criteria for aortic stenosis[iv] will undergo:
    - Multi-Detector Computed Tomography (MDCT) of their peripheral vasculature and aortic annulus to assess anatomic suitability for the Medtronic TAVR, and
    - Local Heart Team assessment to determine his/her operative risk profile for SAVR.
- All study-specific screening assessments will be indicated on the provided consent eCRF in Oracle RDC.
- Subjects confirmed eligible for implantation by the local Heart Team will be assigned to TAVR with the Medtronic TAVR system.
- In case of required coronary revascularization, concomitant percutaneous coronary intervention (PCI)[v] and TAVR is encouraged; however, staging is left to the discretion of the operator.
- Implantation should occur within 90 days of local Heart Team approval.
- All Attempted Implant and Implanted subject's baseline, implant, and follow-up information will be entered in to TVT-R.

Patients should give written consent before undergoing any protocol testing. However, if any of protocol baseline/screening evaluations (eg, echocardiography, MDCT, coronary arteriography, lab work) have been performed for clinical diagnostic purposes prior to consenting, they can be used as the Protocol exams, provided they were obtained within the protocol time windows and contain the necessary information.

[iv] If a subject has balloon aortic valvuloplasty after their qualifying TTE, they must have repeat TTE to confirm he/she meets criteria for severe aortic stenosis as described in Section 3.3.5.1 prior to Heart Team approval of the subject.

[v] Index PCI should be performed at the TAVR implanting center; index PCI operators will be considered investigators.

8.4. Subject Disposition

Sites will maintain electronic records in Oracle RDC of subjects consented (point of subject enrollment) where Subject's ID number will be assigned to each patient. Electronic records in Oracle RDC will also include, date of heart team approval, date attempted and implanted, the name of the implanters and information identifying the devices used. Subjects who are consented but are not taken to the procedure room for implantation will be exited from the trial and will not be followed beyond the date of trial exit. Subjects with an attempted implant who do not receive a TAV for any reason will be followed for the trial duration. Subjects that have their TAV explanted will be followed for the trial duration.

8.5. Assessment of Safety

Adverse events (as identified on the TVT-R data collection forms) will be captured on the AE section of the TVT-R data collection forms through the 12-month follow-up visit and via CMS claims data through 10 years. Due to the limitations of the TVT-R database, this study will not follow ISO14155:2011, MEDDEV 2.7/3, or 21 CFR 812 regarding pre-market safety compliance requirements.

It is the responsibility of the physician(s) to assess the subject for adverse events and capture the required adverse event information on the AE section of the TVT-R data collection form, to ensure site specific safety reporting requirements are met, and follow Medical Device Reporting requirements. Upon data received from the TVT-R or CMS, Medtronic will ensure all device-related adverse events, AEs, SAEs, and Deaths are reviewed and reported upon.

A CRO contracted by ACC/STS will adjudicate Stroke, TIA, and Aortic Valve Reintervention AEs. If necessary, the CRO may request source documentation for an adverse event identified on the TVT-R data collection form for further information.

8.6. Recording Data

Trial sites will assign a unique ID number that is obtained from Oracle RDC to each subject. Records of the subject/subject ID relationship will be maintained by the trial site. Individual subject medical information obtained as a result of this trial will be considered confidential.

This trial will utilize an Oracle RDC system for subject tracking that is the property of Medtronic. This trial will also utilize the TVT-R database system for data collection through 12 months follow up for all attempted implant and implanted subjects.

Trial personnel will be delegated for eCRF completion Delegated Tasks List (DTL) in the TVT-R and RDC system. The Data Collection Forms and eCRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the trial. For Oracle RDC, username and password will be

provided to trial personnel trained and delegated to eCRF completion and / or approval per the DTL. The investigator (or approved sub-investigator) will electronically sign the appropriate pages of each eCRF in Oracle RDC.

After all one year follow-up is complete, sites will no longer enter subject data in the TVT-R database. Standard of care clinical data available through claims data submitted to CMS will be provided for 2- through 10-year follow-up. ACC/STS will link CMS claims data with subject records in TVT-R. The CMS and TVT-R linked data is provided to Medtronic with adverse event tables for 2- through 10-year follow-up reporting requirements.

Any clinical data entered in to the databases must have a corresponding source document.

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

No trial document or image should be destroyed without prior written agreement between Medtronic and the investigator. 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 Medtronic.

