Optimize PRO Study

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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Optimize PRO TAVR Post Market Study
Study Product Name	Medtronic Evolut™ PRO System and Medtronic Evolut™ PRO+ System
Sponsor/Local Sponsor	Global Sponsor (funding source): Medtronic, Inc. Coronary and Structural Heart Clinical [redacted] Local Sponsors: Medtronic of Canada ULC [redacted] (EU Legal Representative) Medtronic Bakken Research Center BV [redacted] Medtronic Australia Pty. Ltd [redacted] Medtronic New Zealand Limited [redacted]
Document Version	6.0, 04 May 2021
Co-Principal Investigators	Dr. Kendra Grubb Emory University Hospital [redacted] Dr. Steven Yakubov

	Riverside Methodist Hospital / Ohio Health Research Institute [redacted]

Confidentiality Statement

1. Investigator Statement

Study product Name	Medtronic Evolut™ PRO and Medtronic Evolut™ PRO+
Sponsor	Medtronic Structural Heart Clinical
Version Number/Date	6.0, 04 May 2021
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to comply with local and internal institutional requirements including the protocol, GCP, and ethical principles that have their origin in the Declaration of Helsinki. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical study without the prior written consent of Medtronic. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.	
Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Term	Definition
2D	Two Dimensional
AE	Adverse Event
ADE	Adverse Device Effect
AF	Atrial Fibrillation
ANZ	Australia, New Zealand
AR	Aortic Regurgitation
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
BAV	Balloon Aortic Valvuloplasty
BNP	Brain Natriuretic Peptide
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CLS	Compression Loading System
CHB	Complete heart block
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CVA	Cerebrovascular Accident
DCS	Delivery Catheter System
DD	Device Deficiency
ECG	Electrocardiogram
e-CRF	Electronic Case Report Form

Term	Definition
EDC	Electronic Data Capture
EF	Ejection Fraction
EMEA	Europe, Middle East, and Africa
EQ-5D	European Quality of Life – 5 Dimensions
HAVB	High Degree Atrioventricular Block
ICF	Informed Consent Form
IRB/REC/EC	Institutional Review Board/Research Ethics Board/Ethics Committee
IFU	Instructions For Use
ITT	Intent-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LBBB	Left Bundle Branch Block
LS	Loading System
MI	Myocardial Infarction
MRS	Modified Rankin Score
MSCT	Multi Slice Computed Tomography
NYHA	New York Heart Association
TAV	Transcatheter Aortic Valve
PCI	Percutaneous Coronary Intervention
TAVR	Transcatheter Aortic Valve Replacement
QoL	Quality of Life
RBBB	Right Bundle Branch Block
SAE	Serious Adverse Event
SAVR	Surgical Aortic Valve Replacement

Term	Definition
SOP	Standard Operating Procedures
STS	Society of Thoracic Surgeons
TEE	Transesophageal Echocardiography
USADE	Unanticipated Serious Adverse Device Effect
VARC	Valve Academic Research Consortium

3. Synopsis

Title	Optimize PRO Study
Devices	• Medtronic Evolut™ PRO Transcatheter Aortic Valve (TAV) • Medtronic Evolut™ PRO+ Transcatheter Aortic Valve (TAV) • Medtronic EnVeo™ PRO Delivery Catheter System (DCS) with EnVeo™ InLine Sheath or EnVeo™ R DCS with EnVeo™ InLine Sheath • Medtronic Evolut™ PRO+ Delivery Catheter System (DCS) • Medtronic EnVeo™ PRO Loading System (LS) or EnVeo™ R LS • Medtronic Evolut™ PRO+ Loading System (LS) • Guidewires (e.g. Confida, etc) • Sheaths
Sponsor	Medtronic Structural Heart Clinical Research
Co-Principal Investigators	Dr. Steven Yakubov and Dr. Kendra Grubb
Product Status	Devices in this study must be commercially approved by the local regulatory agencies in the geography they are used.
Study Objective	The purpose of this post-market study is to collect clinical evidence on valve performance and procedural outcomes associated with an "optimized" TAVR care pathway and post-TAVR conduction disturbance pathway while using the Evolut™ PRO and Evolut™ PRO+ devices
Primary Objective	The primary objective is to collect short-term clinical evidence on the safety and efficacy of the Evolut™ PRO and Evolut™ PRO+ devices in the treatment of symptomatic severe aortic stenosis in subjects necessitating aortic valve replacement
Secondary Objective	The secondary objective is to collect clinical evidence on valve performance and procedural outcomes.

Exploratory Objective	The exploratory objective is to collect longer-term clinical evidence on the safety and efficacy of the Evolut™ PRO and Evolut™ PRO+ devices, as well as collect evidence on hospital readmissions post-TAVR.
Primary Endpoint	Rate of all-cause mortality or all-stroke at 30 days
Secondary Endpoints	• Median days from index procedure to discharge • Percentage of subjects with ≥ moderate aortic regurgitation (AR) at discharge. • Rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days
Additional Exploratory Endpoints	• 30-day and 1-year hospital re-admission rates • 1-year composite of all-cause mortality or all-stroke
Study Design	Post-market, multi-center, prospective, non-randomized
Sample Size	• Up to 46 sites in the United States and Canada with approximately 400 attempted implant subjects and 138 roll-in subjects • Up to 15 sites in Europe, Middle East, and Africa (EMEA) with at least 200 subjects and approximately 45 roll-in subjects • Up to 7 sites in Australia and New Zealand (ANZ) with approximately 50 subjects and 21 roll-in subjects
Patient Population	Subjects with severe, symptomatic aortic stenosis (AS) necessitating valve replacement
Duration	Total study duration is estimated to be 4 years (time from first subject implanted to one-year follow-up on last subject implanted)
Key Inclusion Criteria	• Acceptable candidate for treatment with the Evolut™ PRO or Evolut™ PRO+ system in accordance with the commercial Instructions for Use and local regulations; • Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater; • Subject and the treating physician agree that the subject will return for all required post procedure follow-up visits; • Anatomically suitable for transfemoral TAVR with the Medtronic TAVR system; • Subject meets the legal minimum age to provide Informed Consent based on local regulatory requirements;
Key Exclusion Criteria	• Contraindicated for treatment with the Evolut™ PRO or Evolut™ PRO+ system in accordance with the Instructions for Use

	• Anatomically not suitable for the Evolut™ PRO or Evolut™ PRO+ system;
	• Previous aortic valve replacement;
	• Reduced ventricular function with left ventricular ejection fraction (LVEF) < 35% as measured by resting echocardiogram;
	• Frailty assessments identify:
	  ○ Subject is <80 years of age and three or more of the following apply; OR subject is ≥ 80 years of age and two or more of the following apply
	  ▪ Wheelchair bound
	  ▪ Resides in an institutional care facility (eg. nursing home, skilled care center)
	  ▪ Body Mass Index <20kg/m^2
	  ▪ Grip strength <16kg
	  ▪ Katz Index score ≤4
	  ▪ Albumin <3.5 g/dL
	• Bicuspid valve verified;
	• Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70°.
	• Implanted with pacemaker or ICD;
	• Prohibitive left ventricular outflow tract calcification;
	• Estimated life expectancy of less than 12 months due to associated non-cardiac co-morbid conditions;
	• Other medical, social, or psychological conditions that in the opinion of the Investigator precludes the subject from appropriate consent, adherence to the protocol required follow-up exams;
	• Currently participating in an investigational drug or another device trial (excluding registries);
	• Need for emergency surgery for any reason;
	• Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable.

Study Procedures and Assessments	• Clinical assessment at baseline, discharge, 30 days, and 1 year • Transthoracic echo at baseline, discharge, and 1 year • Multi-Detector Computed Tomography at baseline • Quality of Life pre and post-procedure, 30 days, and 1 year

	• 12-lead ECG at pre and post-procedure, discharge, 30 days, and 1 year

4. Introduction

4.1. Background and Rationale

Transcatheter aortic valve replacement (TAVR) has been shown to be a safe and effective treatment for patients with severe aortic stenosis who are at extreme, high, or intermediate surgical risk[1-3]. Since CoreValve™ became commercially approved in the Europe in 2007, and in United States by the Food and Drug Administration (FDA) in 2014, the procedure and valve iterations have become increasingly efficient with reducing complications. The Evolut™ PRO and Evolut™ PRO+ valve's outer pericardial wrap was designed to enhance annular sealing to promote a decrease in paravalvular leak[4]. There is also a growing shift towards optimizing the TAVR care pathway by protocolizing the pre, peri, and post procedure assessments. This optimization can further increase the efficiency of the procedure and subsequently decrease the length of hospital stay and reduce health care costs[5,6].

This procedural efficiency has not translated to a consistent reduction in permanent pacemaker implantation (PPI) rates. Rates have decreased with newer generation TAVR valves, however, variability continues[7]. There is a lack of consensus regarding the management of post-TAVR conduction abnormalities leading towards heterogenous PPI rates across institutions and potentially unnecessary pacemaker implantations for abnormalities that could have resolved intrinsically over time[8,9]. Previous studies indicate most of high degree atrioventricular block (HAVB) and left bundle branch block (LBBB) occur prior to hospital discharge, and early monitoring is key to identifying and managing persistent TAVR-induced conduction abnormalities[10,11].

The objective of this study is to collect outcome data on valve performance while following a pre-specified TAVR care pathway. Additionally, this study will protocolize the management of the post-TAVR conduction disturbances and evaluate whether a consistent deployment technique will reduce the variability of new onset conduction disturbances.

This study will collect safety and performance data on guidewires and sheaths that are used during the TAVR procedure.

4.2. Purpose

The purpose of this study is to collect clinical evidence on valve performance and procedural outcomes associated with an "optimized" TAVR care pathway and using the Evolut™ PRO and Evolut™ PRO+ devices.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Study Objective

The study objective is to collect post-market clinical evidence on valve performance and procedural outcomes associated with an "optimized" TAVR care pathway and post-TAVR conduction disturbance pathway while using the Evolut™ PRO and Evolut™ PRO+ devices.

5.1.2. Primary Objective

The primary objective is to collect short-term clinical evidence on the safety of the Evolut™ PRO and Evolut™ PRO+ devices.

