Medtronic Transcatheter Aortic Valve Replacement (TAVR) Low Risk Bicuspid Study

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Clinical Investigation Plan

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Clinical Investigation Plan

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1. Glossary

List of terms and definitions and/or acronyms used within this document are listed below.

Term/Acronym	Definition
2D	Two dimensional
3D	Three dimensional
AE	Adverse event
ACT	Active clotting time
ADE	Adverse device effect
AR	Aortic regurgitation
AS	Aortic stenosis
AVR	Aortic valve replacement
BAV	Balloon aortic valvuloplasty
BSA	Body surface area
BNP	B-type natriuretic peptide
CEC	Clinical Events Committee
CIP	Clinical investigational plan
CLS	Compression loading system
CT	Computed tomography
CVA	Cerebrovascular accident
DCS	Delivery catheter system
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FDA	U.S. Food and Drug Administration
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
HIT/HITTS	Heparin-Induced Thrombocytopenia / Heparin-Induced Thrombocytopenia and Thrombosis
ICF	Informed consent form
INR	International normalized ratio
IRB	Institutional Review Board
IFU	Instructions for use
ITT	Intent-to-treat
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MCS	Medtronic CoreValve® System

Term/Acronym	Definition
MI	Myocardial infarction
NYHA	New York Heart Association
PAV	Percutaneous aortic valve
PCI	Percutaneous coronary intervention
RBBB	Right bundle branch block
QoL	Quality of Life
SAE	Serious adverse event
STS	Society of Thoracic Surgeons
TAVI	Transcatheter aortic valve implantation
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TTE	Transthoracic echocardiography
UADE	Unanticipated adverse device effect
VKA	Vitamin K antagonists

2. Synopsis

Title	Transcatheter Aortic Valve Replacement (TAVR) with Medtronic TAVR System in Patients with Severe Bicuspid Aortic Valve Stenosis and at Low Predicted Risk of Mortality with Surgical Aortic Valve Replacement (SAVR)
Product Name	Medtronic TAVR System: • Evolut PRO Transcatheter Aortic Valve (TAV) 23, 26, and 29 mm • Evolut R 23, 26, 29, and 34 mm TAV • EnVeo PRO and EnVeo R Delivery Catheter System • EnVeo PRO and EnVeo R Loading System
Sponsor	Medtronic Coronary and Structural Heart Clinical 8200 Coral Sea St NE, MVS 66 Mounds View, MN55112 United States
Primary Objective	To evaluate the procedural safety and efficacy of the Medtronic TAVR system in patients with bicuspid aortic anatomy and severe aortic stenosis at low risk for SAVR
Primary Endpoints	Safety All-cause mortality or disabling stroke rate at 30 days Efficacy Device success rate, defined as: • Absence of procedural mortality, AND • Correct positioning of a single prosthetic heart valve into the proper anatomical location, AND • Absence of moderate or severe total prosthetic valve regurgitation (at 18 hours to 7 days)
Additional Outcome Measures	1. All-cause mortality at one year, and annually through 10 years 2. All stroke (disabling and non-disabling) at one year, and annually through 10 years 3. New permanent pacemaker implantation at 30 days 4. Myocardial Infarction at 30 days 5. Life-threatening bleeding at 30 days, one year, and annually through 10 years 6. Prosthetic valve endocarditis at 30 days, one year, and annually through 10 years 7. Prosthetic valve thrombosis at 30 days, one year, and annually through 10 years

	8. Valve-related dysfunction requiring repeat procedure at 30 days, one year, and annually through 10 years 9. Repeat hospitalization for aortic valve disease at 30 days, one year, and annually through 10 years 10. Repeat hospitalization for ascending aorta disease at 30 days, one year, and annually through 10 years 11. Hemodynamic performance metrics by Doppler echocardiography • Mean aortic gradient at baseline, 30 days, one year, annually through 5 years and at years 7 and 10 • Effective orifice area at baseline, 30 days, one year, annually through 5 years and at years 7 and 10 • Degree of total, peri, and transvalvular prosthetic regurgitation at baseline, 30 days, one year, annually through 5 years and at years 7 and 10 12. New York Heart Association (NYHA) functional classification at baseline, 30 days, one year and annually through 5 years and at years 7 and 10 13. Health-related quality of life as assessed by • Kansas City Cardiomyopathy (KCCQ) instrument at baseline, 30 days, one year, annually through 5 years • EQ-5D survey at baseline, 30 days and one year
Study Design	Multi-center, prospective, single arm
Investigation Sites	Up to 40 sites in the United States
Number of Subjects	150 subjects with attempted implant
Patient Population	Severe aortic stenosis subjects with bicuspid aortic anatomy and 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	1. Severe aortic stenosis, defined as follows: 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 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. Bicuspid aortic valve anatomy (all sub-types) confirmed by MDCT
Key Exclusion Criteria	1. Significant ascending aortopathy requiring surgical repair 2. Ascending aorta diameter >4.5 cm 3. Age <60 years
Subject Evaluation	1. Clinical assessment at pre and post-procedure, discharge, 30 days, 1 year, and annually through 5 years and at years 7 and 10 2. Transthoracic echo at pre and post-procedure, 30 days, 1 year, and annually through 5 years and at years 7 and 10 3. Multi-Detector Computed Tomography at pre-procedure 4. Blood samples at pre-procedure; I.N.R. for subjects on Vitamin K antagonists (VKA) only at discharge, 30 days and annually through 5 years 5. 12-lead ECG at pre-procedure, discharge, and 30 days
Study Co-Chairs	Jeffrey Popma, MD, Interventional Cardiologist Beth Israel Deaconess Medical Center, Boston MA Michael Reardon, MD, Cardiothoracic Surgeon Houston Methodist Hospital, Houston TX
Study Co-Principal Investigators	John Forrest, MD, Interventional Cardiologist Yale University, New Haven CT Basel Ramlawi, MD, Cardiothoracic Surgeon Winchester Medical Center, Winchester VA
Professional Services	• Independent Echocardiography Core Laboratory • Independent Clinical Events Committee • Independent Data Safety Monitoring Committee • 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)

3. Introduction

3.1. Background

Following the first implantation in 2002 [1] TAVR has evolved to become a standard procedure at specialized heart centers worldwide. TAVR has been established as a safe and effective treatment option for patients with symptomatic severe aortic stenosis who are at intermediate, high and extremely high risk for surgical aortic valve replacement [2-8].

The Medtronic CoreValve TAVR system received the CE Mark in 2007, and FDA approval in 2014. To date, over 65,000 patients have been implanted with the Medtronic CoreValve system in over 70 countries, with more than 20,000 of these patients enrolled in post-approval registries or clinical studies that further confirm the safety and performance of the CoreValve device. There is extensive published experience demonstrating the CoreValve system is fulfilling its intended role with a favorable risk/benefit ratio [9-13]. Rigorous clinical studies have established its safety and effectiveness, with improved mortality and quality of life compared with medical therapy in extreme risk patients [6], superiority to SAVR among high operative risk patients [7] and noninferiority to surgery in patients at intermediate surgical risk [8].

As experience with early generation TAVR devices increased, significant improvements in TAVR outcomes were achieved due to better patient selection, increasing operator experience, and iterations in device technology, important issues remained to be addressed, including the occurrence of major procedural complications [14-16], stroke [17, 18], paravalvular aortic regurgitation [19, 20], vascular complications [21, 22] and need for new permanent pacemaker implantation [23-26].

To this end, Medtronic developed modifications to the CoreValve frame and delivery catheter system to enable resheathing or full recapture of the device before release from the delivery system. These modifications were incorporated in the CoreValve Evolut R system (hereafter “Evolut R system”). The ability to resheath or recapture the device allows the operator to reposition or remove the bioprosthesis if the initial implant positioning was sub-optimal (too high or too low). This feature is desirable in that it facilitates accurate final positioning, which has been shown to mitigate risks associated with sub-optimal positioning such as paravalvular leak [27, 28] acute migration [16] and AV-conduction disturbance related to implant depth [23].

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 valve sizes involving 301 patients have been conducted in Australia, New Zealand, Europe, and the United States. These clinical studies confirmed 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 are 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 26R and

29R valve sizes, and FDA approval in June of 2015 for the Evolut 23R, 26R and 29R sizes. Subsequently, the Evolut R 34 mm size was approved for use in the United States and Europe.

In order to continue striving for improvement with TAVR systems, Medtronic developed additional modifications to the Medtronic Evolut R system. The next-generation Evolut PRO system represents an enhancement to the Evolut R system and the latest Medtronic TAVR technology. The Evolut PRO TAVs feature a porcine pericardial tissue wrap on the outside of the frame (outer wrap) that covers the first 1.5 cells of the inflow portion of the TAV. The wrap is designed to reduce paravalvular leak (PVL). As the outer wrap has been added to the inflow portion of the TAV, a minor design modification has been made to the LS inflow cone to reduce friction during loading of the TAV. The clinical configuration of this iteration to Evolut R was called the Medtronic TAVR 2.0 system (TAVR 2.0).

Medtronic completed a comprehensive protocol of bench testing that collectively demonstrated the functionality of TAVR 2.0, and that the changes associated with the modification to the valve did not impact the structural integrity, hydrodynamic performance, or durability of the TAVR 2.0 bioprosthesis. The next generation device was approved in US for use in clinical trials in March 2016 under the name of Medtronic TAVR 2.0 System and with commercial approval in March 2017 was branded as “Evolut PRO system”.

In July 2017, the Medtronic CoreValve, Evolut R, and Evolut PRO systems were approved for use in the United States for subjects at intermediate risk for SAVR.

In January 2018, FDA approved various minor modifications to the EnVeo R Delivery Catheter System (DCS) and EnVeo R Loading System (LS). The devices, as modified, are marketed under the trade name EnVeo PRO Delivery Catheter System and EnVeo PRO Loading System. With these changes, the most current generation of Medtronic TAVR technology became the Evolut PRO system for 23mm, 26mm and 29mm sizes used with the EnVeo PRO DCS and LS. Evolut R TAV 34mm is the most current generation of the 34 mm and is also compatible with the EnVeo PRO DCS and EnVeo PRO LS.

Over time, regulatory approvals have been received for use of Medtronic TAVR in several additional patient populations (eg, transcatheter aortic valve (TAV) in failed aortic bioprosthesis, end stage renal disease, and patients with severe AS but presenting with low gradient and low flow) who were not included in the original Medtronic TAVR clinical studies. Another subset of patients excluded from the original Medtronic TAVR studies were patients presenting with symptomatic severe aortic stenosis and congenital bicuspid aortic anatomy. It is reported that over 50% of all surgical aortic valve replacements are due to bicuspid aortic valve disease [29], 6% of the general population over 85 years has a bicuspid valve and 2-year mortality for these subjects following presentation of aortic stenosis symptoms with no treatment is 50% [30]. In their 2014 paper, Colombo and Latib reported the prevalence of bicuspid aortic anatomy among patients presenting for SAVR in their 80s and 90s as 18% and 22%, respectively [31]. Current literature does not provide specific information regarding the prevalence of bicuspid aortic valve anatomy among patients considered at low risk for SAVR. However, in their 2012 paper, Roberts et al reported a prevalence of bicuspid aortic valves in 51% of patients between the ages of 51 and 79 who underwent SAVR [56].