8.7. Time Windows for Completion and Submission of eCRFs and Data Collection Forms

The TVT-R Data Collection Forms and Oracle RDC electronic case report forms (eCRFs) should be completed as soon as possible and recommended to be completed within 2 weeks of the applicable follow-up visit.

8.8. Deviation Handling

The investigator shall not deviate from the protocol. Protocol deviations will not be required to be reported for the continued access trial to Medtronic and Medtronic will not be held responsible for reviewing protocol deviations. Investigators are required to adhere to local IRB/EC procedures for reporting deviations.

Medtronic will not be responsible for submitting a report of patients to the FDA that were implanted before obtaining informed consent. Medtronic will also not be responsible for securing or tracking compliance in instances that the investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA.

8.9. Subject Withdrawal or Discontinuation

All subjects will be encouraged to remain in the trial through the last follow-up visit at 10 years. Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of total trial subjects. If a subject is discontinued from the trial early, the reason for discontinuation should be documented in the subject file and a Trial Exit eCRF must be completed.

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

If a subject discontinues the trial at any time, is withdrawn from the trial early, or completes all protocol required follow-up a Trial Exit eCRF must be completed and they should continue to be followed by the implanting site according to their routine clinical practice for aortic valve patients. If, for any reason, this is not possible for a particular subject, or if a subject needs to change their follow-up site at any time point after conclusion of the trial, investigators should refer subjects to a local site with appropriate training and experience in managing patients with implanted aortic valves.

9. Data Review Committees

A Clinical Events Committee (CEC) will not provide independent medical review and adjudication of adverse event data for the continued access trial.

A Data Safety Monitoring Board (DSMB) will not assess interim trial data and provide recommendations to Medtronic regarding trial conduct for the continued access trial.

10. Risks and Benefits

The risks and benefits of the continued access trial are identical to the risks and benefits outlined in the TAVR in Low Risk Patients protocol.

11. Statistical Design and Methods

The statistical analyses will be performed by Medtronic employed statisticians. The study will provide descriptive results only as there are no statistical hypotheses associated with this study.

11.1 Analysis Populations

11.1.1 Approved Population

If the subject signs informed consent, meets all inclusion and none of the exclusion criteria, and the Heart Team determines the subject is suitable for the trial, the subject is assigned TAVR and then added to the approved population. Within the approved population the following analysis sets are distinguished:

- **The attempted implant set:** The attempted implant set consists of all Heart Team approved subjects with an attempted implant procedure, defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed, or any monitoring line placed.
- **The implanted set:** The Implanted set consists of all the attempted implant subjects who are implanted with the TAV device.

The primary analysis for the primary objective, secondary safety objectives and secondary effectiveness objectives (except device success) will use the attempted implant set. Device success will use the implanted set.

11.2 Description of Baseline Variables

Baseline demographic and clinical variables will be summarized. All continuous variables will be summarized as means, medians, standard deviations, interquartile ranges, minima and maxima, and categorical variables will be summarized as frequencies and percentages.

11.3 Sample Size

The sample size of the continued access phase of the TAVR in Low Risk Patients Trial will be determined based on FDA approval. The sample size is not expected to exceed 3660 attempted implant subjects at up to 61 hospitals in the United States.

11.4 Subject Accountability

Follow-up visits at 30-days and one year are conducted by the sites with data collected through TVT-R. The distribution of follow- up visits and visit compliance by one year will be summarized, which include number expected, visit completed, missed visit, deaths, withdrawal, lost to follow-up and visit pending.

When TVT-R data is merged with CMS data, acquired data for longer-term follow-up (2 through 10 years) subjects that are matched between the databases will be included in subject accountability and analysis. CMS data does not have specified follow-up visits. The number of subjects matched between TVT-R and CMS will be provided, with the number of subjects at risk in the cohort for each specified timepoint (1 year, 2 year, 3 year, 4 year, 5 year, 6 year, 7 year, 8 year, 9 year and 10 year).

11.5 Analysis of Endpoints

The endpoints are descriptive and no statistical hypothesis test will be performed. Device success will be summarized using frequencies and percentages. Kaplan-Meier estimates at 30 days will be provided for composite of death, all stroke, life-threatening bleed or major vascular complication and new permanent pacemaker implantation. Kaplan-Meier estimates at 1 year will be provided for prosthetic valve endocarditis, prosthetic valve thrombosis and life-threatening bleeding. In addition, Kaplan-Meier estimates will be provided for all-cause mortality, all stroke and aortic valve dysfunction requiring repeat procedure at 1 year and annually up to 10 years. KCCQ at baseline and 1 year, and KCCQ change from baseline to 1 year will be summarized as means, medians, standard deviations, interquartile ranges, minima, maxima and 95% confidence intervals.