5.1.3. Secondary Objective

The secondary objective is to collect clinical evidence on valve performance and procedural outcomes.

5.1.4. Exploratory Objective

The exploratory objective is to collect longer-term clinical evidence on the safety of the Evolut™ PRO and Evolut™ PRO+ devices, as well as collect evidence on reasons for hospital readmissions post-TAVR.

5.2. Endpoints

The following endpoints will be used to evaluate the study objective as noted in sections 5.1.1, 5.1.2, 5.1.3, and 5.1.4.

5.2.1. Primary Endpoint

The primary endpoint is the rate of all-cause mortality or all-stroke at 30 days.

5.2.2. Secondary Endpoints

The following are the secondary endpoints:

- Median days from index procedure to discharge
- Percentage of subjects with ≥ moderate aortic regurgitation (AR) at discharge
- Rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days

5.2.3. Additional Exploratory Endpoints

The following are additional exploratory endpoints:

- 30-day and 1-year hospital re-admission rates
- 1-year composite of all-cause mortality or all-stroke

5.2.4. Rationale

The basis for the selection of these study endpoints include:

- Clinically relevant outcomes of the Evolut™ PRO and Evolut™ PRO+ devices
- In accordance with objectively measuring the efficacy of an optimized care pathway for TAVR subjects
- Objectively defined and measurable in the majority of subjects
- Consistent with current recommendations for endpoints in TAVR clinical studies[12]

6. Study Design

This is a post market, multi-center, prospective, non-randomized, interventional study. The 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.
- Core labs will evaluate all echocardiograms and ECGs. Echocardiographic trial endpoint results will be based on Core Lab assessments.
- Subjects will be screened to confirm eligibility for enrollment with pre-defined inclusion and exclusion criteria.

6.1. Duration

The enrollment period is estimated to be approximately 36 months and subjects will be followed for up to one year post index procedure; 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 approximately 4 years.

6.2. Study Oversight

The study will utilize a Steering Committee. The Steering Committee advises on the scientific content of the study and provides input for the execution. Members may be study site investigators. The purpose of the Steering Committee is to provide unbiased opinions and expertise to the clinical study design and process. The Steering Committee will support the execution of the Optimize PRO study and provide guidance,

feedback, and direction to the study. The Steering Committee is comprised of the members as indicated in the Steering Committee Charter.

The study will utilize a Screening Committee. The Screening Committee will be utilized when final confirmation of approval is required for a subject to be approved into the study. The Screening Committee is comprised of the members as indicated in the Screening Committee Charter.

6.3. Trial Organization

6.3.1 Participating Sites

This trial may be conducted at up to 46 sites in the United States and Canada, up to 15 sites in EMEA, and up to 7 sites in ANZ. Investigative sites will meet the following criteria:

- The site will have extensive facility experience with TAVR. Operator 1 and Operator 2 must individually meet the minimum of ≥ 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:
    - Minimum of 2 TAVR implanters with expertise in transcatheter aortic valve replacement as noted above
    - Electrophysiologist
    - Echocardiographer
    - Trial coordinator

6.3.2 Site Principal Investigator

Each site will have a Principal Investigator (PI) who is a TAVR implanter among the Heart Team. The PI will 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 trial data generated by their site, and for ensuring the trial is conducted in compliance with the Clinical Investigation Plan and IRB/REB/EC requirements.

6.3.3 Heart Team

Each site will utilize a local Heart Team to assess eligibility of the prospective subject for the trial according to the site's standard process and payer requirements.

At a minimum, the local Heart Team should include the TAVR implanter. The site PI may also serve as a member of the Heart Team.

6.3.4 Publication Committee

A Publication Committee will provide direction and support in the development of clinical publications. The Publication Committee will consist of steering committee members. The Publication Committee will be responsible to:

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

The Committee will be in charge of publication efforts until the completion of the primary endpoint. All publication activities post the primary endpoint will be facilitated by the Medtronic TAVR Global Evidence Committee.

6.3.5 Trial Training

Prior to participating, center activation, or subsequent involvement in study activities, Medtronic will provide training to the investigative team on the trial methods, procedures, and requirements. Training may be conducted via site initiation visits, investigator meetings, and/or other media sessions. Medtronic and the site will maintain documentation of these training sessions. Additionally, Medtronic representative(s) may be present at each site's implant procedures as part of the ongoing procedure support process.

7 Product Description

7.1 Description of Devices

All products used in this study will be market released in the geographies they are used.

7.1.1 Medtronic Evolut PRO and Evolut™ PRO+ Systems

The Medtronic Evolut PRO System is a TAVR implantation system comprised of the following 3 components (Table 1):

- Medtronic Evolut PRO TAV
- Medtronic EnVeo PRO DCS with EnVeo InLine Sheath
- Medtronic EnVeo PRO LS

The system components for the Evolut PRO System are shown in Table 1 and detailed descriptions provided in Sections 7.1.2.1, 7.1.2.3, and 7.1.2.5.

Table 1. Evolut™ PRO System Components

Component	US Model Number	Canadian Model Number	European/Israeli Model Number	Australia/New Zealand Model Number	Size (mm)	Aortic Annulus Diameter (mm)
Medtronic Evolut PRO TAV	EVOLUTPRO-23-US	EVOLUTPRO-23	EVOLUTPRO-23	EVOLUTPRO-23	23	18 – 20
	EVOLUTPRO-26-US	EVOLUTPRO-26	EVOLUTPRO-26	EVOLUTPRO-26	26	20 – 23
	EVOLUTPRO-29-US	EVOLUTPRO-29	EVOLUTPRO-29	EVOLUTPRO-29	29	23 – 26
EnVeo PRO DCS with EnVeo InLine Sheath (20 Fr/16eFr)	ENVPRO-16-US	ENVPRO-16	ENVPRO-16	ENVPRO-16	Used with 23,26, and 29 mm TAVs	Not applicable
EnVeo PRO LS	L-ENVPRO-1623US	L-ENVPRO-1623	L-ENVPRO-1623	L-ENVPRO-1623	Used with 23 mm TAV	Not applicable
	L-ENVPRO-16-US	L-ENVPRO-16	L-ENVPRO-16	L-ENVPRO-16	Used with 26 and 29 mm TAV	Not applicable

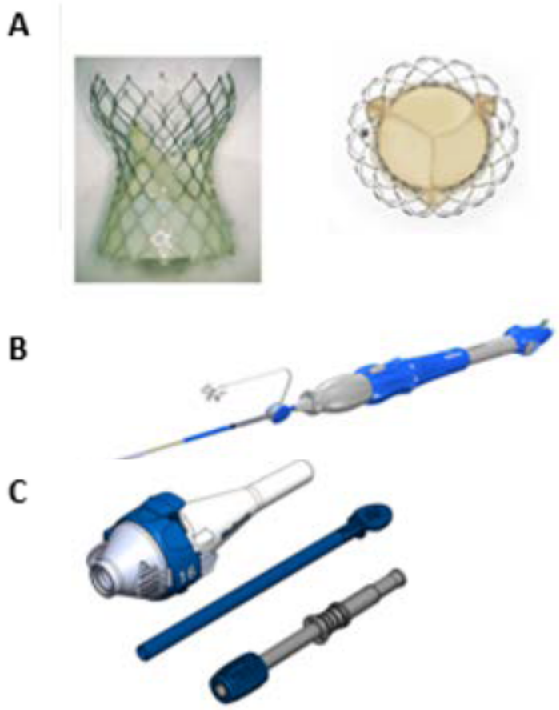

Figure 1. (A) Evolut PRO TAV; **(B)** EnVeo PRO DCS and EnVeo InLine Sheath; **(C)** EnVeo PRO LS

The Medtronic Evolut PRO+ System is a TAVR implantation system comprised of the following 3 components (Table 2):

- Medtronic Evolut PRO+ TAV
- Medtronic Evolut PRO+ DCS
- Medtronic Evolut PRO+ LS

The system components for the Evolut PRO+ System are shown in Table 2 and detailed descriptions provided in Sections 7.1.2.2, 7.1.2.4, and 7.1.2.6.

Table 2 Evolut™ PRO+ System Components

Component	US Model Number	Canadian Model Number*	European/Israeli Model Number*	Australia/New Zealand Model Number*	Size (mm)	Aortic Annulus Diameter (mm)
Medtronic Evolut PRO+ TAV	EVPROPLUS-23US	EVPROPLUS-23	EVPROPLUS-23	EVPROPLUS-23	23	18 – 20
	EVPROPLUS-26US	EVPROPLUS-26	EVPROPLUS-26	EVPROPLUS-26	26	20 – 23
	EVPROPLUS-29US	EVPROPLUS-29	EVPROPLUS-29	EVPROPLUS-29	29	23 – 26
	EVPROPLUS-34US	EVPROPLUS-34	EVPROPLUS-34	EVPROPLUS-34	34	26 - 30
Medtronic Evolut PRO+ DCS	D-EVPROP2329US	D-EVPROP23-29	D-EVPROP23-29	D-EVPROP23-29	Used with 23, 26, and 29 mm TAVs	Not applicable
	D-EVPROP34US	D-EVPROP34	D-EVPROP34	D-EVPROP34	Used with 34mm TAV	Not applicable
Medtronic Evolut PRO+ LS	L-EVPROP2329US	L-EVPROP23-29	L-EVPROP23-29	L-EVPROP23-29	Used with 23,26, and 29 mm TAVs	Not applicable
	L-EVPROP34US	L-EVPROP34	L-EVPROP34	L-EVPROP34	Used with 34 mm TAV	Not applicable