Multiple publications have indicated that use of TAVR in subjects with bicuspid aortic valve anatomy is feasible; however, additional research is required to determine benefits of TAVR compared to SAVR [32-35]. Wijesinghe and colleagues [32] evaluated 11 high-risk patients with a bicuspid aortic valve treated with a balloon-expanded TAV. They found that 27% and 14% of subjects experienced grade 2+ paravalvular leak (PVL) at post-procedure and at 1 year, respectively. Mortality was reported as 7% at 30 days and 36% at the 1 year. At 1 year, all surviving subjects were either NYHA class I or II. Similarly, Himbert and colleagues examined 15 bicuspid aortic valve patients deemed to be high-risk implanted with a self-expanding TAV [33]. They reported that 7% of subjects experienced grade 2+ PVL post-procedure. Mortality was reported as 7% at 30 days and 13% at a mean follow-up time of 8 months and of the surviving patients at 8 months, 79% were in either NYHA class I or II. Two other studies examining a total of 247 bicuspid patients who received a TAV reported 1-year mortality as 18% and 17% [34, 35]. These studies have reported permanent pacemaker implant rates from 19-40% [33-35]. The 30-day post implant rate of ≥ grade 2 PVL was 28.4%; however, it was only 17.4% in patients that had MSCT-based sizing used to determine the appropriate valve size.

As an extension of the established use of the Medtronic TAVR system in extreme, high, and intermediate risk severe aortic stenosis patients, Medtronic initiated the TAVR in Low Risk Patients IDE in March 2016. The low risk IDE is ongoing and will evaluate the safety and effectiveness of the Medtronic TAVR system in tricuspid aortic valve patients with aortic stenosis who are at low predicted risk for mortality with SAVR. The current study will be conducted under the Medtronic TAVR in Low Risk Patients IDE and will evaluate the procedural safety and efficacy of Medtronic TAVR (Evolut PRO system and Evolut R system) in patients with severe bicuspid aortic valve stenosis who are at low predicted risk of mortality with SAVR.

Data from this study will be used to support regulatory submissions related to the use of Medtronic TAVR in patients with severe bicuspid aortic valve stenosis who are at a low predicated risk of mortality with SAVR.

3.2. Purpose

This study will evaluate procedural safety and efficacy of the Medtronic Transcatheter Aortic Valve Replacement system (Evolut PRO and Evolut R systems) in patients with severe bicuspid aortic valve stenosis who are at low predicted risk of mortality at 30 days with SAVR.

4. Objectives and Endpoints

4.1. Objectives

Primary Objective

The primary objective is to assess procedural safety and efficacy of the Medtronic TAVR system in patients with severe bicuspid aortic valve stenosis who are at low predicted risk of mortality at 30 days with SAVR.

Primary Endpoints

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

Safety

All-cause mortality or disabling stroke rate at 30 days

Efficacy

Device success rate, defined as:

- Absence of procedural mortality, AND
- Correct positioning of a single prosthetic heart valve into the proper anatomical location, AND
- Absence of moderate or severe total prosthetic valve regurgitation (at 18 hours to 7 days)

Additional Outcome Measures

Additional outcome measures are listed below.

1. All-cause mortality at one year, and annually through 10 years
2. All stroke (disabling and non-disabling) at one year, and annually through 10 years
3. New permanent pacemaker implantation at 30 days
4. Myocardial infarction at 30 days
5. Life-threatening bleeding at 30 days, one year, and annually through 10 years
6. Prosthetic valve endocarditis at 30 days, one year, and annually through 10 years
7. Prosthetic valve thrombosis at 30 days, one year, and annually through 10 years
8. Valve-related dysfunction requiring repeat procedure at 30 days, one year, and annually through 10 years
9. Repeat hospitalization for aortic valve disease at 30 days, one year, and annually through 10 years
10. Repeat hospitalization for ascending aorta disease at 30 days, one year, and annually through 10 years
11. Hemodynamic performance metrics by Doppler echocardiography
    - Mean aortic gradient at baseline, 30 days, one year, annually through 5 years and at years 7 and 10
    - Effective orifice area at baseline, 30 days, one year, annually through 5 years and at years 7 and 10
    - Degree of total, peri, and transvalvular prosthetic regurgitation at baseline, 30 days, one year, annually through 5 years and at years 7 and 10
12. New York Heart Association (NYHA) functional classification at baseline, 30 days, one year and annually through 5 years and at years 7 and 10
    NYHA function classification will be reported as proportions at each specified time point.
13. Health-related quality of life as assessed by

- Kansas City Cardiomyopathy (KCCQ) instrument at baseline, 30 days, one year, annually through 5 years
- EQ-5D survey at baseline, 30 days and one year

5. Study Design

This is a multi-center, prospective, single-arm clinical study. The study objective will be assessed by evaluating procedural efficacy and safety results at 30 days.

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

- 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 Echocardiography Core Laboratory will evaluate all echocardiograms; echocardiographic endpoint results will be based on Core Lab assessments.
- Study sites should follow their institutional procedures for maintenance of imaging and laboratory equipment used for assessing the study variables.

5.1. Duration

Subjects will be followed up for 10 years. The enrollment period is estimated to be between 12-24 months therefore the estimated total duration of the study (first subject enrolled to last subject completing his/her last follow-up exam) is estimated to be 12 years.

5.2. Rationale

The safety and effectiveness of balloon-expandable and self-expanding TAVR systems has been established in patients with severe symptomatic aortic stenosis who are considered at intermediate through extreme risk for SAVR [2-8], and is currently being evaluated in low risk patients. However, patients with bicuspid aortic valve anatomy were excluded from these pivotal studies.

Anatomical differences between bicuspid and tricuspid aortic valves include increased annular ellipticity; asymmetrical, bulky and heavily calcified leaflets, and commissural fusion in bicuspid patients [31]. These anatomical differences can present challenges for TAVR systems and can impact positioning of the prosthetic valve within the annulus, expansion of valve frame, and sealing of valve annulus [31]. The bicuspid aortic valve anatomy differences could theoretically lead to sub-optimal procedural outcomes resulting in higher rates of procedural mortality, stroke, paravalvular regurgitation, or implantation of multiple devices. Therefore, the impact of the anatomical differences between bicuspid and tricuspid aortic valve anatomies on the clinical performance of TAVR systems can be assessed by evaluating procedural and short term (30 day) clinical outcomes.

Previous studies with TAVR in patients with tricuspid aortic valves have shown a consistent mortality hazard after the procedural period [36]. In addition, similar one and two-year mortality rates have been reported for patients with bicuspid and tricuspid aortic valve anatomy [37, 38]. Hence, it is reasonable to assume that if the procedural outcomes are similar between patients with bicuspid and tricuspid anatomies, outcomes beyond the procedural period will be similar.

Therefore, the primary endpoints in this study measured at 30 days will effectively assess the clinical performance in patients with bicuspid aortic valve anatomy. The endpoints are clinically relevant and address the most important procedural safety and efficacy aspects of the Medtronic TAVR System in subjects with bicuspid aortic valves. In addition, the endpoints are objectively defined, measurable in the majority of the subjects, and consistent with current recommendations for endpoints in TAVR clinical studies. This observational study is not hypothesis driven; however, the results from the primary endpoints the Low Risk bicuspid study cohort will be compared to and analyzed in the context of the procedural safety and efficacy results from the TAVR arm of the Low Risk Trial randomized cohort. Therefore, the clinical study as described is justified.

6. Product Description

The Medtronic CoreValve Evolut PRO system (hereafter "Evolut PRO system") and CoreValve Evolut R system (hereafter "Evolut R system") will be used in this study. The systems are collectively referred to as "Medtronic TAVR systems".

The study devices include the followings and described in the following sections:

- Evolut PRO Transcatheter Aortic Valve (TAV) 23 mm, 26 mm, 29 mm
- Evolut R Transcatheter Aortic Valve (TAV) 23 mm, 26 mm, 29 mm, 34 mm
- EnVeo PRO and EnVeo R Delivery Catheter System (DCS)
- EnVeo PRO and EnVeo R Loading System (LS)

6.1. Evolut PRO System

The Evolut PRO system has similar principles of operation and critical performance as the Evolut R system. The Evolut PRO system comprises the following components:

- Transcatheter Aortic Valve (TAV)
- Delivery Catheter System (DCS)
- Loading System (LS)

A listing of the system components is provided in Table 1.

Table 1. The Evolut PRO system components

Component	Model Number	Size (mm)	Aortic Annulus Diameter (mm)
Evolut PRO TAV	TAV-MDT2-23-C	23	18 – 20
	TAV-MDT2-26-C	26	20 – 23
	TAV-MDT2-29-C	29	23 – 26
EnVeo R Catheter Delivery System with EnVeo InLine Sheath (20 Fr)	EnVeoR-N-C DS-MDT2-C	23, 26, and 29	Not applicable
EnVeo PRO Catheter Delivery System (16eFr)	ENVPRO-16-C	23, 26, and 29	Not applicable
EnVeo R Loading System (for Pro TAVs)	LS-MDT2-23-C LS-MDT2-2629-C	23, 26, and 29	Not applicable
EnVeo PRO Loading System (16eFr)	LS-ENVPRO-1623-C	23	Not applicable
	LS-ENVPRO-16-C	26 and 29	Not applicable

Transcatheter Aortic Valve Prosthesis (TAV)

The transcatheter aortic valve (TAV) is a single-use, implantable device. The Evolut PRO TAV is available in three sizes (23, 26 and 29mm), covering an aortic annulus diameter of 18 to 26 mm (Table 1). The TAV is comprised of three leaflets and a sealing skirt constructed from glutaraldehyde-fixated porcine pericardium, sewn to a compressible and self-expandable Nitinol support frame (Figure 1). 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. The Evolut PRO TAVs are identical to the Evolut R TAVs, with the exception of a minor design modification incorporated to aid in sealing of the TAV in the native anatomy, and a minor change in one region of suture material on the 23 mm TAV, which is also used on the larger Evolut R TAVs.