12. Ethics

12.1.Statement(s) of Compliance

The trial will be conducted in compliance with the protocol, and 21 CFR Parts 36, 43, 47, 50, 54, and 56. In addition, the trial will be conducted in compliance with 21 CFR Part 11 and in accordance with the Declaration of Helsinki. The principles of the Declaration of Helsinki are implemented in this trial by means of the Patient Informed Consent (IC) process, Ethics Board approval, trial training, clinical trial registration, pre-clinical testing, risk benefit assessment, and publication policy.

The trial will follow 21 CFR Part 812 except where noted in the clinical investigation plan and FDA approval documentation.

Regulatory authority notification/approval to conduct the trial is required. 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.

13. Study Administration

13.1. Study Training

Prior to involvement in the continued access trial activities, Medtronic and ACC/STS will provide training to the investigative team on the trial methods, procedures, data entry, and requirements. Medtronic will maintain documentation of these training sessions.

13.2. Monitoring

No source data verification will occur, and subject records will not be reviewed by Medtronic. If necessary, source documents may be requested for safety event analysis.

Measures to ensure data cleanliness and integrity in the TVT-R database will be consistent with TVT-R processes and procedures.

13.3. Data Management

For data stored in Oracle RDC, Medtronic will be responsible for the processing and quality control of the data. Centralized data review, database cleaning and issuing and resolving data queries will be done according to Medtronic internal SOPs and the Data Management Plan for this trial. The trial database will be developed and validated per the Data Management Plan for this trial. The Oracle RDC database will maintain an audit trail of all changes made to the eCRFs.

For data stored in TVT-R, ACC/STS will be responsible for data quality review and processing. Data review will be conducted by programmatic quality checks throughout the data entry and submission process.

13.4. 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 is to be recorded on all trial documents to link them to the subject's medical records at the site. To maintain confidentiality, the subjects' name or any other personal identifiers should not be recorded on any trial document other than the informed consent form. In the event a subject's name is included for any reason, it will be masked as applicable. In the event of inability to mask the identification (eg, digital media), it will be handled in a confidential manner by the authorized personnel.

13.5. Liability

Medtronic (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 IRB/EC if required.

13.6. CIP Amendments

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

13.7. Record Retention

The investigator must retain the Investigator Site File, source documents, and any other data collection records, until informed by Medtronic they no longer need to be retained. At a minimum, the investigator must retain records for at least 2 years (or for 15 years if required by local law) after the last approval of a marketing application and until there are no pending or contemplated marketing applications. The investigator should take measures to prevent accidental or early destruction of the trial related materials.

13.8. Publication and Use of Information

Medtronic and the Low Risk Publications Committee can utilize the data from the continued access trial as desired for publications or other use of information. 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.

13.9. Suspension or Early Termination

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

Medtronic may decide to suspend or prematurely terminate an investigation site. If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB.

If any action is taken by an EC/IRB with respect to the investigation, that information will be forwarded to the sponsor.

14 Appendices

APPENDIX I: DEFINITIONS OF STS FACTORS AND OTHER CO-MORBIDITIES

1.0 STS Factors

The STS Risk Calculator can be found at www.sts.org

Factor	Definition
Heart Failure	Physician documentation or report that the patient has been in a state of heart failure within the past 2 weeks. Heart failure is defined as physician documentation or report of any of the following clinical symptoms of heart failure described as unusual dyspnea on light exertion, recurrent dyspnea occurring in the supine position, fluid retention; or the description of rales, jugular venous Distension, pulmonary edema on physical exam, or pulmonary edema on chest x-ray presumed to be cardiac dysfunction. A low ejection fraction alone, without clinical evidence of heart failure does not qualify as heart failure. An elevated BNP without other supporting documentation should not be coded as CHF.
Diabetes	History of diabetes diagnosed and/or treated by a healthcare provider. The American Diabetes Association criteria include documentation of the following: 1. Hemoglobin A1c ≥6.5%; or 2. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L); or 3. 2-h Plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test; or 4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L) This does not include gestational diabetes.
Dialysis	Subject currently (prior to surgery) undergoing dialysis