*The Evolut PRO+ System may be used upon commercial availability

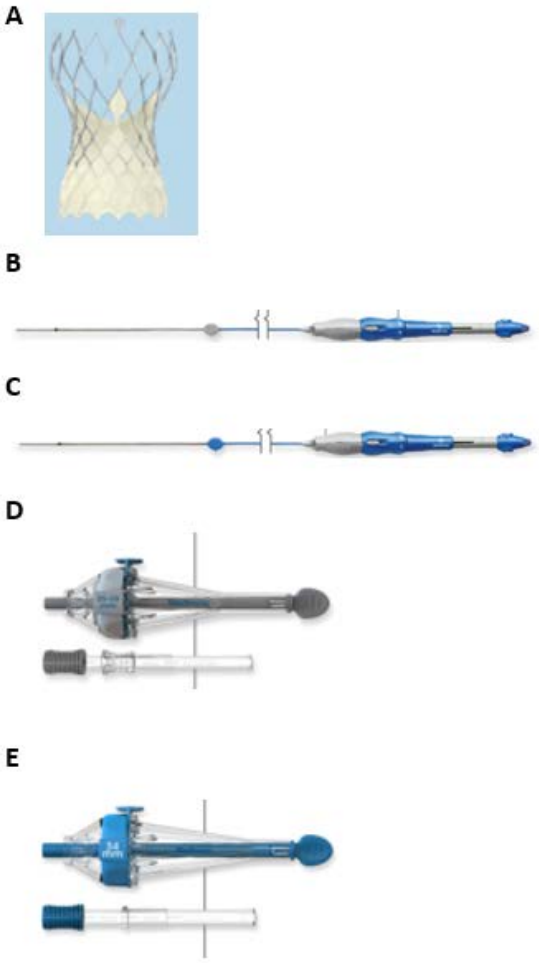

Figure 2. (A) Evolut PRO+ TAV**; (B)** Evolut PRO+ 23-29mm DCS; **(C)** Evolut PRO+ 34mm DCS **(D)** Evolut PRO+ 23-29mm LS **(E)** Evolut PRO+ 34mm LS

7.1.2.1 Medtronic Evolut PRO Transcatheter Aortic Valve

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

7.1.2.2 Medtronic Evolut PRO+ Transcatheter Aortic Valve

The Medtronic Evolut PRO+ TAV is available in certain geographies in 4 sizes (23, 26, 29, 34mm), covering an aortic annulus diameter of 18 to 30 mm. For the 26mm and 29mm bioprostheses: If the patient's annulus diameter is within 0.5 mm of the upper or lower bound of the range, use of the larger valve size can be considered, provided additional dimensional criteria as outlined in the CIP are met. The TAV is comprised of 3 leaflets, a sealing skirt, and outer tissue wrap constructed from glutaraldehyde-fixated porcine pericardium, sewn to a compressible and self-expandable Nitinol support frame. The TAV is processed with an anti-mineralization treatment of AOA, a compound derived from oleic acid, a naturally occurring long-chain fatty acid.

7.1.2.3 Medtronic EnVeo PRO Delivery Catheter System with EnVeo InLine Sheath

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

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

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

The catheter packaging contains an integrated loading bath and a removable tray with 3 rinsing bowls for loading and rinsing the bioprosthesis. The integrated loading bath features a mirror, which aids in accurate

placement of the bioprosthesis frame paddles during loading. In addition, the device packaging is swiveled and secured to facilitate the bioprosthesis loading procedure.

7.1.2.4 Medtronic Evolut PRO+ Delivery System

The Evolut PRO+ catheter facilitates the placement of the bioprosthesis within the annulus of the aortic valve. The catheter assembly is flexible and compatible with a 0.035 in (0.889 mm) guidewire. The distal (deployment) end of the system features an atraumatic, radiopaque catheter tip and a capsule that covers and maintains the bioprosthesis in a crimped position. The capsule includes a distal flare to enable the bioprosthesis to be partially or fully recaptured 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. A PRO+ 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 catheter is compatible with an 18 Fr (6.0 mm) introducer sheath for the 23, 26, and 29 mm TAVs and a 22 Fr (7.3 mm) introducer sheath for the 34 mm TAV.

The DCS consists of a catheter with an integrated handle to assist 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 deployment knob turns to deploy the bioprosthesis. Arrows on the deployment knob indicate the direction of rotation required to deploy the bioprosthesis. If desired, the deployment knob can be turned in the opposite direction to partially or fully recapture the bioprosthesis if the radiopaque capsule marker band has not yet reached the distal end of the radiopaque paddle attachment. Once the radiopaque capsule marker band reaches the distal end of the radiopaque paddle attachment, it is at the point of no recapture. The deployment knob also features a trigger, which can be engaged to make macro adjustments to the capsule position. A blue hand rest connects to the deployment knob. 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 to these features, the device packaging is swiveled and secured to facilitate the bioprosthesis loading procedure.

7.1.2.5 EnVeo PRO Loading System

The EnVeo PRO LS is a system of reduction cones and tubing designed to gradually reduce the diameter of the TAV radially to an optimal diameter to facilitate manual loading of the Evolut PRO TAV into the deployment sheath capsule of the EnVeo PRO DCS. The EnVeo PRO loading system incorporates minor modifications including a change to the capsule guide tube (CGT) to include a locking collar, which reduces the ability of the user to load the TAV with a paddle in the incorrect position by preventing movement of the frame paddles once positioned in the spindle pockets. Additionally, manufacturing process changes and

a minor design and material change, including the color differentiation between the two loading system sizes, was implemented on the catheter tip guide tube (TGT) components. A third modification is to the inner diameter of the inflow ring designed to allow multiple TAVs to seat securely into the inflow ring.

7.1.2.6 Evolut PRO+ Loading System

The Evolut PRO+ LS compresses the bioprosthesis into the catheter. Note: verify the correct delivery system and loading system are used for the Evolut PRO+ 34 mm valve. This loading system is designed for compatibility with this specific TAV and delivery system.

7.2 Manufacturer

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

Medtronic CoreValve LLC

[redacted]

7.3 Intended Population

The study population includes patients with symptomatic native aortic valve stenosis necessitating valve replacement. Patients who undergo an emergency procedure should not be included in this study.

7.4 Product Training Requirements

The Evolut PRO and Evolut PRO+ devices will be used within the local commercially approved indication in the geographies in which each device is approved, with exception to any inclusion and exclusion criteria in this protocol and obtained by the study sites according to standard hospital procedures for commercial products. Local existing approved procedures for commercial product regarding training, distribution, shipment, storage, and handling will be followed. In the event of a device malfunction or explant, please refer to section 10.5.

7.5 Product Labeling, Tracking, and Accountability

Subjects enrolled in this study will be treated using commercial product. Device lot and serial numbers, as applicable, will be collected in the Device Identification CRF. As this is not an investigational trial, Product Accountability Logs (PALs) will not be utilized. Sites will follow their institutional standard practice for device ordering and replenishment of commercial product for use in this study.

7.6 Product Storage

Sites will follow their institutional standard practice for storing commercial TAVR product.

8 Study Site Requirements

8.1 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the clinical investigation plan, informed consent, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB/REB/EC approval (and voting list, as required by local law) of the current version of the CIP and IC.
- Fully executed CTA: Medtronic contracts with participating institutions/investigators through a Clinical Trial Agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic.
- CV of investigators and key members of the investigation study site team (as required). The signature on the CV must be dated within 3 years prior to the date of activation of the study site.
- Documentation of delegated tasks
- Documentation of study training

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study related activities.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

9 Selection of Subjects

9.1 Study Population

The study population includes patients with symptomatic native aortic valve stenosis that necessitates valve replacement who meet the criteria for on-label use of the Evolut PRO and/or Evolut PRO+ system in accordance with Instructions for Use and local regulations.

9.2 Subject Enrollment

This study will involve approximately 650 subjects in the US, Canada, EMEA, and ANZ (not including roll-in subjects) based on the number of subjects with an attempted TAVR procedure among all active sites. To ensure a widespread distribution of data and to minimize bias in the study results, no site will implant more than 50 subjects without prior authorization from Medtronic. Subjects who exit from the study after implantation will not be replaced.

9.2.1 Roll-In Subjects

For all participating centers, the first three subjects implanted will be considered "roll-in" subjects and will not be included in the 650 'attempted implant' cohort. The purpose of the roll-in subjects is to provide Investigators the time for training and familiarization with the protocolized implant technique. The Training and Education team will review and provide recommendations for transition of sites from roll-in phase to attempted implant analysis phase. Medtronic will notify each site with official correspondence on approval to move into the as-treated analysis phase.

Roll-in subjects will complete in-clinical follow-up evaluations as noted in section 10.1.5 Follow-Up Evaluations however the results for the roll-in population will be analyzed separately from the primary analysis cohorts.

9.3 Inclusion Criteria

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

1. Acceptable candidate for treatment with the Evolut PRO or Evolut PRO+ system in accordance with the commercial Instructions for Use and local regulations;
2. Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater;
3. Subject and the treating physician agree that the subject will return for all required post procedure follow-up visits;
4. Anatomically suitable for transfemoral TAVR with the Medtronic TAVR system;
5. Subject meets the legal minimum age to provide Informed Consent based on local regulatory requirements.

9.4 Exclusion Criteria

Subjects are not eligible for study participation if they meet ANY of the following exclusion criteria:

1. Contraindicated for treatment with the Evolut PRO or Evolut PRO+ system in accordance with the Instructions for Use

2. Anatomically not suitable for the Evolut PRO or Evolut PRO+ system;
3. Reduced ventricular function with left ventricular ejection fraction (LVEF) < 35% as measured by resting echocardiogram;
4. Previous aortic valve replacement;
5. Frailty assessments identify:
    - Subject is <80 years of age and three or more of the following apply; OR subject is ≥ 80 years of age and two or more of the following apply
        - Wheelchair bound
        - Resides in an institutional care facility (e.g. nursing home, skilled care center)
        - Body Mass Index <20kg/m^2
        - Grip strength <16kg
        - Katz Index score ≤4
        - Albumin <3.5 g/dL
6. Bicuspid valve verified;
7. Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70°.
8. Implanted with pacemaker or ICD;
9. Prohibitive left ventricular outflow tract calcification;
10. Estimated life expectancy of less than 12 months due to associated non-cardiac co-morbid conditions;
11. 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;
12. Currently participating in an investigational drug or another device trial (excluding registries);
13. Need for emergency surgery for any reason.
14. Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable*.

** Notes: Vulnerable subjects include individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. EXAMPLE Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.* [13]

10 Study Procedures

10.1 Schedule of Events

Follow-up protocol required evaluations should be performed at the trial site, however remote visits via phone contact are permitted, if necessary. The protocol required evaluations for each trial interval are listed as follows and summarized in Table 3.