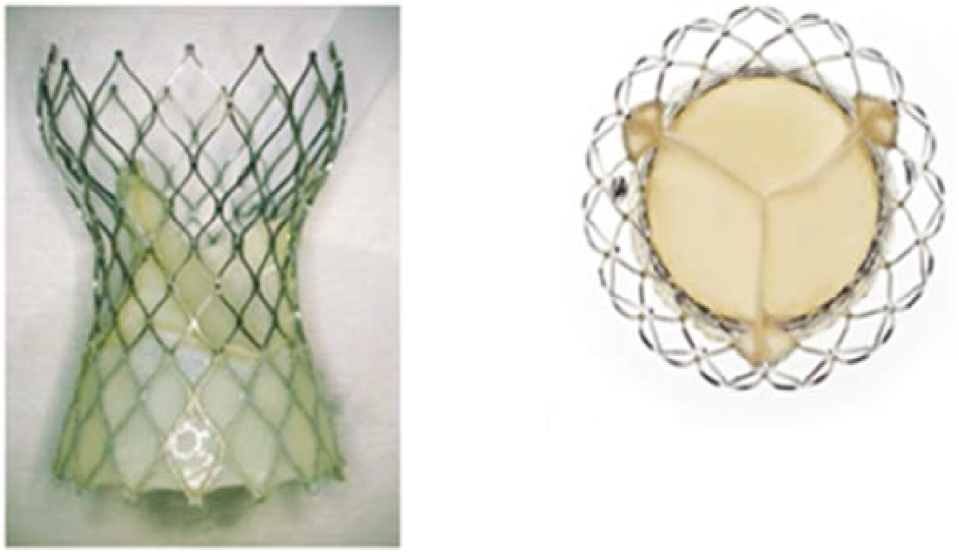

Figure 1. Evolut PRO TAV

EnVeo PRO Delivery Catheter System with InLine Sheath

EnVeo PRO Delivery Catheter System facilitates the placement of the TAV within the annulus of the aortic valve (Figure 2). 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 is compatible with 18 Fr or 20 Fr introducers, respectively.

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.

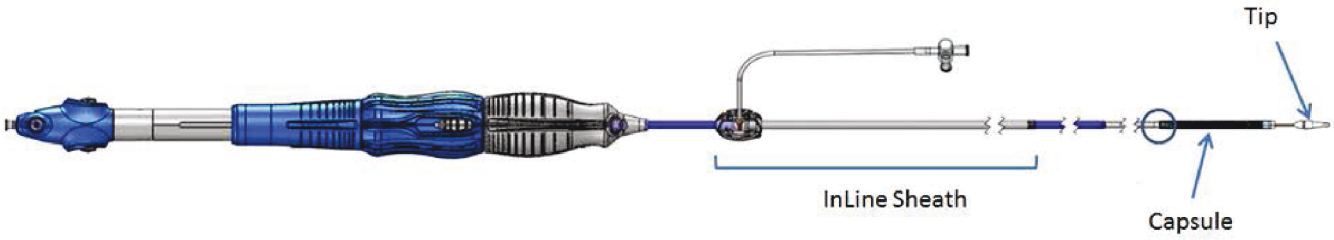

Figure 2. EnVeo PRO Delivery Catheter System

EnVeo PRO Loading System

The EnVeo PRO 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 3). 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.

Figure 3. EnVeo PRO Loading System

The EnVeo R Catheter Delivery System and EnVeo R Loading System, also compatible with the Evolut PRO TAV, are described in Section 6.2.

6.2. 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 for the bicuspid low risk patients. 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 2., and a description of the system components is provided in the following sections.

Table 2. Evolut R System components

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

Evolut R TAV

As Evolut PRO TAV, Evolut R TAV is a single-use, implantable device. It is available in 4 sizes (23, 26, 29, 34 mm) covering an aortic annulus diameter of 18 to 30 mm. As Evolut PRO TAV, 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 4). 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.

Figure 4 . Evolut R TAV

6.2.1. 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 5). 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.

Figure 5 . EnVeo R catheter delivery system and EnVeo R InLine sheath

6.2.2. EnVeo R Loading System

The EnVeo R loading system (Figure 6) 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. 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.

Figure 6 . EnVeo R catheter delivery system and EnVeo R InLine sheath EnVeo R loading system

The EnVeo PRO Catheter Delivery System and EnVeo PRO Loading System were described in Section 6.2.

6.3. Manufacturer

The manufacturer and design site of the Evolut PRO and Evolut R systems is as follows:

Medtronic CoreValve LLC
1851 E Deere Avenue
Santa Ana, CA 92705
USA

6.4. Labeling

Labeling of the Medtronic TAVR system will be provided to the clinical sites. The labeling will indicate that the device is for investigational use only, and only to be used by qualified investigators, and consistent with the regulatory requirements.

The Instructions for Use for the Medtronic TAVR Systems used in this study 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 requirements.

6.5. Study Materials and Study Specific Equipment

Medtronic will control the supply of investigational devices and study 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 study-specific equipment to the sites. Equipment used for assessing study variables (eg, echocardiographic systems) should be maintained per the site's standard procedures.

6.6. Product Storage and Accountability

The Evolut PR0 and Evolut R systems used in this trial are identical to the commercial devices; however, they are not approved for use in low risk patients with bicuspid aortic valve anatomy; 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 commercial applications. 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 (when applicable)
- Date of implant or use (when applicable)
- ID number of subject receiving or using the device (when applicable)
- 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 study 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.

6.7. Product and Study Training Requirements

Prior to investigational center activation or subsequent involvement in study activities, Medtronic will provide training to the investigative team on the study 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 study team members that join the study after site activation, the PI may provide training on the study with permission from Medtronic. Additionally, Medtronic representative(s) may be present at each site's implant procedures as part of the ongoing training process.

6.8. Product Storage

The method of storage shall prevent the use of investigational devices outside the applications as mentioned in this Clinical Investigational Plan. In addition, all information for the use, storage and handling of the investigational device as indicated in the Instructions for Use, must be taken into account.

6.9. Product Return for Malfunction or Explant

In the event of a malfunction of the Medtronic TAVR system prior to implant, or in the event a product is explanted after implant (due to reintervention or autopsy), the affected components 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.

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 and have bicuspid aortic valve anatomy.

7.2. Subject Enrollment

The point of enrollment is when written informed consent is obtained from the subject.

7.3. Inclusion Criteria

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

- 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. Bicuspid aortic valve anatomy (all sub-types) confirmed by MDCT.
4. The subject and the treating physician agree that the subject will return for all required 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. Any condition considered a contraindication for placement of a bioprosthetic valve (eg, subject is indicated for mechanical prosthetic valve).
2. Age less than 60 years
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 cells/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 or drug eluting stent performed within 30 days prior to screening committee 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 study/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 required follow-up exams.
16. Currently participating in an investigational drug or another device study (excluding registries).
17. Evidence of an acute myocardial infarction ≤30 days before the study 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 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. 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 ascending aortopathy requiring surgical repair
30. Ascending aorta diameter >4.5 cm

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 Evolut PRO 23R, 26R, 29 R mm 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[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 23mm, 26mm, and 29mm TAV, and 6.0 mm for the Evolut 34mm and Evolut PRO TAV.

8. Study Procedures

8.1. Schedule of Events

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

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)[ii]

- Clinical assessment and history (eg, clinical history, STS-PROM, co-morbidities, NYHA)[iii]
- 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
- Modified Rankin Score
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Euro-Qol (EQ-5D) Quality of Life survey
- Anti-thrombotic medications
- Adverse events

Implant Procedure

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

18 hours to 7 days Post Procedure

- TTE (for device success)
- 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

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

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

- Anti-thrombotic medications
- INR (for subjects on VKA)
- Adverse events

30 days (between 30 to 45 days post implant)

- Clinical assessment
- TTE
- 12 lead ECG
- Modified Rankin Score
- KCCQ
- EQ-5D
- Anti-thrombotic medications
- INR (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
    - INR. (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
- INR. (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
- INR (for subjects on VKA)
- Adverse events

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

- Adverse events

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

- Clinical assessment
- TTE
- Adverse events

Other Evaluations

- A Modified Rankin Score assessment should be conducted at 1 and 3 months following any suspected or confirmed stroke event.

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
1 Year	Between 365 and 395 days post implant
2 Year	Between 730 and 760 days post-implant
3 – 10 Years	Between implant anniversary date and +/-60 days after

Table 3. Summary of visit schedule and required evaluations through 5 years

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

Table 4. Summary of visit schedule and required evaluations from 6 through 10 years

	Years 6, 8, and 9[1]	Years 7 and 10
Clinical Assessment		X
Adverse Events	X	X
TTE		X

[1] Follow-up visits at years 6, 8 and 9 may be conducted remotely (eg, phone call)

8.2. Screening

The process of patient screening is as follows:

1. Patients identified by or presented to the study site with aortic stenosis will be screened by the investigative team for the criteria described in section 7.0 Selection of Subjects, using available medical records, including relevant imaging studies previously performed for diagnostic purposes.
2. If the patient is deemed a potential candidate for the study the investigational status of the Medtronic TAVR System and all aspects of the study will be explained to the patient.
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[i] will undergo:
    a. Multi-Detector Computed Tomography (MDCT) of their peripheral vasculature and aortic annulus to confirm bicuspid aortic valve anatomy and 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 and bicuspid aortic valve anatomy [ii]
7. The Screening Committee will review the clinical information to confirm the eligibility of the subject for implantation.
8. Concomitant percutaneous coronary intervention (PCI)[iii] with TAVR is allowed; however, staging is left to the discretion of the operator. Elective intervention/repair of the mitral or tricuspid valve is not allowed during the TAVR procedure.
9. Implantation should occur within 90 days of Screening Committee approval.

8.3. 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

[i] 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 7.3 prior to submission to the screening committee.

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

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

procedures to the implanting physicians and study site staff relative to the use of the investigational devices.

8.4. Subject Consent

8.4.1. 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. 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, study procedures, anticipated benefits, and potential risks of participation in the study. 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 study records and a copy of the informed consent will be provided to the patient.

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.

8.4.2. 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 study. The revised information will be sent to the investigator for 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.

8.5. Subject Disposition

Sites will maintain a log of subjects consented, 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 study and will not be followed beyond the date of study exit.

Subjects who are taken to the procedure room for implantation but do not receive a TAV for any reason will be followed for safety events for 30 days post-index procedure. Subjects that have their TAV bioprosthesis explanted will be followed for safety events for 30 days after the explant.

8.6. TAVR Implant Procedure

The implantation procedure is performed according to the standard procedures of the implanting physicians. In countries where required, including the United States, 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. 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, 45)
- 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 (Definitions of resheath/recapture use are provided in Appendix IV)
- Occurrence of adverse events
- If TAV implantation not attempted, reason why

8.7. Post-Implant Anti-thrombotic Therapy

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.

8.8. Clinical Assessment

Clinical assessment is required at the following post-implant intervals: discharge, 30 days, 1 year, 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 and years 6 through 10)
- EQ-5D (except at discharge, 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)

8.9. Assessment of Safety

Definitions, procedures of evaluation, documentation and reporting of adverse events and device deficiencies are presented in section 10.0 Adverse Events and Device Deficiencies.

8.10. Echocardiography

Transthoracic echocardiography (TTE) is required at the following intervals: pre-implant, 18 hours to 7 days (for device success), 30 days, 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 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)
- 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
- 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, [39])
- 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 may 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.

8.11. Missed Follow-up Visits

Every effort should be made to ensure subjects return to the clinic for all protocol required follow-ups, with the exception of the 6, 8 and 9-year follow-up visits which may be conducted remotely (eg, phone call). 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 8.14 Deviation Handling.

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.

8.12. 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.