1.0 STS Factors (continued)

Factor	Definition
Hypertension	Any of the following: • documented history of hypertension diagnosed and treated with medication, diet and/or exercise, • prior documentation of blood pressure >140 mmHg systolic or 90 mmHg diastolic for patients without diabetes or chronic kidney disease, or prior documentation of blood pressure >130 mmHg systolic or 80 mmHg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease • currently on pharmacologic therapy to control hypertension
Immunocompromise	Indicate whether immunocompromise is present due to immunosuppressive medication therapy within 30 days preceding the operative procedure or existing medical condition. This includes, but is not limited to systemic steroid therapy, anti-rejection medications and chemotherapy. This does not include topical steroid applications, one time systemic therapy, inhaled steroid therapy or preprocedure protocol.
Arrhythmia	• History or preoperative arrhythmia (sustained ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial flutter, third degree heart block, second degree heart block, sick sinus syndrome) that has been treated with any of the following modalities: • ablation therapy • AICD • pacemaker • pharmacologic treatment • electrocardioversion, defibrillation
Atrial fibrillation/atrial flutter	Presence of atrial fibrillation or flutter within 30 days of the procedure
Myocardial infarction	History of at least one documented myocardial infarction at any time prior this surgery

1.0 STS Factors (continued)

Factor	Definition
Endocarditis	Indicate whether the patient has a history of endocarditis. Endocarditis must meet at least 1 of the following criteria: 1. Patient has organisms cultured from valve or vegetation. 2. Patient has 2 or more of the following signs or symptoms: fever (>38°C or >100.4°F), new or changing murmur*, embolic phenomena*, skin manifestations* (ie, petechiae, splinter hemorrhages, painful subcutaneous nodules), congestive heart failure*, or cardiac conduction abnormality. *with no other recognized cause and at least 1 of the following: a. organisms cultured from 2 or more blood cultures b. organisms seen on Gram's stain of valve when culture is negative or not done c. valvular vegetation seen during an invasive procedure or autopsy d. positive laboratory test on blood or urine (eg, antigen tests for H mmunocom, S mmunocom, N mmunocompro, or Group B Streptococcus) evidence of new vegetation seen on echocardiogram and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.
Chronic lung disease	Presence of lung disease and severity level as follows: None Mild: FEV1 60% to 75% of predicted, and/or on chronic inhaled or oral bronchodilator therapy. Moderate: FEV1 50% to 59% of predicted, and/or on chronic steroid therapy aimed at lung disease. Severe: FEV1 <60 or Room Air pCO2 >50. CLD present, severity not documented Unknown A history of chronic inhalation reactive disease (asbestosis, mesothelioma, black lung disease or pneumoconiosis) may qualify as chronic lung disease. Radiation induced pneumonitis or radiation fibrosis also qualifies as chronic lung disease. (if above criteria is met) A history of atelectasis is a transient condition and does not qualify. Chronic lung disease can include patients with chronic obstructive pulmonary disease, chronic bronchitis, or emphysema. It can also include a patient who is currently being chronically treated with inhaled or oral pharmacological therapy (eg, beta-adrenergic agonist, anti-inflammatory agent, leukotriene receptor antagonist, or steroid). Patients with asthma or seasonal allergies are not considered to have chronic lung disease.

1.0 STS Factors (continued)

Factor	Definition
Peripheral vascular disease	History of peripheral arterial disease (includes upper and lower extremity, renal, mesenteric, and abdominal aortic systems). This can include: • claudication , either with exertion or at rest • amputation for arterial vascular insufficiency • vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (excluding dialysis fistulas and vein stripping) • documented aortic aneurysm with or without repair • positive noninvasive test (eg, ankle brachial index ≤0.9, ultrasound, magnetic resonance or computed tomography imaging of >50% diameter stenosis in any peripheral artery, ie, renal, subclavian, femoral, iliac), or angiographic imaging **Excludes disease in the carotid cerebrovascular arteries, or thoracic aorta. PVD does not include deep vein thrombosis*
Cerebrovascular disease	Indicate whether the patient has a current or previous history of any of the following: a. Stroke: Stroke is an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, where the neurological dysfunction lasts for greater than 24 hours. b. TIA: is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction, where the neurological dysfunction resolves within 24 hours. c. Noninvasive or invasive arterial imaging test demonstrating ≥50% stenosis of any of the major extracranial or intracranial vessels to the brain d. Previous cervical or cerebral artery revascularization surgery or percutaneous intervention. This does not include chronic (nonvascular) neurological diseases or other acute neurological insults such as metabolic and anoxic ischemic encephalopathy.
Cerebrovascular accident	History of stroke. Stroke is an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, where the neurological dysfunction lasts for greater than 24 hours.
Previous cardiac interventions	Any previous cardiovascular intervention, either surgical or non-surgical, which may include those done during the current admission.