10.1.1 Screening Procedures

The following assessments must be completed within 12 weeks prior to TAVR index procedure unless otherwise indicated:

- Clinical assessment, history, and concomitant medications
    - Physical examination including height, weight, systolic and diastolic blood pressure, and body surface area.
    - 5-Meter Gait Speed
    - Grip Strength
- NYHA classification
- MSCT angiogram – *within 1 year prior to procedure*
- TTE – *within 10 weeks prior to procedure*
- Heart Team eligibility assessment
- Laboratory tests – glomerular filtration rate (GFR), hemoglobin, international normalized ratio (INR) for subjects on warfarin, and serum creatinine
- Modified Rankin Score – conducted by certified site personnel
- Quality of Life Questionnaires
    - EQ-5D
    - KCCQ
- STS Risk Score
- Katz Index of Independence in Activities of Daily Living

The Optimize PRO study will include a Confirmation of Qualification process conducted by Medtronic Clinical Analysts and an independent Screening Committee to review the anatomical characteristics of potential subjects identified by the sites for enrollment. Depending on whether a subject's anatomical characteristics meet entry criteria for the study, a recommendation to proceed with treatment or to re-evaluate / exit the subject will be provided to the site.

10.1.2 Enrollment

Subjects will be considered enrolled into the study at the time of Informed Consent. Due to the inclusion/exclusion criteria, not all patients enrolled in the study will be treated. All sites will be required

to maintain a record of patients screened for the trial meeting general inclusion criteria who have signed the approved Informed Consent document. For subjects that do not meet study criteria, the reason for not continuing in the trial must be documented and recorded in the EDC system.

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

Subjects must have their TAVR procedure as soon as possible and no later than 90 days post-enrollment.

10.1.3 Implant Procedure (TAVR)

Procedural aspects specific to the Medtronic TAVR system should be performed according to the Instructions for Use. Concomitant procedures including percutaneous coronary intervention (PCI) are not permitted to be completed during the index procedure.

The valve deployment will be completed in accordance to the cusp overlap technique via procedural angiogram, and the standard procedures of the implanting physicians and the TAVR clinical pathway protocol requirements noted below. This described TAVR clinical pathway should serve as a guide for accelerated discharge. Institutional clinical TAVR pathways can be followed as long as the modifications are consistent with an accelerated discharge.

Pre-procedure:

- 12-lead ECG – *within 48 hours prior to procedure*
- Develop "early discharge plan" (including frailty, mental assessment, and home health if required) with multi-disciplinary team along with optimized screening checklist for first and / or second visit leading up to TAVR procedure.
- Standardize room layout – team composition in procedure room (planning with multi-disciplinary team).

Peri-Procedure:

- No pre-deployment balloon aortic valvuloplasty TAVR procedure unless medically necessary
- General anesthesia should be avoided unless deemed necessary (e.g. for placement of a transesophageal echo), and it is believed that its use will not impede an early discharge
- Percutaneous and transfemoral access only
- No urinary catheter
- Minimize central lines: no Swan-Ganz catheterization or internal jugular vein unless for temporary transvenous pacing

Post Procedure Recovery:

- Complete 12-lead ECG within 2 hours after the TAVR procedure

- If no ECG changes compared to pre-procedure ECG and subject did not have pre-existing RBBB:
  - Remove all remaining lines within 2 hours of TAVR procedure
  - Repeat 12-lead ECG prior to discharge to confirm no new ECG changes
- Refer to Appendix 18.1 Conduction Disturbance Management if new ECG changes or subject had pre-existing RBBB

- Mobilize within 4 - 6 hours of TAVR procedure
- Minimal intensive care unit (ICU) utilization: consider post-anesthesia care unit (PACU) in place of ICU or transfer straight to stepdown floor or telemetry unit

10.1.3.1 Cusp Overlap Procedural Steps

Ensure the following procedural steps are captured in the recorded fluoroscopy and submitted to Medtronic in DICOM format.

1. Conduct initial deployment in the cusp overlap projection and conduct aortogram to obtain the estimated implant depth at the NCC.
2. Use of Double Curved Lunderquist guidewire is highly recommended unless clinically contraindicated.
3. Ensure guidewire is properly positioned within the left ventricle.
4. Begin deployment with the marker band positioned at mid-pigtail or higher.
5. Do not exceed 3mm depth at the NCC prior to full annular contact.
6. Initiate pacing at the third node and rapidly deploy to point of no recapture (80% deployment).
7. Discontinue pacing at point of no recapture.
8. Assess depth in cusp overlap view at 80% deployment.
9. At the point of no recapture, roll LAO (at least 25˚) and remove any remaining parallax at the inflow of the TAV. Conduct pre-release aortogram to obtain the estimated depth of implant from this view at the LCC (80% deployment).
10. Determine if appropriate to deploy or recapture (recapture or resheath if depth at NCC is <1mm or >5mm).
11. Redeployment in cusp overlap view, if applicable.
12. Retract the wire prior to release.
13. Demonstrate very slow release of the TAV.
14. Centralize the nosecone prior to withdrawal of the delivery catheter system.
15. Assess final implant depth on the NCC by aortography in the original cusp overlap projection.

10.1.4 Prior to Discharge

- Physical examination including weight, systolic and diastolic blood pressure, and concomitant medications.
- NYHA classification
- 12-lead ECG (refer to Appendix 18.1 Conduction Disturbance Management for discharge 12-lead ECG requirements for subjects with conduction abnormalities)

- Laboratory tests - glomerular filtration rate (GFR), hemoglobin, international normalized ratio (INR) for subjects on warfarin, and serum creatinine
- TTE – should be done between 12 hours and 7 days post TAVR
- Adverse event review

10.1.5 Follow-Up Evaluations

All treated subjects will undergo follow-up evaluations at the following time points post procedure. All follow-up periods are defined as the number of days after the date of the index procedure.

Day 0 = day of index procedure

- 30 days (30 + 14 days)
- 12 months (365 ± 30 days)

30 Days

- Physical examination including weight, systolic and diastolic blood pressure, and concomitant medications.
- NYHA classification
- 12-lead ECG
- Quality of Life Questionnaires – KCCQ and EQ-5D
- In-office pacemaker interrogation for subjects implanted with pacemakers post index TAVR procedure
- Adverse event review

12 Months

- Physical examination including weight, systolic and diastolic blood pressure, and concomitant medications.
- NYHA classification
- 12-lead ECG
- Quality of Life Questionnaires – KCCQ and EQ-5D
- TTE
- In-office pacemaker interrogation for subjects implanted with a pacemaker post index TAVR procedure
- Adverse event review

Other Evaluations

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

Table 3. Summary of Visit Schedule and Required Evaluations

	Screening	TAVR Procedure	Discharge	30 Days	12 Months
Informed Consent and HIPAA Authorization	X				
Clinical Assessment (Physical Assessment and Concomitant Medications)	X		X	X	X
NYHA Classification	X		X	X	X
TTE	X		X		X
MSCT Angiogram	X				
Procedural Angiogram		X			
Laboratory Test	X		X		
12-Lead ECG[1]		X[5]	X	X	X
Modified Rankin Score[2]	X				
Quality of Life Questionnaires[3]	X			X	X
STS Risks Assessment	X				
Katz Index of Independence in Activities of Daily Living	X				
5-Meter Gait Speed	X				
Grip Strength	X				
Pacemaker Interrogation[4]				X	X
Adverse Event Review		X	X	X	X

[1] Refer to Appendix 18.1 Conduction Disturbance Management for discharge 12-lead ECG requirements

[2] A Modified Rankin Score assessment should be conducted at 1 and 3 months following any stroke event.

[3] Quality of Life Questionnaires include EQ-5D and KCCQ.

[4] In-office pacemaker interrogations at pacemaker implant, 30-days, and 12 months and CareLink™ Transmissions at 3, 6, and 9 months required for subjects implanted with pacemakers post index TAVR procedure.

[5] ECGs are required within 48 hours pre-procedure and then again within 2 hours post-procedure. Depending on the Conduction Disturbance pathway the subject is in post-procedure, additional ECGs may be required at 24 hours and 48 hours post-procedure.

10.1.6 Additional Evaluations for Pacemaker Implants

Medtronic brand pacemakers are required to be implanted for subjects that require pacemaker implantation post the TAVR index procedure through the duration of their study participation in order to collect device data from pacemakers. Device data will be collected remotely via CareLink™ system at 3, 6, and 9 months post pacemaker implantation and during in-office pacemaker interrogations at pacemaker implant, 30-day, and 12-month follow-up visit.

For subjects that require pacemaker implantation, a final 'Interrogate All' device interrogation file must be obtained and saved in a digital format (Save-to-Media/.pdd) at pacemaker implant, 30 day, and 12-month

follow-up visit. One copy will be stored at the site and another copy will be sent to Medtronic (device data must not be cleared). A device interrogation (final 'Interrogate All')/Save-to-Media (or CareLink™ transmission) should also be completed at the time of study exit (prior to 12 months visit) and in the case of a death (where possible).

10.1.7 Missed Follow-Up Visits

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

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.

10.1.8 Core Labs

Transthoracic echocardiography (TTE), ECGs, explants, and angiogram imaging will be sent to core labs for central assessment. Further details of the echocardiography methods are provided in Appendix 18.3.

10.1.9 Subject Consent

Prior to enrolling in the trial, patients should be fully informed of the details of trial participation as required by applicable regulations, the site's IRB/REB/EC and the Declaration of Helsinki. 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/REB/EC and by Medtronic, Inc. All Informed Consent Forms, including Authorization/Data Protection or other consenting forms required per local requirements and/or short form consents, must be approved by Medtronic, Inc. prior to use. 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/REB/EC to sign the Informed Consent Forms must also comply.

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

The original signed consent form will be retained in the patient's trial records and a copy of the Informed Consent Form 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 (e.g. echocardiography, MSCT, 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.

Medtronic will provide each site with the study specific informed consent separately from this CIP.

10.2 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 trial. The revised information will be sent to the investigator for approval and presented to subjects in an updated informed consent (if required by IRB/REB/EC).