8.13. Recording Data

8.13.1. Data Collection

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

This study will utilize 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). Study 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 username 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 study. The investigator (or approved sub-investigator) will approve the eCRFs by electronically signing 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 study. 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 study-related documents must be retained until notified by Medtronic that retention is no longer required. Medtronic will inform the investigator/institution when these documents are no longer required to be retained.

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

8.13.2. Time Windows for Completion and Submission of eCRFs

The Device Use Notification eCRF should be completed as soon as possible after device use. Effort should be made for all other eCRFs to be completed and approved within 3 weeks of the applicable follow-up visit.

8.13.3. 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 study. The study database will be developed and validated per the Data Management Plan for this study, 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 study database will maintain an audit trail of all changes made to the eCRFs.

8.13.4. 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 study data collection or adverse event reporting. Identified discrepancies between source documents and the eCRFs will be resolved through the online 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 (echocardiography variables, MDCT variables, catheterization, procedural data variables, local heart team assessment, Modified Rankin Score) may vary from center to center; therefore, the site may use technical worksheets if identified as source documents.

Source documents must be retained by the investigational site 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 may be requested to support event adjudication by the Clinical Events Committee. In some geographies, availability of source documentation may be limited due to institutional policies. If a specific source document is not available, necessary information may be transcribed onto the relevant eCRF page.

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

8.13.5. Subject Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique subject ID number (SID) to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID is to be recorded on all study 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 study document other than the informed consent form. In the event a subject's name is included for any reason, it will be masked as applicable. In the event of inability to mask the identification (eg, digital media), it will be handled in a confidential manner by the authorized personnel.

8.14. Deviation Handling

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[i]
- 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

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[ii]).

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.

Deviations are analyzed, their significance is assessed, and any corrective and/or preventative actions that maybe warranted are identified. Medtronic is responsible for analyzing deviations, assessing their

[i] 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.

[ii] In the case of a missed study visit (eg, followup visit), completion of only one protocol deviation eCRF is sufficient and additional eCRFs are not required for each assessment missed at that visit.

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.

8.15. Subject Withdrawal or Discontinuation

All subjects will be encouraged to remain in the study 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 study subjects. If a subject is discontinued from the study early, the reason for discontinuation should be documented in the subject file and a Study Exit eCRF must be completed.

The study 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 or e-mail and if contact via these methods is not successful, a traceable letter from the investigator should be sent to the subject's last known address. Should telephone, e-mail 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 the subject's medical records.

If a subject discontinues the study at any time, is withdrawn from the study 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 subject needs to change their follow-up site at any time point after conclusion of the study, investigators should refer subjects to a local site with appropriate training and experience in managing patients with implanted aortic valves.

9. Risks and Benefits

9.1. Potential Risks

Description of Risk Analysis

Risk Analysis procedures were completed in accordance with ISO 14971:2012. Medtronic has determined the Medtronic TAVR system to be a significant risk medical device. Therefore, Medtronic is sponsoring this clinical study to support approvals for the use of the Medtronic TAVR system to patients with aortic stenosis at low risk for 30-day mortality for SAVR and with bicuspid aortic anatomy.

Risks

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

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.

Measures to Mitigate Risks to Study Subjects

The following measures will be implemented to minimize risks to the study 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 receiving study device will be followed over the course of the study
- An independent data safety monitoring board (DSMB) will review adverse events and interim results in order to advise Medtronic regarding study conduct, should safety concerns be identified

Alternatives

Presently, therapeutic alternatives for patients participating in this clinical study include the following:

- Medical therapy
- Balloon aortic valvuloplasty
- Surgical aortic valve replacement

9.2. Potential Benefits

The primary potential benefit to subjects participating in the study is restored function of their diseased (stenotic) bicuspid 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 intermediate risk through extreme risk for operative mortality with SAVR.

9.3. Risk-Benefit Rationale

TAVR is now established as a safe and effective treatment option for patients with symptomatic severe aortic stenosis who are at intermediate, high and extremely high risk for surgical aortic valve replacement [2-8]. The Medtronic CoreValve system has been used widely after receiving the CE Mark in 2007, and there is extensive published experience demonstrating the CoreValve system is fulfilling its intended role with a favorable risk/benefit ratio [9-13]. Rigorous clinical studies have established its safety and effectiveness, with improved mortality and quality of life compared with medical therapy in extreme risk patients [6], superiority to SAVR among high operative risk patients [7] and noninferiority to surgery in patients at intermediate surgical risk [8].

The Evolut R and Evolut PRO systems are built upon the same fundamental design principles and mode of operation as the predicate Medtronic CoreValve System. The Evolut R system introduces the feature of recapturability, and the Evolut PRO system builds upon Evolut R and introduces a design feature for reduction of paravalvular regurgitation. A comprehensive protocol of bench and animal testing has indicated the Evolut R and PRO systems are equivalent to the CoreValve system in terms of structural integrity, hydrodynamic performance, and valve durability. Clinical studies of the Evolut R and PRO system have confirmed the safety and efficacy of the Evolut R and PRO systems to be equivalent to the CoreValve system, with no new clinical risks associated [40-42]. Further, no new Zone III risks were identified for patients with bicuspid aortic valve anatomy through Risk Analysis [43].

The risks and benefits of the Medtronic TAVR systems in low risk patients are expected to be similar to those at intermediate through extreme risk for SAVR. The Medtronic TAVR Low Risk IDE trial will evaluate the safety and effectiveness of the Medtronic TAVR systems in tricuspid aortic valve patients with aortic stenosis who are at low predicted risk for mortality with SAVR. This study will be conducted under the Medtronic TAVR Low Risk IDE, and will evaluate the procedural safety and efficacy of Medtronic TAVR (Evolut PRO system and Evolut R system) in patients with severe bicuspid aortic valve stenosis who are at low predicted risk of mortality with SAVR.

Although there are risks to the subjects for participation in the study, they are anticipated to be similar to the risks of undergoing TAVR outside of the study. The potential benefits outweigh the design and use-related risks established through risk analysis.

10. Adverse Events and Device Deficiencies

Definitions for Adverse Events, Adverse Device Effects, and Device Deficiencies are provided below.

10.1. Definitions/Classifications

10.1.1. Definitions

The definitions to be applied for the purposes of reporting adverse events are provided in Table 5.

Table 5. 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 (47) *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 (47). *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 (47).* *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 (47, 48).
Unanticipated Adverse Device Effect	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

(UADE) (21 CFR 812.3)	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 (49).

10.2. Reporting of Adverse Events

10.2.1. 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 5) observed in study subjects from the time they are enrolled until they are exited from the study. All AE should be followed through their resolution or until subject's study exit.

All AEs that occur during the study need to be reported to Medtronic via the AE eCRF. Documented pre-existing conditions are not considered to be reportable unless there is a change in the nature or severity of the condition. Pre-existing events should be reported as 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 SAEs 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 abnormal laboratory findings), diseases or injuries that are not untoward in nature; specifically, those resulting from the intended injury such as the index TAVR procedure. The events listed in Table 6 are expected for patients undergoing 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 6. 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
- Date of site's first awareness
- 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 DCS and/or LS

- Causal relationship of the event to the 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 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 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

10.2.2. Anticipated Adverse Events

Adverse events that are anticipated for subjects participating in this study are provided in Section 9.1, Risks.

10.2.3. Adverse Event Reporting Requirements for Clinical Sites

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

Table 7. Required timeframes for adverse event reporting to Medtronic

Event Type	Timeframe for Reporting
Adverse Event (AE)	No later than 10 working days of the investigator's/site's first knowledge of the event
Serious Adverse Event (SAE)	Immediately, but no later than 72 hours of the investigator's/site's first knowledge of the event
Adverse Device Effect (ADE) or Device Related Adverse Event	Immediately, but no later than 72 hours of the investigator's/site's first knowledge of the event
Serious Adverse Device Effect (SADE)	Immediately, but no later than 72 hours of the investigator's/site's first knowledge of the event
Unanticipated Adverse Device Effect (UADE)	Immediately, but no later than 72 hours of the investigator's/site's first knowledge of the event

Event Type	Timeframe for Reporting
Device Deficiency	No later than 72 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 study to the Regulatory Authorities and IRB/EC as per local requirements. The applicable timeframes are described in the Safety Plan associated with this study.

10.2.4. Documentation and Reporting of Device Deficiencies

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

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

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

11. Data Review Committees

11.1. Clinical Events Committee

A Clinical Events Committee (CEC) will provide independent medical review and adjudication of adverse event data used in the safety assessment of the investigational device. The CEC will adjudicate, at a minimum, all deaths and safety endpoint-related adverse events reported by the investigators. The analysis of the study 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 study and will be independent from both the study and investigators and Medtronic. The committee will consist of at least 3 independent experts (non-Medtronic employed physicians) with expertise relevant to the study. This will include experience in the areas of:

- Cardiac surgery
- Interventional cardiology
- Neurology
- Electrophysiology

A CEC charter will be established that describes the Committee roles, responsibilities, and processes.

11.2. Data Safety Monitoring Board

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

The DSMB will consist of a minimum of 3 members who will have experience in the areas of:

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 established that describes the Committee roles, responsibilities, and processes. 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 study 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 study status such as continuing the study without modifications, continuing the study with modifications, stopping or suspending enrollment, or recommendations regarding study conduct including recommendations around enrollment or protocol deviations.

In the case of UADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical study within 5 working days after making that determination and no later than 15 working days after Medtronic first receives notice of the effect. All 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 study. All data presented at the meetings will be considered confidential.

12. Statistical Design and Methods

12.1. Sample Size and Results Reporting

This study will involve 150 subjects with an attempted implant with the Medtronic TAVR system. The primary analysis will be performed when 150 consecutive subjects with an attempted implant have had the chance to complete 30-day follow-up. Results from the primary analysis will be used for regulatory submissions. Another analysis may be performed when all 150 subjects with an attempted implant have completed 1 year follow-up. The final analysis will be performed with all implanted subjects have completed 10-year follow-up.

This is not a hypothesis-driven study, therefore the sample size of 150 for the analysis was not determined by statistical sample size methods. However, a sample size of 150 subjects is adequate for a descriptive assessment of the procedural safety and efficacy of the Medtronic TAVR system in subjects with bicuspid aortic valves. The results from the primary endpoints of the Low Risk bicuspid study cohort will be compared to the procedural safety and efficacy results from the TAVR arm of the Low Risk Trial randomized cohort.

12.2. Enrolled Subjects and Analysis Sets

Enrolled Subjects

All subjects with severe aortic stenosis and bicuspid anatomy 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.

Analysis Sets

There are two different analysis sets that are defined for this study. The primary analysis will be the "attempted implant" analysis. Analysis sets used for each objective are defined under the corresponding objective section. The analysis subsets are defined as follows:

Attempted implant set: The attempted implant set consists of all enrolled 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). Day 0 is date of first attempted procedure.

Implanted set: The implanted set consists of all the attempted implant subjects who are actually implanted with the TAV. Day 0 is date of first attempted procedure.