1.0 STS Factors (continued)

Factor	Definition
Number of diseased vessels	The number of diseased major native coronary vessel systems: LAD system, Circumflex system, and/or Right system with ≥50% narrowing of any vessel preoperatively. NOTE: Left main disease (≥50%) is counted as TWO vessels (LAD and Circumflex, which may include a Ramus Intermedius). For example, left main and RCA would count as three total. A vessel that has ever been considered diseased, should always be considered diseased.
Inotropes	Subject received IV inotropic agents within 48 hours preceding surgery.
Cardiogenic shock	A sustained (>30 min) episode of hypoperfusion evidenced by systolic blood pressure <90 mm Hg and/or, if available, cardiac index <2.2 L/min per square meter determined to be secondary to cardiac dysfunction and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support (eg, IABP, extracorporeal circulation, VADs) to maintain blood pressure and cardiac index above those specified levels. Note: Transient episodes of hypotension reversed with IV fluid or atropine do not constitute cardiogenic shock. The hemodynamic compromise (with or without extraordinary supportive therapy) must persist for at least 30 min.
Resuscitation	Patient required cardiopulmonary resuscitation before the start of the operative procedure which includes the institution of anesthetic management. Capture resuscitation timeframe: within 1 hour or 1-24 hours pre-op
Incidence	Indicate if this is the patient's: • first surgery • first re-op surgery • second re-op surgery • third re-op surgery • fourth or more re-op surgery. Surgery is defined as cardiothoracic operations (heart or great vessels) surgical procedures performed with or without cardiopulmonary bypass (CPB). Also include lung procedures utilizing CPB or tracheal procedures utilizing CPB. Reoperation increases risk due to the presence of scar tissue and adhesions.

1.0 STS Factors (continued)

Factor	Definition
Cardiac presentation on admission	Indicate the patient's cardiac symptoms at the time of this admission. No Symptoms: No Symptoms, no angina. Stable Angina: Angina without a change in frequency or pattern for the prior 6 weeks. Angina is controlled by rest and/or oral or transcutaneous medications. Unstable Angina: There are three principal presentations of unstable angina: 1. Rest angina (occurring at rest and prolonged, usually >20 minutes); 2. New-onset angina (within the past 2 months, of at least Canadian Cardiovascular Society Class III severity); or 3. Increasing angina (previously diagnosed angina that has become distinctly more frequent, longer in duration, or increased by 1 or more Canadian Cardiovascular Society class to at least CCS III severity). –Non-ST Elevation MI (Non- STEMI): The patient was hospitalized for a non-ST elevation myocardial infarction (STEMI) as documented in the medical record. Non-STEMIs are characterized by the presence of both criteria: a. Cardiac biomarkers (creatinine kinase-myocardial band, Troponin T or I) exceed the upper limit of normal according to the individual hospital's laboratory parameters with a clinical presentation which is consistent or suggestive of ischemia. ECG changes and/or ischemic symptoms may or may not be present. b. Absence of ECG changes diagnostic of a STEMI –ST Elevation MI (STEMI): The patient 'presented with a ST elevation myocardial infarction (STEMI) or its equivalent as documented in the medical record. STEMIs are characterized by the presence of both criteria:

	a. ECG evidence of STEMI: New or presumed new ST segment elevation or new left bundle branch block not documented to be resolved within 20 minutes. ST segment elevation is defined by new or presumed new sustained ST-segment elevation at the J-point in two contiguous electrocardiogram (ECG) leads with the cutoff points: ≥0.2 mV in men or ≥0.15mV in women in leads V2-V3 and/or ≥0.1 mV in other leads and lasting greater than or equal to 20 minutes. If no exact ST-elevation measurement is recorded in the medical chart, physician's written documentation of ST elevation or Q waves is acceptable. If only one ECG is performed, then the assumption that the ST elevation persisted at least the required 20 minutes is acceptable. Left bundle branch block (LBBB) refers to new or presumed new LBBB on the initial ECG. b. Cardiac biomarkers (creatinine kinase-myocardial band, Troponin T or I) exceed the upper limit of normal according to the individual hospital's laboratory parameters a clinical presentation which is consistent or suggestive of ischemia. Angina equivalent Other: Presentation/symptom not listed above.