10.3 Assessment of Efficacy

The following methods will be used for assessing, recording, and analyzing efficacy. Refer to section 10.1 Schedule of Events for timing of these assessments.

- STS risk score
- Heart team assessment
- MSCT
- TTE
- 12-lead ECG
- NYHA functional classification
- EQ-5D and KCCQ quality of life questionnaires

10.4 Assessment of Safety

10.4.1 Adverse Events and Device Deficiencies

Serious adverse events (SAE), device deficiencies (DD), and non-serious VARC-2 adverse events (that are outlined in Appendix 18.6) will be collected from the time of enrollment until the end of the study or until study exit, whichever comes first.

The safety assessment performed during this study will be based on the relatedness to the TAVR implant procedure and the following devices:

- Commercial Study Devices:

  - Medtronic Evolut™ PRO Transcatheter Aortic Valve (TAV)
  - Medtronic EnVeo™ PRO Delivery Catheter System (DCS) with EnVeo™ InLine Sheath
  - Medtronic EnVeo™ PRO Loading System (LS)
  - Medtronic Evolut™ PRO+ Transcatheter Aortic Valve (TAV)
  - Medtronic Evolut™ PRO+ Delivery Catheter System (DCS)
  - Medtronic Evolut™ PRO+ Loading System (LS)
- Commercial Accessory Devices:
  - Sheath
  - Guidewire

10.5 Device Malfunction or Explant

In the event of a device malfunction of the TAV device or its components prior to implant or in the event that a TAV is explanted after implant (due to reintervention or autopsy), the TAV and/or affected components should be returned to Medtronic to the following:

Medtronic, Inc.

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.

10.6 Data Collection

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

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

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

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

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

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

10.6.1 Source Documents

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

The eCRFs may not serve as source documents. Source documentation for data elements not routinely captured in medical records (e.g. echocardiography variables, MSCT variables, catheter and procedural data variables, Heart Team assessment, Modified Rankin Score) may vary from center to center. The site may use technical worksheets if identified as source documents.

Source documents must be retained by the participating site for a period of two years after trial conclusion (or longer as required by local law) and made available for monitoring or auditing by the sponsor's representative or representatives of the US FDA and other applicable regulatory agencies or IRB/REB/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 original source documents, or where copies of source documents are retained as original 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.

10.7 Deviation Handling

Protocol deviations will be reported regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency.

A protocol deviation is to be completed for each trial protocol deviation, including, 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/REB/EC approval before the start of the study
- Implanted subject did not meet inclusion/exclusion criteria
- Enrollment of subjects during lapse of IRB/REB/EC 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 (e.g. subject did not attend scheduled follow-up visit).

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

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

10.8 Subject Exit, Withdrawal or Discontinuation

Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of total trial subjects. If a subject is discontinued from the trial early, the reason for discontinuation should be documented in the subject file and a Study Exit eCRF must be completed. If discontinuation is because of safety concerns or lack of effectiveness, the subject shall be asked to be followed for collection of ongoing safety data outside the clinical investigation.

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

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

11 Risks and Benefits

11.1 Potential Risks

There are possible risks and side effects connected to the Evolut PRO or Evolut PRO+ TAV implant, but the risks are the same as those for an implant of the Evolut PRO or Evolut PRO+ TAV without participation in this study. Standard risks associated with the Evolut PRO and Evolut PRO+ systems in the study are provided in the Instructions for Use.

Risks and events will be continuously monitored, assessed and documented by the investigator.

11.2 Potential Benefits

Participation in this clinical study will not result in any direct benefit to the patient. Trial subjects implanted with an Evolut PRO or Evolut PRO+ device receive the same medical treatment as if they were not participating in this post-market study. Participation contributes to expansion of the knowledge base with respect to the use of the Evolut PRO and Evolut PRO+ systems in a routine hospital setting.

11.3 Risk-Benefit Rationale

11.3.1 Risk Minimization

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

- Implanting physicians will have considerable experience with TAVR
- Study sites will have significant experience with TAVR
- Patients will undergo thorough imaging assessment during their pre-implant workup
- Patients will be rigorously followed over the course of the study

11.3.2 Alternative Therapies

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

- Medical therapy
- Balloon aortic valvuloplasty
- Surgical aortic valve replacement
- TAVR with a non-Medtronic system

11.3.3 Results from the Risk Analysis and Justification for the Study

TAVR is now established as having an acceptable safety profile and is considered an effective treatment option for patients with symptomatic severe aortic stenosis who are at extreme, high, or intermediate risk for surgical aortic valve replacement. The Medtronic CoreValve™ system, the Evolut R system, the Evolut PRO system, and the Evolut PRO+ system (referred jointly as Medtronic TAVR) have been in widespread use since the first generation received CE Mark in 2007, and there is now extensive published experience demonstrating the Medtronic TAVR system is fulfilling its intended role with a favorable risk/benefit ratio.[14-17] Rigorous clinical trials have established its safety and effectiveness, with improved mortality and quality of life compared with medical therapy in extreme, high and intermediate risk patients. [1-4]

Optimizing a TAVR care pathway may lead to procedural efficiencies that result in a decrease of new onset AV conduction disturbance and length of hospital stay post TAVR; while protocolizing a conduction disturbance pathway may lead to a decrease in permanent pacemaker implantation. There are no additional associated risks to following these pathways.

12 Adverse Events and Device Deficiencies

12.1 Definitions/Classifications

Serious adverse events (SAE), non-serious VARC-2 adverse events, and device deficiencies are collected for this study. The definitions to be applied for the purposes of reporting adverse events are provided in Table 4. The list of non-serious VARC-2 adverse events that will be collected for this study and their definitions are provided in Appendix 18.6.

Table 4. Adverse Event Definitions for Reporting Requirements

Event Type	Definition
Adverse Event (AE) (ISO 14155:2020, 3.2)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved.

	NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
Serious Adverse Event (SAE) (ISO14155:2020 3.45)	AE that led to any of the following a) death, b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic disease, 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) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.[13] Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE
Device Deficiency (ISO 14155:2020, 3.19)	Inadequacy of a medical device with respect to its identify, quality, durability, reliability, usability, safety or performance. NOTE 1: DD includes malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.
Serious Adverse Device Effect (SADE) (ISO 14155:2020, 3.44)	Adverse device effect (adverse event related to the use of an investigational medical device) that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155:2020, 3.51)	(Serious adverse) device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment NOTE 1: ASADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

Notes:

- The interpretation of Seriousness will exclude certain interventions considered standard of care during hospitalization (e.g. IV hydration, certain medications delivered intravenously due to available intravenous access or NPO (nothing by mouth) status, and the delivery of electrolytes to maintain electrolyte balance or to address mild electrolyte depletion). Any nonoral medication or fluid delivery used to treat an acute physical decompensation/deterioration episode or to otherwise resuscitate a subject will be considered serious by definition in that it prevents a permanent impairment of a body structure or deterioration of the health of a subject.
- 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.

- Hospitalization requires admission for at least 24 hours.
- Ballooning as needed during the implant procedure is standard practice and should not be considered a reintervention.

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures:

- No Relationship: No relationship between the AE and the administration of study treatment and a known relationship to other etiologies such as concomitant medications, surgical procedure, or subject's clinical state.
- Possible Relationship: An AE that follows a reasonable temporal sequence from administration of the study treatment and follows a known response pattern to the study treatment but could have been produced by the participant's clinical state or by other therapies.
- Probable Relationship: An AE that follows a reasonable temporal sequence from administration of the study treatment; follows a known response pattern to the study treatment; and cannot be reasonably explained by the known characteristics of the participant's clinical state or by other therapies.
- Causal Relationship: An AE that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the study treatment. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
- Unknown relationship: Given the information available, sequence and timing of events, it is unknown or impossible to determine the relationship of the AE with the study treatment.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected.

12.1.1 Evaluation and Documentation of Adverse Events

Investigators are required to evaluate and document in the subject's medical records all serious adverse events, non-serious VARC-2 related events outlined in Appendix 18.6, device deficiencies, and device deficiencies with SADE potential (per the definitions in Table 5) observed in trial subjects from the time of enrollment until they are exited from the trial. All SAEs should be followed through their resolution.

Documented pre-existing conditions are not considered to be reportable unless there is a change in the nature or severity of the condition and meets definition of a SAE per definition in Table 5 or a non-serious VARC-2 AE in Appendix 18.6. Pre-existing events should be reported as an SAE in the situation where a new treatment has to be started or an existing treatment has to be changed to treat the adverse event and the event is accompanied with signs and symptoms.

Unavoidable events are conditions which do not fulfill the definition of an Adverse Event, meaning those medical occurrences, clinical signs (including toward abnormal laboratory findings), diseases or injuries that

are not untoward in nature; specifically, those resulting from the intended injury such as the index TAVR procedure. The events listed in Table 5 are expected for patients undergoing TAVR, and do not need to be reported as an AE, unless they worsen during the timeframe or occur outside of the stated timeframe, or are otherwise considered to be an SAE according to the treating investigator, or are suspected or confirmed to be device-related.

Table 5. Non-Reportable Medical Occurrences Associated with the Index 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 (e.g. 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 (e.g. 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)

12.1.2 Evaluation and Documentation of Device Deficiencies

Device deficiency information will be collected throughout the trial and reported to Medtronic. Device deficiencies should be reported on a Device Deficiency eCRF (one for each Device deficiency) or on the AE

CRF if the deficiency led to an adverse event (any untoward medical occurrence, unintended disease or injury, or untoward clinical signs).

Device Deficiencies that did not lead to an AE but could have led to a SADE (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting.

12.2 Reporting of Adverse Events

Investigators are required to report all serious adverse events (SAE) and non-serious VARC-2 adverse events outlined in Appendix 18.6 observed in the study subjects from the point of enrollment until completion of follow-up.

The VARC-2 document provides standardization of endpoint definitions for studies evaluating the use of TAVI. This study follows VARC-2 to allow for improved comparability and interpretability of study results. In addition, Investigators are obligated to report adverse events in accordance with the requirements and timeframes per their reviewing IRB/REB/EC and local regulations, if applicable.

The Sponsor is obligated to report adverse events and device deficiencies that occur during this trial to the IRB/REB/EC as per local requirements.