12.3. Description of Baseline Variables

Baseline demographic and clinical variables will be summarized for as attempted implant analysis set. All continuous variables will be summarized with means, medians, standard deviations, minimums, and maximums. Categorical variables will be summarized with frequencies and percentages.

12.4. Endpoint Analysis

All endpoints are descriptive and no statistical hypothesis test will be performed.

12.5. Primary Safety Endpoint #1 – All-cause Mortality or Disabling Stroke Rate at 30 Days

This endpoint will be analyzed for a**s** attempted implant set. The Kaplan-Meier rate and a 95% two-sided confidence interval will be calculated.

12.6. Primary Efficacy Endpoint #1 – Device Success Rate

This endpoint will be analyzed for the implanted set. The number and percentage of subjects that meet device success criteria will be calculated. A 95% two-sided confidence interval for the device success rate will be calculated.

12.7. Additional Outcome Measures

Additional Outcome Measures are listed as follows:

1. All-cause mortality at one year, and annually through 10 years
2. All stroke (disabling and non-disabling) at one year, and annually through 10 years
3. New permanent pacemaker implantation at 30 days
4. Myocardial Infarction at 30 days
5. Life-threatening bleeding at one year, and annually through 10 years
6. Prosthetic valve endocarditis at one year, and annually through 10 years
7. Prosthetic valve thrombosis at one year, and annually through 10 years
8. Valve-related dysfunction requiring repeat procedure at one year, and annually through 10 years
9. Repeat hospitalization for ascending aorta disease at 30 days, one year, and annually through 10 years
10. Repeat hospitalization for aortic valve disease at one year, and annually through 10 years
11. Hemodynamic performance metrics by Doppler echocardiography
    - Mean aortic gradient at baseline, 30 days, one year, and annually through 10 years
    - Effective orifice area at baseline, 30 days, one year, and annually through 10 years
    - Degree of total, peri, and transvalvular prosthetic regurgitation at baseline, 30 days, one year, and annually through 10 years
12. New York Heart Association (NYHA) functional classification at baseline, 30 days, one year and annually through 10 years
13. Health-related quality of life as assessed by

- Kansas City Cardiomyopathy (KCCQ) instrument at baseline, 30 days, one year, annually through 5 years
- EQ-5D survey at baseline, 30 days and one year

Analyses of the additional endpoints will be descriptive. Attempted implant set will be used for safety and quality of life outcomes. However, the hemodynamic performance outcomes will be analyzed for the implanted set. Continuous variables will be summarized as the number of subjects, means, standard deviations, medians, minimums, maximums, and interquartile ranges. Categorical variables will be summarized as frequencies and percentages. A Kaplan-Meier estimate will be performed for time-to-event analysis.

12.8. Missing Data

Every effort will be undertaken to minimize missing data. Missing (accidentally, due to withdrawal, missing follow-up or loss to follow-up, etc.), unused and spurious data will remain identifiable in the database. Data from subjects that cannot be analyzed for a specific variable will be displayed as missing in the relevant summary tables. In this manner, all data for a specific variable are accounted for.

12.9. Number of Subjects and Investigational Devices, Study Duration

This study will involve up to 150 total attempted implant subjects among all active sites. No site will implant more than 20% of the total number of attempted subjects without prior authorization from Medtronic. Subjects who exit from the study after implantation will not be replaced.

Subjects will be consented for follow-up through 10 years. The enrollment period is estimated to be between 12 to 24 months; therefore, the estimated total duration of the study (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 study is estimated to between 150 and 200 (based on sample size).

13. Ethics

13.1. Statement(s) of Compliance

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

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. The clinical investigation

shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The principles of the Declaration of Helsinki are implemented in this study by means of the Patient Informed Consent (IC) process, Institutional Review Board approval, study training, clinical study registration, pre-clinical testing, risk benefit assessment, and publication policy.

The study 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.

Regulatory authority notification/approval to conduct the study is required. Investigational sites will be not be activated, nor begin enrolling subjects until the required approval/favorable opinion from the regulatory agency has been obtained (as appropriate). Additionally, any requirements imposed by an Institutional Review Board shall be followed, as appropriate.

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

13.2. Institutional Review Board

The study will be conducted in accordance with the requirements of local IRBs. The responsible IRB at each investigational site must approve the study protocol and informed consent form. Study activities will not commence prior to receipt of documentation of IRB approval by the site and Medtronic. The Investigator and study staff must comply with the requirements of their IRB, including any additional requirements imposed by the IRB after initial approval.

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

IRB approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the study 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 roster or letter of compliance, to allow verification that the investigator, other center study staff, and/or Medtronic personnel are not members of the IRB. If they are members of the IRB, 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 approval once the investigation site has started enrollment. If any action is taken by an IRB with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

13.3. 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 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 Study Agreement.

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

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

Any revisions or amendments to the CIP or Informed Consent documents will be submitted to the Regulatory Authority. A final report will be submitted to the Regulatory Authority upon study closure.

13.4. Ethical Conduct of the Study

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

The principles of the Declaration of Helsinki have been implemented by means of the patient informed consent process, IRB approval, study training, clinical study registration, preclinical testing, risk benefit assessment, and publication policy. Pediatric, legally incompetent, or otherwise vulnerable patients are not eligible for the study. Further, the Medtronic TAVR system will not be used as an emergency treatment.

14. Study Administration

14.1. Monitoring

Investigational sites will be monitored to ensure compliance with the study protocol, adherence to applicable regulations, and accuracy of study 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 study

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. Study data submitted will be reviewed against subject charts and other sources containing original records of subject data. Source document verification will occur in accordance to a Monitoring Plan.

The progress of the study will be monitored by:

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

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

Upon completion of the study, Site Closeout Visits will be conducted, as outlined in the Monitoring Plan. After the study has been completed, medical care will be provided to the subjects upon the discretion of the treating physician.

14.2. 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 study conduct, independent of the personnel directly involved in the study. 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.

14.3. Data Management

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

Refer to Recording Data section for further information regarding data collection and management procedures.

14.4. Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique subject ID number (SID) to each

subject. Records of the subject/SID relationship will be maintained by the study site. The SID is to be recorded on all study 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 study document other than the informed consent form. In the event a subject's name is included for any reason, it will be masked as applicable. In the event of inability to mask the identification (eg, digital media), it will be handled in a confidential manner by the authorized personnel.

14.5. Liability

Medtronic, Inc. (including all wholly owned subsidiaries) maintains appropriate clinical study 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 Study Insurance statement/certificate will be provided to the IRB.

14.6. CIP Amendments

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

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

14.7. Record Retention

The investigator must retain the Investigator Site File, source documents, and the records listed in [Responsibilities of the Investigator], until informed by Medtronic they no longer need to be retained. At a minimum, the investigator must retain records for at least 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 study related materials.

14.8. Publication and Use of Information

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

Medtronic is committed to the widespread dissemination of all primary and secondary endpoint results. The results will be posted publicly on clinicaltrials.gov no later than 1 year after the conclusion of the

primary and secondary endpoints as well as no later than two years after the completion of data collection. A full report of the outcomes will be made public no later than three years after the completion of data collection as abstracts and presentations in scientific conferences publications and in peer-reviewed journals as described below. A Publication Plan will be implemented and followed.

At the conclusion of the study and no later than three years after the completion of data collection, 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 study is not allowed until both the preparation and publication of the multisite results, and then only with written permission from Medtronic.

Following analysis and presentation of the endpoint results, active participation of all participating investigators, CEC/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 study requires approval by the Principal Investigators after review by the Publications Committee.

14.9. Suspension or Early Termination

14.9.1. Early Suspension or Termination of the Study

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

14.9.2. Early Suspension or Termination of a Study 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.

14.10. Study Organization

14.10.1. Investigational Sites

This study may be conducted at up to 40 sites in the United States. Investigative sites will meet the following criteria:

- 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.
- 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
  - study coordinator

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

14.10.2. Study Site Investigative Team Members

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

14.10.2.1. 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 study at the site, including protecting the rights, safety, and welfare of the study subjects at their site, the integrity of the study data generated by their site, and for ensuring the study is conducted in compliance with the Clinical Investigation Plan, 21 CFR 812, and IRB/EC requirements.

14.10.2.2. Heart Team

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

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.

14.10.2.3. 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 TAVR qualification as described in Section 14.10.1.

14.10.2.4. 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.

14.10.2.5. Study Coordinator

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

14.10.3. Screening Committee

A Screening Committee will be used to ensure patient selection is appropriate and consistent among study 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 anatomically suitable for implantation for TAVR and have bicuspid aortic valve anatomy

The Screening Committee will include interventional cardiologists and cardiac surgeons. The Screening Committee will establish a charter that describes its roles, responsibilities, and processes.

14.10.4. Publication Committee

A Publication Committee may provide direction and support in the development of clinical publications. The Publication Committee may consist of study investigators and Medtronic representatives. The Publication Committee may 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

14.10.5. 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 study 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 study.

14.10.6. 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.

14.10.7. 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, ROPI, 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 10. 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 Section 10.2 (Required timeframes for adverse event reporting to Medtronic).

Table 8. 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))*

14.10.8. Responsibilities of the Sponsor

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

- All essential correspondence related to the clinical study
- Signed Investigator Agreement
- Signed and dated current curriculum vitae for each Investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event and device deficiency information
- 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
- Study training records for site participants and internal study staff members
- Contact lists of all participating investigators/investigative sites, Ethics Board information, study monitors and Sponsor staff members; Sponsor will maintain these lists and provide updates to the necessary parties.
- Sample of device labeling attached to investigational device
- Insurance certificates
- Ethics Board approval documentation and voting list
- Regulatory authority notification and approval documentation
- Lab certificates /Lab normal ranges
- Statistical analyses
- Clinical 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 9.

Table 9: 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))*

Report	Submit To	Description/Constraints
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))*
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators quarterly. *(*ISO 14155:2011*)*

15. Other Institutions and Professional Services

This study will utilize an Echo 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 study reports.

16. 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.

17. Sponsor Study 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 study centers.

18. Report of Prior Investigations

Report of Prior Investigations per requirements (21 CFR 812.27) for this study will be provided under a separate cover to the relevant sites and regulatory agencies.

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20. Appendices List

The list of Appendices is as follows:

I. Echocardiography Procedures
II. MDCT Acquisition Guidelines: Pre-TAVR Planning
III. Definitions of STS Factors and Other Co-morbidities
IV. Resheath and Recapture Definitions
V. Definitions: Safety Endpoints and Efficacy Events
VI. Sample Informed Consent Form

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
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:
  - Study site ID number
  - Subject ID number
  - Exam date
  - Study 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, 46)
- 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 7 A and B) [44, 45]. 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 7 C and D) [44-46]. 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 7 E and F) [44].