1.0 STS Factors (continued)

Factor	Definition
Status of the procedure	Elective: The patient's cardiac function has been stable in the days or weeks prior to the operation. The procedure could be deferred without increased risk of compromised cardiac outcome. Urgent: Procedure required during same hospitalization in order to minimize chance of further clinical deterioration. Examples include but are not limited to: Worsening, sudden chest pain, CHF, acute myocardial infarction (AMI), anatomy, IABP, unstable angina (USA) with intravenous (IV) nitroglycerin (NTG) or rest angina. Emergent: Patients requiring emergency operations will have ongoing, refractory (difficult, complicated, and/or unmanageable) unrelenting cardiac compromise, with or without hemodynamic instability, and not responsive to any form of therapy except cardiac surgery. An emergency procedure is one in which there should be no delay in providing operative intervention. The patient's clinical status includes any of the following: a. Ischemic dysfunction (any of the following): (1) Ongoing ischemia including rest angina despite maximal medical therapy (medical and/or IABP)); (2) Acute Evolving Myocardial Infarction within 24 hours before surgery; or (3) pulmonary edema requiring intubation. b. Mechanical dysfunction (either of the following): (1) shock with circulatory support; or (2) shock without circulatory support. Emergent Salvage: The patient is undergoing CPR en route to the OR or prior to anesthesia induction or has ongoing ECMO to maintain life.

1.0 STS Factors (continued)

Co-morbidity	Definition/Criteria
Porcelain aorta or severely atherosclerotic aorta	Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible.
Frailty	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence Criteria: • 5 meter walking time • Grip strength • BMI <20 kg/m^2 and/or weight loss 5 kg/yr • Serum albumin <3.5 g/dL • Cognitive impairment or dementia
Sever liver disease/cirrhosis	Any of the following: • Child-Pugh class C • MELD score ≥10 • Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt • Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction
Hostile chest	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications from prior surgery • Evidence of severe radiation damage (eg, skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) • History of multiple recurrent pleural effusions causing internal adhesions
IMA or other critical conduit(s) crossing midline and/or adherent to posterior table of sternum	A patent IMA graft that is adherent to the sternum such that injuring it during re-operation is likely. A patient may be considered extreme risk if any of the following are present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. • The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3 mm of the posterior table.
Severe pulmonary hypertension Severe right ventricular dysfunction	Primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure Criteria as defined by the guidelines (eg, TAPSE <15mm, RV end-systolic area >20 cm^2)

APPENDIX II: TVT-R DATA COLLECTION FORM IDENTIFED ADVERSE EVENTS

2.0 Adverse Events

- Myocardial Infarction
- Coronary Compression or Obstruction
- Endocarditis
- Conduction/Native Pacer Disturbance Requiring Pacer
- Conduction/Native Pacer Disturbance Requiring ICD
- Cardiac Arrest
- Atrial Fibrillation
- Annular Dissection
- Aortic Dissection
- Perforation with or without Tamponade
- Bleeding at Access Site
- Hematoma at Access Site
- Retroperitoneal Bleeding
- GI Bleed
- GU Bleed
- Other Bleed
- Device Migration
- Device Embolization Left Ventricle
- Device Embolization Aorta
- Device Recapture or Retrieval Transient Ischemic Attack
- Ischemic Stroke
- Hemorrhagic Stroke
- Undetermined Stroke
- Device Fracture
- Device Thrombosis
- Other Device Related Event
- New Requirement for Dialysis
- Aortic Valve Re-intervention
- Unplanned Other Cardiac Surgery or Intervention
- Unplanned Vascular Surgery or Intervention
- Percutaneous Coronary Intervention
- Valve Related Readmission
- Non-Valve Related Readmission
- Major Vascular Complication
- Minor Vascular Complication
- Transapical Related Event
- Major Bleeding Event
- Life Threatening Bleeding

15 Version History

Version	Summary of Changes	Author(s)/Title
1A	Initial Release	Morgan Lillehei /Senior Clinical Research Specialist