12.3 Emergency Contact Details for Reporting AEs and Device Deficiencies

Investigators should contact their Medtronic clinical trial monitor 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.

12.4 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the Regulatory Authorities (e.g. Competent Authority) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.

- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
  - Life-threatening illness or injury
  - Permanent impairment of a body function or permanent damage to a body structure
  - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

13 Statistical Design and Methods

13.1 General Aspects of Analysis

13.1.1 Enrolled Population

Within the enrolled population the following analysis sets are distinguished:

- **The attempted implant set:** The attempted implant set consists of all enrolled subjects with an attempted TAVR implant procedure, defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia or conscious sedation administered, vascular line placed, TEE placed, or any monitoring line placed. Subjects will be analyzed according to their first attempted procedure. Enrolled subjects that do not receive an attempted TAVR implant are to be exited from the study.
- **The implanted set:** The implanted set consists of all the attempted implant subjects who are actually implanted with the TAV. Subjects with an attempted implant that do not actually receive a TAV are to be exited from the study following discharge from the index hospitalization.
- **Per protocol (PP) set 1 for TAVR care pathway:** This per protocol set consists of all implanted subjects with percutaneous and transfemoral access only and no concomitant procedures including percutaneous coronary intervention (PCI). This per protocol set 1 will be used for the secondary endpoint median days from index procedure to discharge. Time zero begins on the date of the first attempted implant procedure.
- **Per protocol (PP) set 2 for conduction disturbance pathway:** This per protocol set consists of all attempted implant subjects whose peri and post TAVR index procedure follows the conduction disturbance pathway management and cusp overlap technique. This per protocol set 2 will be used for the secondary endpoint rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days.
- **Roll-in:** Roll-in subjects will not be analyzed with the attempted implant, implanted, or per protocol set and will be analyzed separately using descriptive statistics. See section 9.2.1 for definition of roll-in subjects.

The primary analysis for the primary endpoint and secondary safety and effectiveness endpoints will use the attempted implant set.

13.2 Description of Baseline Variables

Baseline demographic and clinical variables will be summarized for the attempted implant, implanted, and per protocol sets. Continuous variables will be summarized as means, medians, standard deviations, interquartile ranges, minima and maxima and categorical variables will be summarized as frequencies and percentages.

13.3 Primary Analysis

The study objective and endpoints are descriptive, and no statistical hypothesis testing will be performed. The first interim analysis will be conducted after 100 subjects are enrolled in the attempted implant set and followed through 30 days post procedure.

Roll-in subjects will not be included in the primary analysis; however, the data will be summarized separately with descriptive statistics.

The rates of permanent pacemaker implantation at 30 days by region (US/CAN, EMEA, and ANZ) will be provided and compared. Additional information regarding this analysis can be found in the TAVR Low Risk Post Market Clinical Follow-Up Plan.

13.3.1 Primary Endpoint

The primary endpoint is the rate of all-cause mortality or all-stroke at 30 days. A Kaplan-Meier survival analysis will be performed with results summarized at 30 days and 12 months. This endpoint is descriptive, and no statistical hypothesis test will be performed.

13.4 Sample Size

The sample size for the attempted implant population from each geography is approximately 400 subjects at up to 46 sites in the US and Canada, at least 200 subjects at up to 15 sites in EMEA, and approximately 50 subjects at up to 7 sites in ANZ. The sample size for the roll-in population is approximately 204 subjects. The total combined sample size with all analysis populations is approximately 854 subjects.

This is not a hypothesis-driven study, therefore the attempted implant set sample size of approximately 650 subjects was not determined by statistical sample size methods. With >25% of TAVR patients experiencing new conduction disturbances[10], 650 patients will provide a sufficient sample (~160 patients) to evaluate the conduction disturbance management pathway.

13.5 Secondary Endpoints

The following are the secondary endpoints:

- Median days from index procedure to discharge
- Percentage of subjects with ≥ moderate aortic regurgitation (AR) at discharge
- Rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days

13.6 Additional Exploratory Endpoints

The following are additional exploratory endpoints:

- 30-day and 1-year hospital re-admission rates
- 1-year composite of all-cause mortality or all-stroke

13.7 Missing Data

Every effort will be undertaken to minimize missing data. However, some missing data is inevitable, and the trial is designed with the expectation that there may be up to 6% of primary data missing at 12 months.

14 Ethics

14.1 Statement of Compliance

The study will be conducted in accordance with the protocol, ICH E6 R2 GCP, and ethical principles that have their origin in the Declaration of Helsinki. Laws and regulations of the countries in which the study is conducted, including data protection laws, will be following.

In addition, in Europe the study will be conducted in compliance with the Medical Device Regulation (EU) 2017/745 (MDR). Each site must fulfill all local regulatory requirements prior to enrolling subjects and throughout the duration of the study, as applicable.

Participating sites will not be activated nor begin enrolling subjects until the required approval/favorable opinion from the local IRB/REB/EC and regulatory agency has been obtained (as appropriate).

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

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

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

In addition to the requirements outlined above, any additional requirements imposed by the IRB/REB/EC or regulatory authority shall be followed, if appropriate.

15 Study Administration

15.1. Monitoring

Participating sites will be monitored to ensure compliance with the trial protocol, adherence to applicable regulations, and accuracy of trial data. Monitoring visits will be conducted primarily to ensure the safety and well-being of the subjects is preserved. Sites should provide appropriate access to the source data. Site personnel will complete eCRFs following each subject visit. Trial data submitted will be reviewed against subject charts and other sources containing original records of subject data. Source document verification will occur via a risk-based approach as outlined in the Monitoring Plan.

The progress of the trial will be monitored by:

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

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

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

Prior to the first site activation a monitoring plan will be established outlining the above activities, as well as trial materials to be supplied to sites, the process for corrective and preventive actions and Investigator disqualification procedures.

15.2. 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 trial. The trial database will be developed and validated per the Data Management Plan for this trial and will employ validation programs (e.g. range and logic checks) on entered data to identify possible data entry errors and to facilitate data validation. The trial database will maintain an audit trail of all changes made to the eCRFs.

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

15.3. Direct Access to Source Data/Documents

Medtronic may conduct audits at participating clinical sites. The purpose of an audit is to verify the performance of the monitoring process and the trial conduct, independent of the personnel directly involved in the trial.

The investigator and/or institution shall permit Medtronic, regulatory bodies, and IRB/REB/EC direct access to source data and documents.

15.4. Confidentiality

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

15.5. Liability

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

15.6. CIP Amendments

The investigator may propose any appropriate modification(s) of the CIP. 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 investigators to obtain approval from their IRB/REB/EC. The investigator will only implement the amendment after approval of the IRB/REB/EC, and Medtronic. Administrative amendments to the CIP will be submitted to the IRB/REB/EC for notification. Furthermore, investigators shall sign any approved amendment for agreement.

Medtronic will maintain a list of internal CIP approvers separate from this document.

15.7. Record Retention

At a minimum, the investigator must retain records for at least 2 years (or in accordance with local law) or at least two years have elapsed since the formal discontinuation of clinical development of the devices. The investigator should take measures to prevent accidental or early destruction of the trial related materials.

15.8. Publication and Use of Information

Medtronic is committed to the widespread dissemination of all primary and secondary endpoint results. A Publication Plan will be implemented and followed. At the conclusion of the trial, a multisite abstract reporting the primary results will be prepared by the Principal Investigators (in collaboration with others including but not limited to the echo core lab physicians, and the CEC). A multisite publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single site experience within the trial is not allowed until both the preparation and publication of the multisite results, and then only with written permission from Medtronic and the Study Publication Committee.

Following analysis and presentation of the endpoint results, active participation of all participating investigators, CEC committee members, and core laboratory personnel will be solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications regarding the primary endpoint and secondary endpoints from the trial requires approval by the Principal Investigators after review by the Publications Committee.

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

15.9. Suspension or Early Termination

15.9.1 Suspension or Early Termination of the Trial

If the trial is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB/REB/EC. Medtronic will provide a written statement to the investigators to enable prompt notification of the IRB/REB/EC. If trial enrollment is terminated early, follow-up visits will continue for all implanted subjects.

15.9.2 Suspension or Early Termination of a Trial Site

Medtronic may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing IRB/REB/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/REB/EC.

16 Other Institutions and Professional Services

This study will utilize an Echo Core Lab, ECG Core Lab, a Pathology Core Lab, an angiogram Core Lab, a membranous septum Core Lab, Steering Committee, Screening Committee, and a Clinical Events Committee. Information and contact details for each of these parties will be maintained in a separate document and provided to the study sites. A definitive list of all participating parties will be provided in clinical reports. In addition, a list of the names and addresses of participating institutions will be maintained and provided to the sites upon request.

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18 Appendices

18.1 Conduction Disturbance Management

The following section is intended to provide consistency in the management of subject's conduction disturbance peri and post the TAVR index procedure.

All subjects are required to have 12-lead ECG within the 2 hours following the TAVR procedure and the day of discharge. The 2-hour post procedure ECG, peri-procedural rhythm abnormalities, and pre-existing conduction abnormalities will determine the pathway.

Subjects with pre-existing conduction disturbances (eg RBBB) or new conduction disturbances may be discharged prior to the recommended timeframes with continuous ECG monitoring. Pacing wires may be removed prior to recommended timeframe and telemetry may be discontinued prior to the recommended timeframe to allow for early discharge.

No ECG Changes Immediately (2 Hours) Post Procedure:

- No new ECG changes refers specifically to PR and QRS increase < 20 ms on the ≤ 2-hour post-op ECG compared to the pre-procedure ECG.
- Subjects Without Pre-Existing RBBB:
    - Temporary pacing wires can be removed within 2 hours of the TAVR index procedure with continuous telemetry for 24 hours post-op.

- If there are no new changes between the ECG done 24 hours post-op compared to the 2-hour post-op ECG done, then the subject is eligible to be discharged 1-day post op.
- Proceed with pacemaker implantation if there is an occurrence of HAVB/CHB any time during the post-TAVR period.