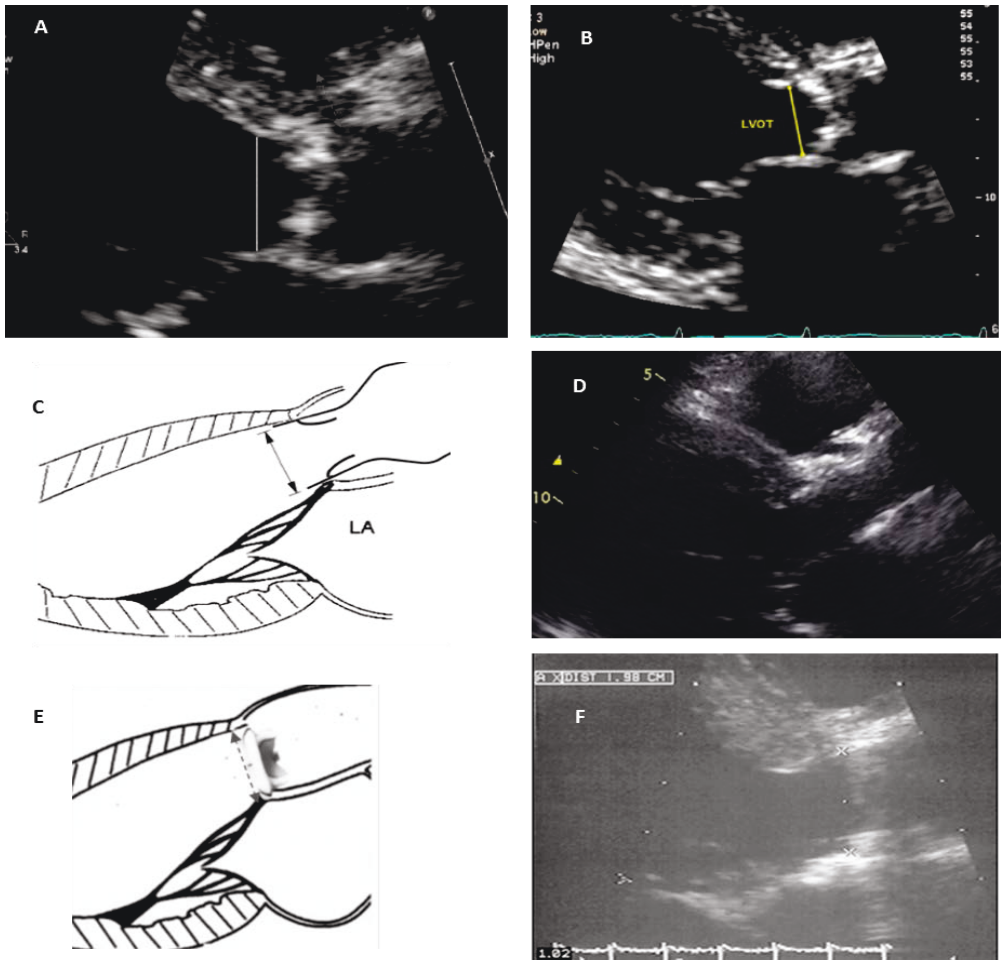

Figure 7. (A) and **(B)** Examples of measurement of pre-implant LVOT diameter. LVOT diameter is measured from the white-black interface of the septal endocardium to the anterior mitral leaflet, parallel to the aortic valve plane, approximately 0.5 cm below the level of the aortic annulus, and in mid 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 8 A) [44].

Post TAV implantation, the sample volume should be placed proximal to the inflow aspect of the stent [45]. 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 8 C and D) [46, 47].

The LVOT VTI is measured by tracing the modal velocity (middle of the dense signal) for use in the continuity equation [44].

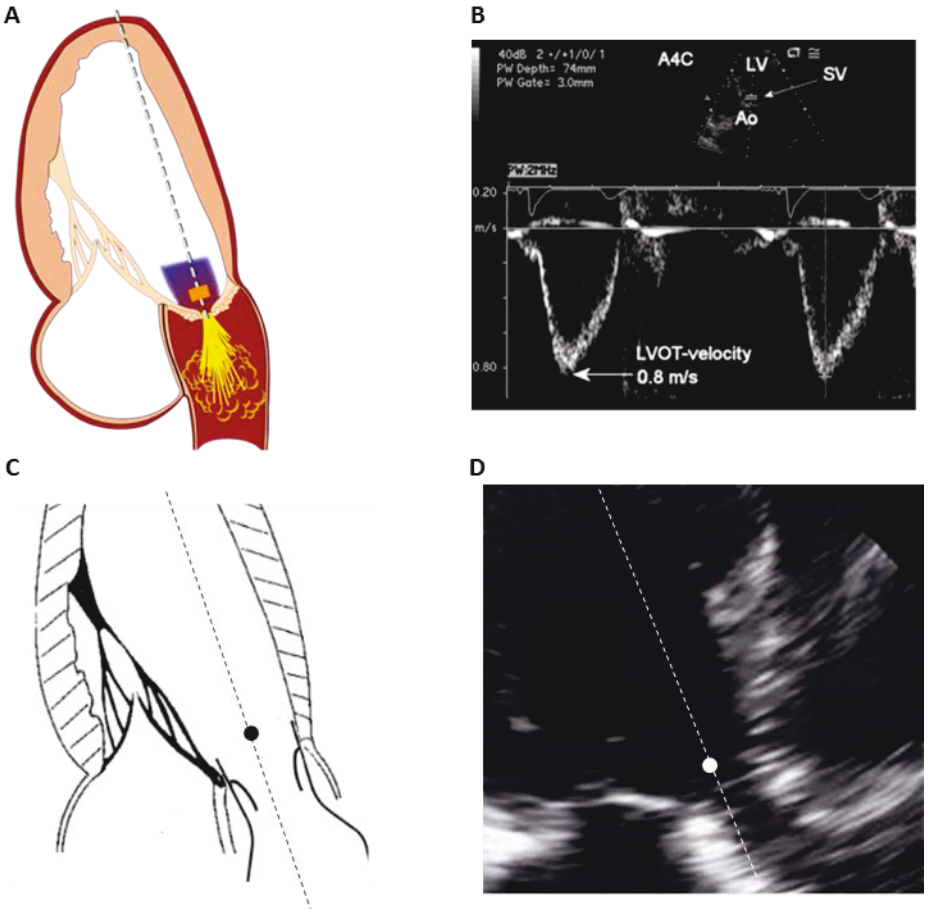

Figure 8. (A) Sample volume placement just proximal to zone of pre-valve acceleration (*illustration by Mayo Clinic, used with permission)* **(B)** Optimal LVOT velocity signal showing a smooth spectral Doppler recording with a narrow velocity range at each time point **(C)** Illustration showing correct 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 9) [44].

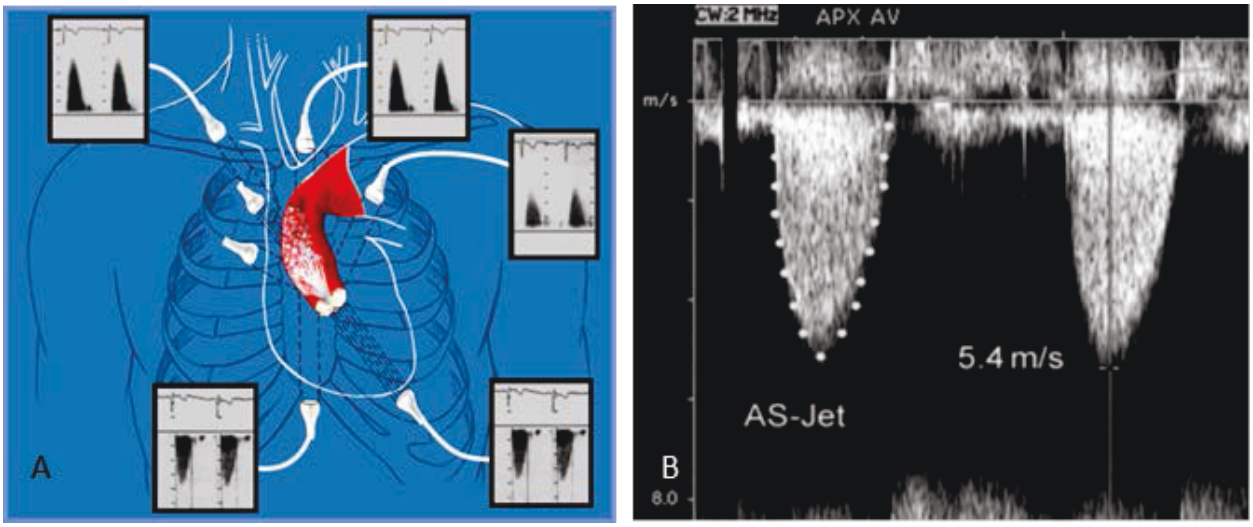

Figure 9. (A) Aortic valve velocities interrogated from multiple transducer positions *(illustration by Mayo Clinic, used with permission)* **(B)** CW Doppler of severe aortic stenosis showing tracing of the velocity curve from mean gradient and VTI, and measurement of max velocity.

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 [48, 49].

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 10 [49]. 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 10. 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 (quantitative)						
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 11 [50].

Table 11. 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 12 [50].

Table 12. 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 10). Left ventricular chamber dimensions, septal thickness, and posterior wall thickness are measured using the American Society of Echocardiography (ASE) measurement convention (blood-tissue interface, [49]). 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.

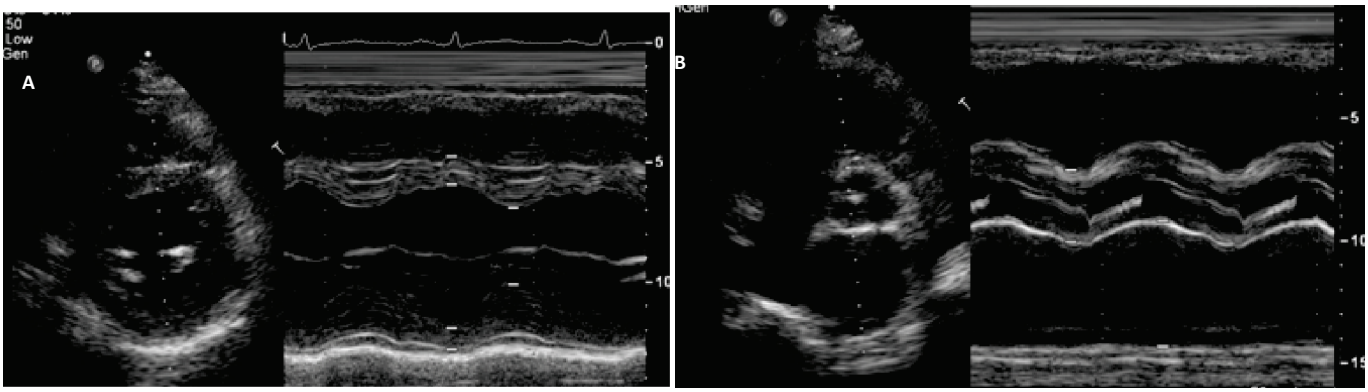

Figure 10. Measurements of the left ventricle **(A)** and left atrium **(B)** using 2-D guided m-mode.