- Subjects With Pre-Existing RBBB:
  - Maintain temporary pacing until after 24 hours post the TAVR index procedure.
  - If there are no changes between the ≤ 2-hour post-op ECG compared to the 24-hour post-op ECG, then the temporary pacing wire can be removed. Continue telemetry for 1 day and if there continues to be no new ECG changes then the subject is eligible to be discharged 2 days post index procedure
  - If there are ECG changes of at least ≥ 20 ms in the PR or QRS duration compared to the ECG 2-hour post-op, then refer to instructions for New ECG Changes.
  - Proceed with pacemaker implantation if there is an occurrence of HAVB/CHB any time during the post-TAVR period.

ECG Changes (Increase of PR or QRS ≥ 20 ms) in patients with pre-existing conduction disturbance:

- If there are ECG changes of ≥ 20 m/s in the PR or QRS duration on the ≤ 2-hour post op ECG compared to the ECG done pre-procedure, and subjects have pre-existing RBBB, LBBB, IVCD with QRS ≥ 120 ms or 1st degree AVB pre-procedure, then temporary pacing must be maintained until 24 hours post the TAVR index procedure.
  - If ECG changes resolve (regression to baseline value, irrespective of QRS/PR interval duration), OR there are no further changes between the ≤ 2-hour post-op ECG compared to the 24-hour post-op ECG and QRS ≤ 150 ms and PR ≤ 240 ms, then the temporary pacing wire can be removed. Continue telemetry for 1 day. If there are no further ECG changes and/or bradyarrythmias, the subject is eligible to be discharged 2 days post index procedure.
  - If there are ECG changes of ≥ 20 ms in the PR or QRS duration OR the QRS > 150 ms or PR > 240 ms, then maintain temporary pacing for an additional 24 hours.
    - If ECG changes resolve (regression to baseline value, irrespective of QRS/PR interval duration), OR no further ECG changes and QRS ≤ 150 ms and PR ≤ 240 ms then temporary pacing wire can be removed; continue telemetry for 1 day. If there are no further ECG changes and/or bradyarrythmias, the subject is eligible to be discharged 2 days post index procedure.
    - If there are no further ECG changes, but QRS >150 ms or PR >240 ms OR further ECG changes of ≥20 ms in the PR or QRS duration consider one of the following:
      - Invasive EP study to guide the decision about pacemaker implantation
      - Continuous ECG monitoring until the 30-day follow-up visit.
      - Pacemaker implantation (not in patients with PR >240 ms but QRS <120 ms)

- Proceed with pacemaker implantation if there is an occurrence of HAVB/CHB any time during the post-TAVR period.

New Onset LBBB Post Procedure:

- Maintain temporary pacing until after 24 hours post the TAVR index procedure.
  - If there are no changes between the ≤ 2-hour post-op ECG compared to the 24-hour post-op ECG or the LBBB is resolved, then the temporary pacing wire can be removed and continue telemetry for 1 day:
    - If there continues to be no new ECG changes or arrythmias and the LBBB resolves, then the subject is eligible to be discharged 2 days post index procedure without continuous monitoring.
    - If the LBBB continues and QRS ≤ 150 ms and PR ≤ 240 ms compared to the 24-hour post-op ECG then the subject must be discharged with a continuous ECG monitoring system; which could occur as soon as 2 days post index procedure. The subject should maintain the continuous ECG monitoring system until the 30-day follow-up visit.
    - If the LBBB continues and QRS > 150 ms or PR > 240 ms then consider one of the following:
      - Invasive EP study to guide the decision about pacemaker implantation
      - Continuous ECG monitoring until the 30-day follow-up visit
      - Pacemaker implantation
  - If there are further ECG changes of at least ≥ 20 ms in the PR or QRS duration between the 2-hour post-op ECG compared to the 24-hour post-op ECG, then maintain temporary pacing for an additional 24 hours.
    - If no further ECG changes compared to 24-hour ECG (PR or QRS increase < 20 ms)or LBBB is resolved, then refer to instruction noted above.
    - If the ECG changes do not resolve and there is further ≥ 20 ms changes in the PR or QRS duration, then consider one of the following:
      - Invasive EP study to guide the decision about pacemaker implantation
      - Continuous ECG monitoring until the 30-day follow-up visit
      - Pacemaker implantation
  - Proceed with pacemaker implantation if there is an occurrence of HAVB/CHB any time during the post-TAVR period.

HAVB/CHB (transient or persistent) during the TAVR procedure:

- Maintain temporary pacing until after 24 hours post the TAVR index procedure.

- If the subject continues to experience HAVB/CHB then proceed with implanting a permanent pacemaker.
- If the HAVB/CHB resolves and there is not recurrent heart block, then the temporary pacing wire can be removed and continue telemetry for 1 day.
  - If the HAVB/CHB reoccurs then proceed with implanting a permanent pacemaker.
  - If the HAVB/CHB does not re-occur and there are no new ECG changes compared to the 24-hour post op ECG, then the subject is eligible to be discharged 2 days post index procedure. Refer to instructions above for any changes to the ECG.

Conduction Disturbances Definitions:

Conduction Disturbances (infra nodal block)	
Right Bundle Branch Block (RBBB)	1) QRS duration ≥120 ms 2) rsr′, rsR′, rSR′, or rarely a qR in leads V1 or V2. The R′ or r′ deflection is usually wider than the initial R wave 3) In a minority of patients, a wide and often notched R wave pattern may be seen in lead V1 and/or V2 4) S wave of greater duration than R wave or >40 ms in leads I and V6 5) Normal R peak time in leads V5 and V6 but peak R wave >50 ms in lead V1
Left Bundle Branch Block (LBBB)	1) QRS duration ≥120 ms 2) Broad notched or slurred R wave in leads I, aVL, V5, and V6 and an occasional RS pattern in V5 and V6 attributed to displaced transition of QRS complex 3) Absent Q waves in leads I, V5, and V6, but in the lead aVL, a narrow Q wave may be present in the absence of myocardial pathology 4) R peak time >60 ms in leads V5 and V6 but normal in leads V1, V2, and V3, when small initial R waves can be discerned in the precordial leads 5) ST and T waves usually opposite in direction to predominant QRS voltage
Non-specific intraventricular conduction delay (IVCD) with QRS interval ≥120 ms	QRS interval duration ≥120ms where morphology criteria for RBBB or LBBB are not present

Atrioventricular Block

First-degree atrioventricular block	P waves associated with 1:1 atrioventricular conduction and a PR interval >200 ms
Mobitz I	Mobitz I heart block is characterized by progressive prolongation of the PR interval on consecutive beats followed by a blocked P wave (i.e., a 'dropped' QRS complex)
High-degree atrioventricular block (HAVB)	HAVB is defined as any of the following: Second degree AV block type 2 (Mobitz II) in the presence of a QRS ≥120 ms 2:1 AV block in the presence of a QRS ≥120 ms ≥2 consecutive P waves at a constant physiologic rate that do not conduct to the ventricles Transient third degree AV block In the setting of AF, a prolonged pause (> 3 seconds) or a fixed slow (<50 bpm) ventricular response rate
Third-degree atrioventricular block (Complete heart block [CHB])	P waves with a constant rate with dissociated ventricular rhythm (no association between P waves and R waves) or fixed slow ventricular rhythm in the presence of atrial fibrillation

18.2 Quality of Life Questionnaires

Quality of Life Questionnaires used in this trial include:

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EuroQol (EQ-5D)

These questionnaires will be provided under separate cover.

18.3 Echocardiography Procedure

18.3.1 Required Exams

Transthoracic echocardiography is required at the following intervals:

Interval	Time Window
Screening	Within 10 weeks prior to procedure
Discharge	Between 12 hours and 7 days post-procedure

1 year	Day 365 ± 30 days

18.3.2 General Imaging and Recording Procedures

- A list of recommended images is provided in Section 19.3.3, 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 (e.g., LVOT diameter, velocities) should be captured. In addition, still frames of spectral Doppler tracings without the measurements should be captured to facilitate analysis by the Echo Core Lab. Still frames of spectral Doppler tracings should contain a minimum of 3 cardiac cycles for subjects in sinus rhythm, and a minimum of 5 cardiac cycles for subjects in atrial fibrillation (two sequential frames per variable may be necessary).
- Spectral Doppler waveforms should be recorded at a minimum sweep speed of 50 mm/sec.
- Echocardiograms should be recorded and archived on a DICOM digital format for transmission to the Echo Core Lab.
- Exams will be transmitted to the Echo Core Lab via compact disc (CD-R) or Web-based picture archiving and communication system. Details of the image transmission process for each site will be established during site initiation process.
- Exams sent to the Echo Core Lab via CD-R should be DICOM files in a true or pure DICOM format.
- The following information should be documented on any CD-R disks sent to the Echo Core Lab:
  - Trial site ID number
  - Subject ID number
  - Exam date
  - Trial interval

18.3.3 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

18.3.4 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 19.3.5, 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)[18]
- 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.