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 **11**). 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

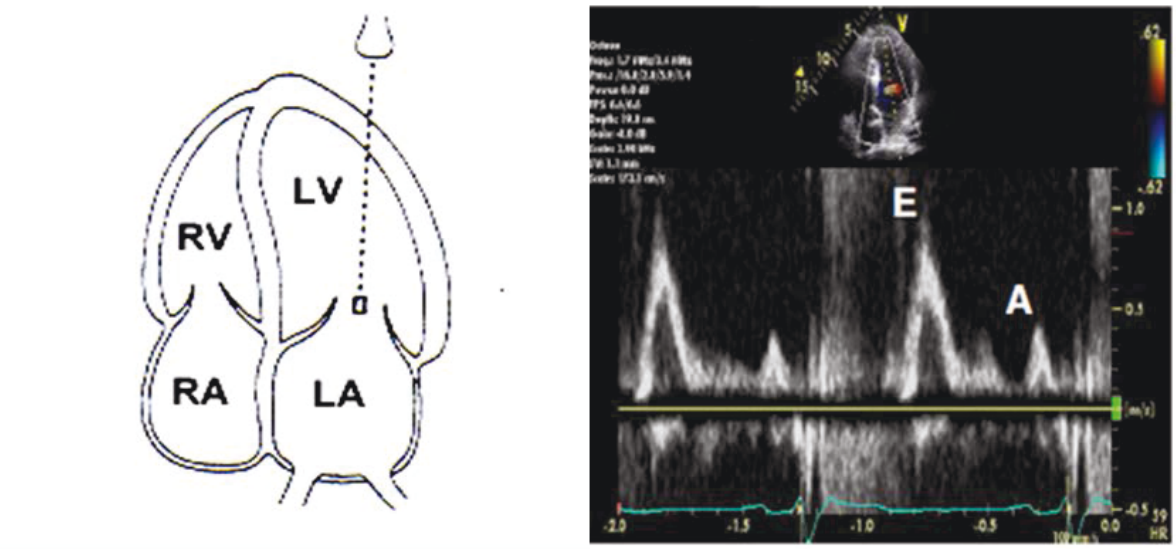

Figure 11**.** Positioning of the sample volume for recording of mitral inflow velocities**.**

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 [51].

4.0 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 study.

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 [50, 52].

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[i]

- Effective Orifice Area (EOA) in cm2
  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 m2
  BSA = 0.007184 x (height in cm$^{0.725}$ x weight in kg$^{0.425}$)

[i] 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 13.

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 13. 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

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)

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)

Dimensional sizing criteria for the Evolut PRO and Evolut R TAV are provided in Tables 16 and 17.

3.2.1 Reformatting of Images

Reformatting of the images is as follows [53]:

- 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 12, upper left panel).
- In the sagittal window, the horizontal line is rotated clockwise or counter-clockwise to align with virtual basal plane (Figure 12, 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 13). 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.

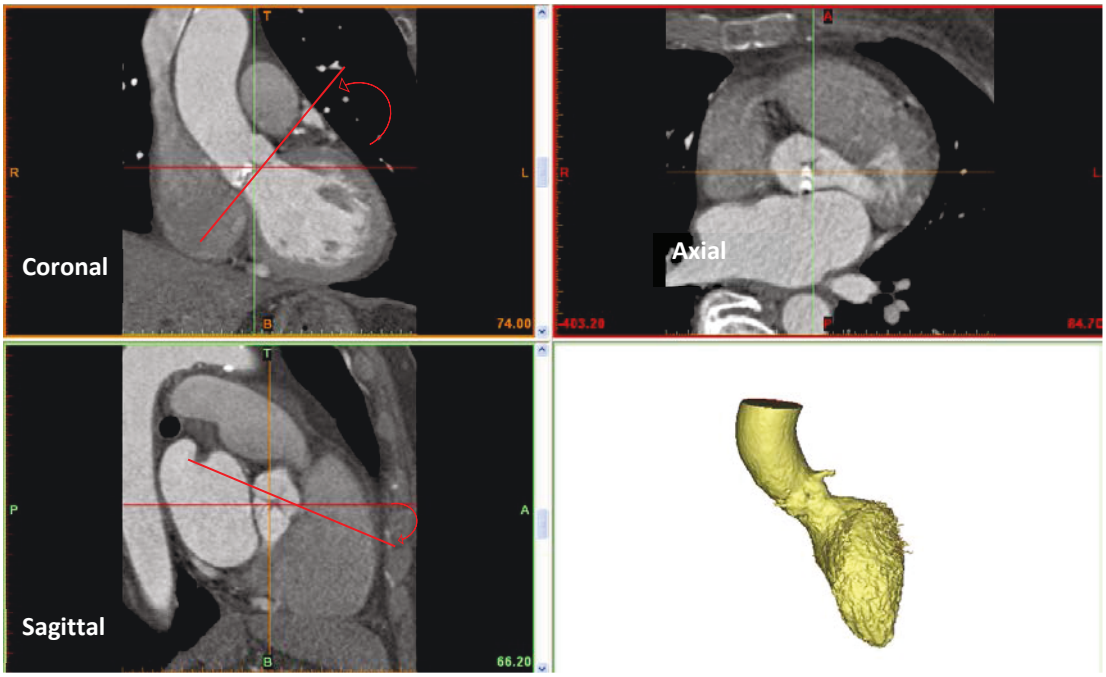

Figure 12. Example images in original orientation (axial, coronal, and sagittal). Red curved arrow and line indicate adjustment of coronal and sagittal planes to align with aortic basal annulus**.**

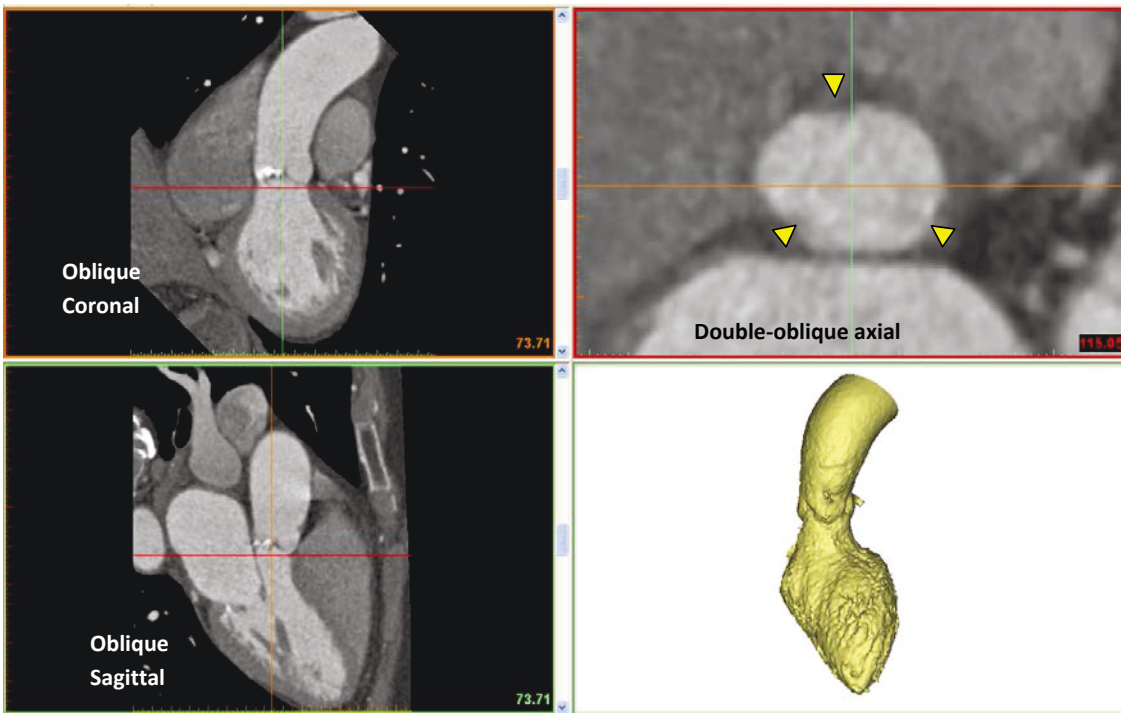

Figure 13. Example images of reformatted oblique coronal (upper left), oblique sagittal (lower left), double oblique axial (upper right), and 3D reconstruction (lower right). Yellow arrowheads indicate most caudal attachment of three leaflets of the aortic valve).

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 14, 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 14, right).

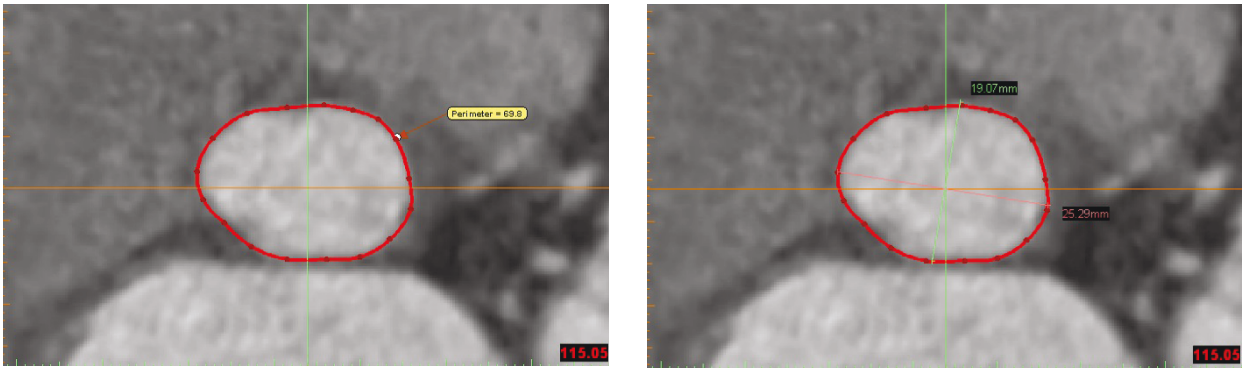

Figure 14. Example of perimeter measurement (left) and major and minor diameter measurements (right).

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, Reformatting of Images.

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 15).

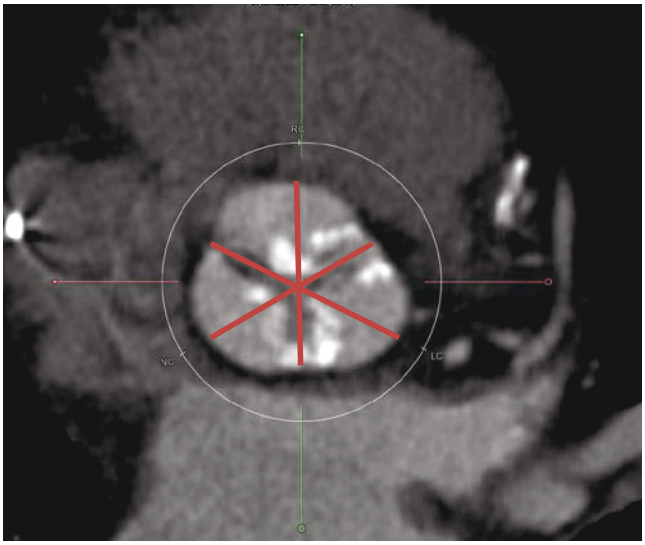

Figure 15. Example of sinus of Valsalva diameters

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 16).

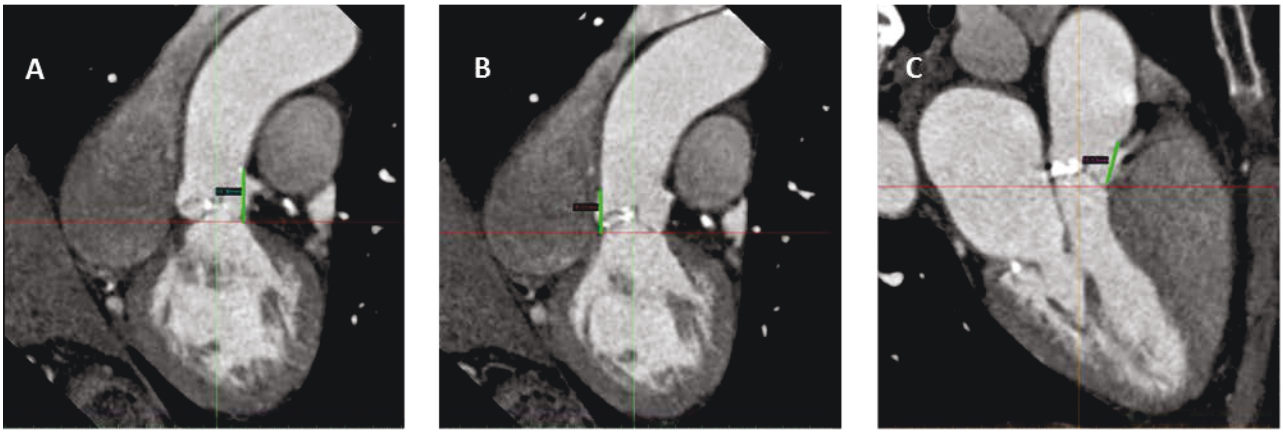

Figure 16. Examples of sinus of Valsalva heights **(A)** left coronary **(B)** non coronary **(C)** right coronary

4.0 Evolut PRO and Evolut R TAV Sizing Matrix

Table 14. 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

Table 15. 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

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

1.0 STS Factors (continued)

Factor	Definition
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/atral 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: • organisms cultured from 2 or more blood cultures • organisms seen on Gram's stain of valve when culture is negative or not done • valvular vegetation seen during an invasive procedure or autopsy • 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.

1.0 STS Factors (continued)

Factor	Definition
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.
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*

1.0 STS Factors (continued)

Factor	Definition
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 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.
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: 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. 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 [54]

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, Panel D below).
Reposition	Repositioning of the TAV proximally or distally before final deployment
Retrieve	Retrieval of a partially deployed TAV

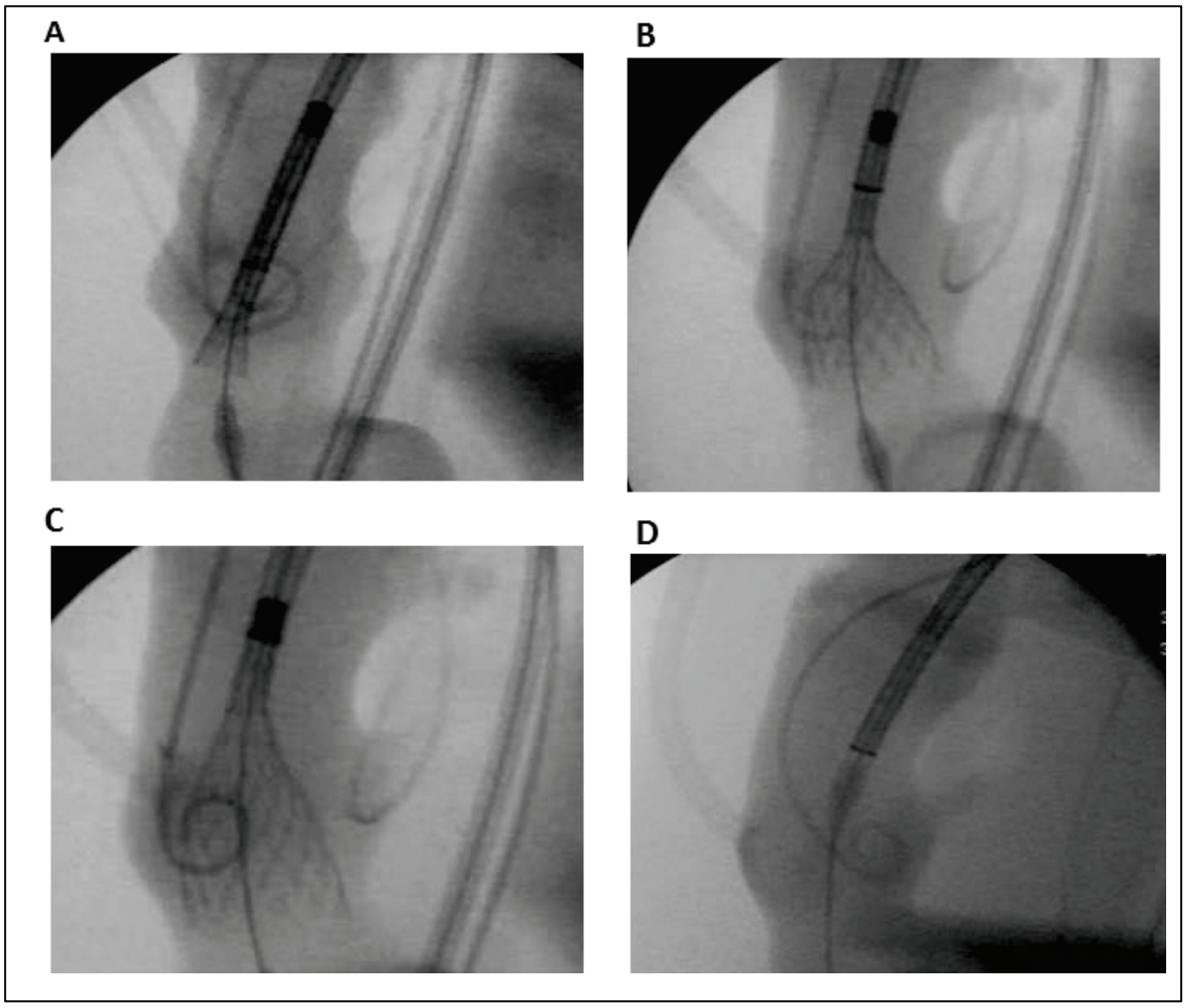

Figure 17. (A) Between 0 and 1/3 of the valve length outside of the capsule **(B)** between 1/3 and 2/3 of the valve length outside of the capsule **(C)** Point of no return: capsule marker in alignment with the spindle marker **(D)** Full recapture: entire valve resheathed into the capsule until there 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 [54]. 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)

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

2.0 Other Related Complications

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

2.0 Other Related Complications (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

2.0 Other Related Complications (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 [54]

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 (continued)

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 Related Complications (continued)

PROSTHETIC VALVE ENDOCARDITIS
Any of the following: 1) Fulfillment of the following Duke criteria for definite endocarditis [55]: • 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 10, 3 grade scheme)
Paravalvular regurgitation: severe	Severe paravalvular regurgitation (per echo criteria in Table 10, 3 grade scheme) per echo criteria in CIP)
Transvalvular regurgitation: moderate	Moderate paravalvular regurgitation (per echo criteria in Table 10, 3 grade scheme)
Transvalvular regurgitation: severe	Severe transvalvular regurgitation (per echo criteria in Table 10, 3 grade scheme)
Total regurgitation: moderate	Moderate total regurgitation (per echo criteria in Table 10, 3 grade scheme)
Total regurgitation: severe	Severe total regurgitation (per echo criteria in Table 10, 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.

3.0 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

4.0 Classification of Causal Relationships

The following definitions are intended as guidelines for classifying causal relationships between the event and the TAV, the catheter delivery system, and the TAVR implant procedure. Timeframe for assessing implant procedure relationships begin when subject is being prepared for the TAVR implant (or re-implant) procedure.

Causal relationships between event and the TAV

Not related to the TAV	The relationship to TAV can be excluded when: • the event is not a known side effect of the TAV product category the device belongs to or of similar devices; • The event has no temporal relationship with the TAV • The event does not follow a known response pattern to the TAV 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	The relationship with the TAV 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	The relationship with the TAV 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	The relationship with TAV seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal relationship "Related" to the TAV	The event is associated with the TAV beyond reasonable doubt when: • the event is a known side effect of the TAV 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 • the TAV or surgical valve is applied to; • the TAV of surgical valve has an effect on; • the event follows a known response pattern to the TAV; • 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 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 system 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 system 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 implant procedure

Not related to the TAVR implant procedure	The relationship with the TAVR implant procedure can be excluded when: • the event is not a known side effect of the TAVR implant procedure; • The event has no temporal relationship with the TAVR implant relationship • The event does not follow a known response pattern to the TAVR 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 implant procedure	The relationship with the TAVR 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 implant procedure	The relationship with the TAVR 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 implant procedure	The relationship with TAVR 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 implant procedure beyond reasonable doubt when: • the event is a known side effect of the TAVR implant procedure; • the event has a temporal relationship with the TAVR implant procedure; • the event involves a body-site or organ that • the TAVR is applied to; • the TAVR implant procedure has an effect on; • the event follows a known response pattern to the TAVR 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 refer 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

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

Version History

Version	Summary of Changes	Author(s)/Title
1A	Not Applicable, New Document	Hatice Bilgic Lim, PhD, Principal Clinical Research Specialist
1B	Revised sample size to 150 subjects with attempted implant Documented that the primary endpoint results from the TAVR Bicuspid Low Risk cohort will be compared to the results from the from TAVR arm of randomized Low Risk cohort Documented that Enveo R and Enveo PRO delivery catheter systems could be used in the study.	Charles Boldt, MA, Sr Clinical Program Manager
1C	Added "Myocardial infarction at 30 days" as an additional outcome measure Clarified the required follow-up evaluations for the KCCQ and EQ-5D to provide consistency throughout the protocol that KCCQ instrument will be performed at baseline, 30 days, one year, annually through 5 years; and EQ-5D survey will be performed at baseline, 30 days and 1 year Added information regarding the prevalence of bicuspid valve anatomy at specific risk populations and ages into Background section Clarified timeline of when the endpoint results will be publicly posted for the trial	Hatice Bilgic Lim, PhD, Principal Clinical Research Specialist
1D	Removed Exclusion Criteria: Age >65 Changed exclusion criteria of "ascending aorta diameter >4 cm" to "ascending aorta diameter >4.5 cm"	Hatice Bilgic Lim, PhD, Principal Clinical Research Specialist
1E	Added Exclusion Criteria: Age <60 years	Hatice Bilgic Lim, PhD, Principal Clinical Research Specialist