18.3.5 Acquisition of Key Variables

18.3.5.1 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 2 A and B).[19,20] 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 2 C and D) [19-21] 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 2 E and F).[19]

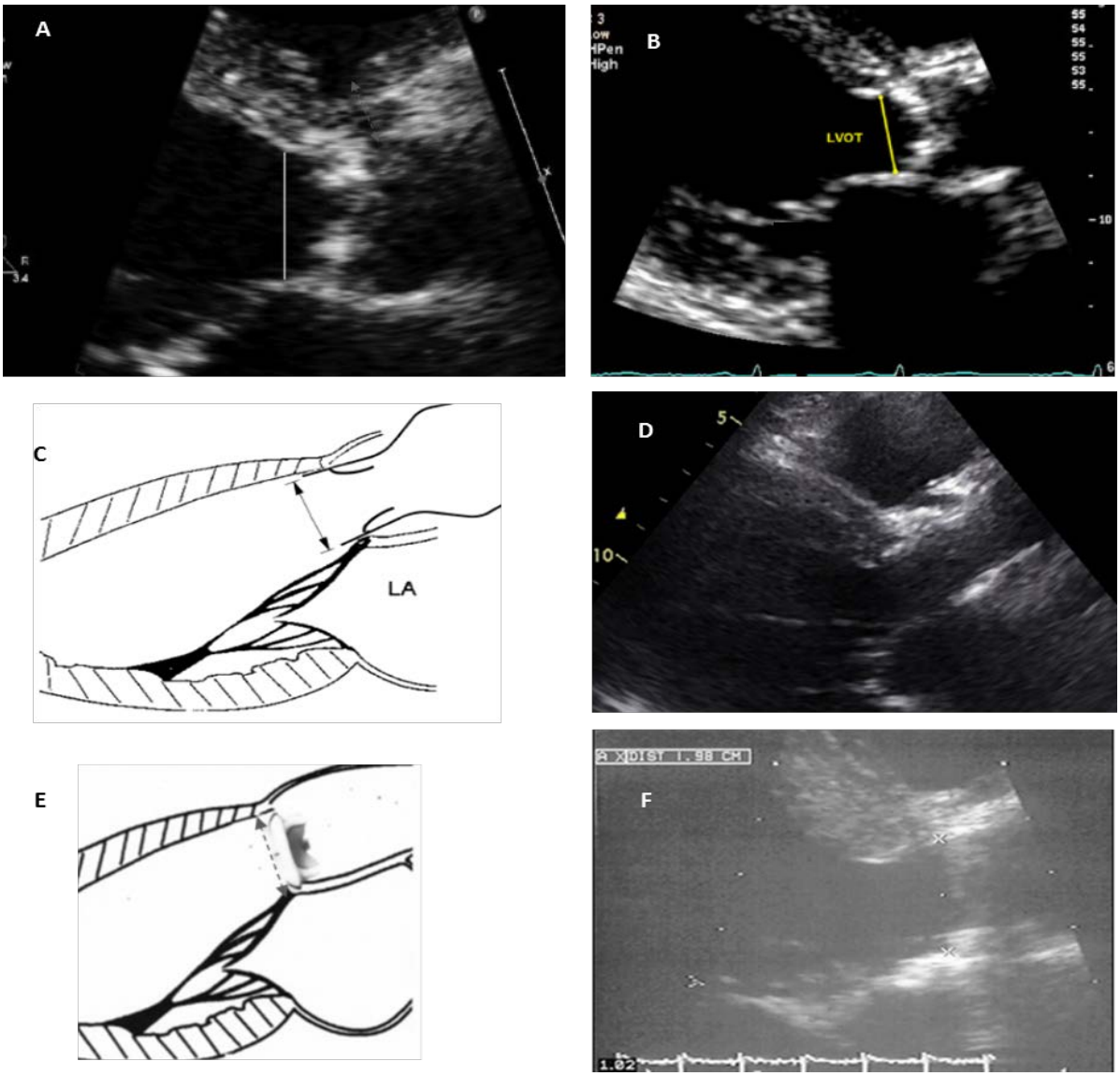

Figure 2 (A) and **(B)** Examples of measurement of pre-implant LVOT diameter. LVOT diameter is measured from the white-black interface of the septal endocardium to the anterior mitral leaflet, parallel to the aortic valve plane, approximately 0.5 cm below the level of the aortic annulus, and in mid 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.

18.3.5.2 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 3).[19]

Post TAV implantation, the sample volume should be placed proximal to the inflow aspect of the stent.[22] 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 3 C and D).[22,23]

The LVOT VTI is measured by tracing the modal velocity (middle of the dense signal) for use in the continuity equation.[19]

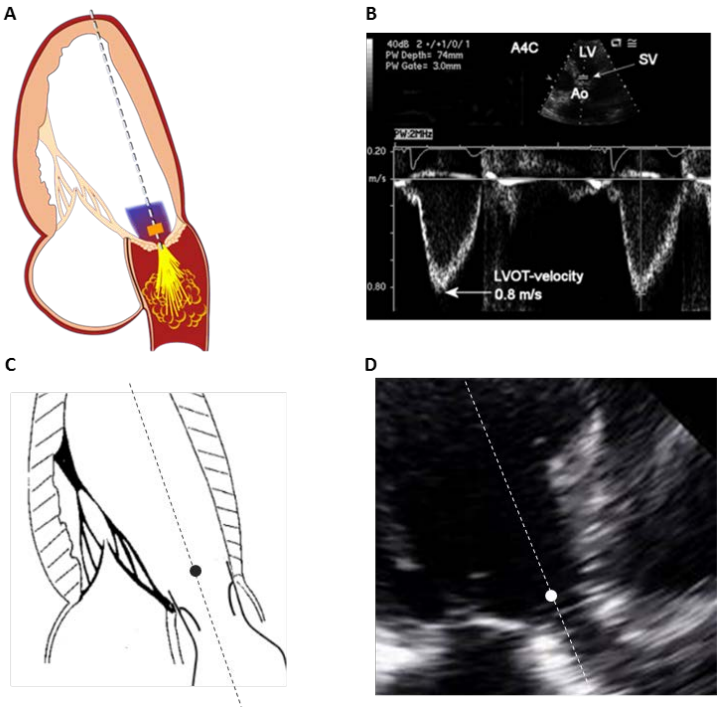

Figure 3 (A) Sample volume placement just proximal to zone of pre-valve acceleration (illustration by Mayo Clinic, used with permission) **(B)** Optimal LVOT velocity signal showing a smooth spectral Doppler recording with a narrow velocity range at each time point **(C)** Illustration showing correct 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.

18.3.5.3 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 4).[19]

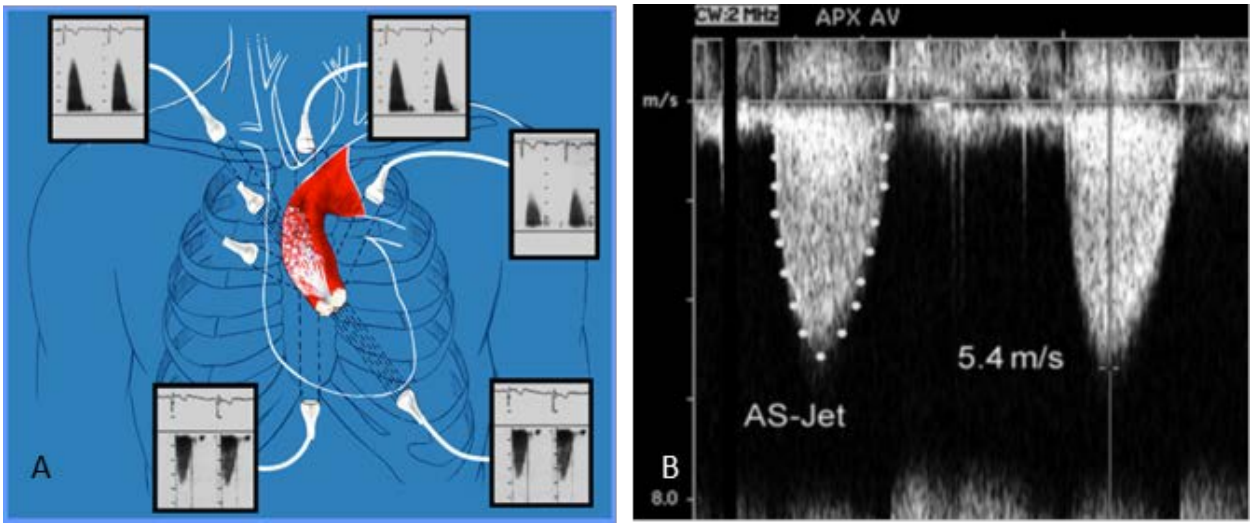

Figure 4 (A) Aortic valve velocities interrogated from multiple transducer positions *(illustration by Mayo Clinic, used with permission)* **(B)** CW Doppler of severe aortic stenosis showing tracing of the velocity curve from mean gradient and VTI, and measurement of max velocity.

18.3.5.4 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.[24,25]

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 6.[25] 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 6.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 semiquantitative)						
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

18.3.5.5 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 7.[26]

Table 7. 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

18.3.5.6 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 8.[26]

Table 8. 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

18.3.5.7 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 5). Left ventricular chamber dimensions, septal thickness, and posterior wall thickness are measured using the American Society of Echocardiography (ASE) measurement convention[27] (blood-tissue interface). In addition, standard 2-D views of the left ventricle should be obtained from parasternal and apical transducer positions for visual estimation and quantitative assessment of left ventricular ejection fraction using the modified Simpson's rule, and for assessment of regional wall motion.

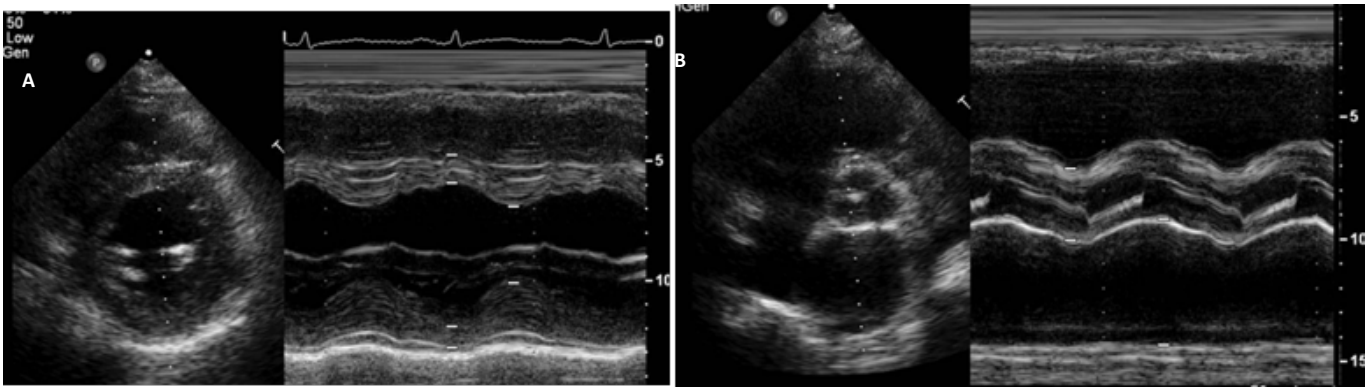

Figure 5. Measurements of the left ventricle **(A)** and left atrium **(B)** using 2-D guided m-mode.

18.3.5.8 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 6). 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

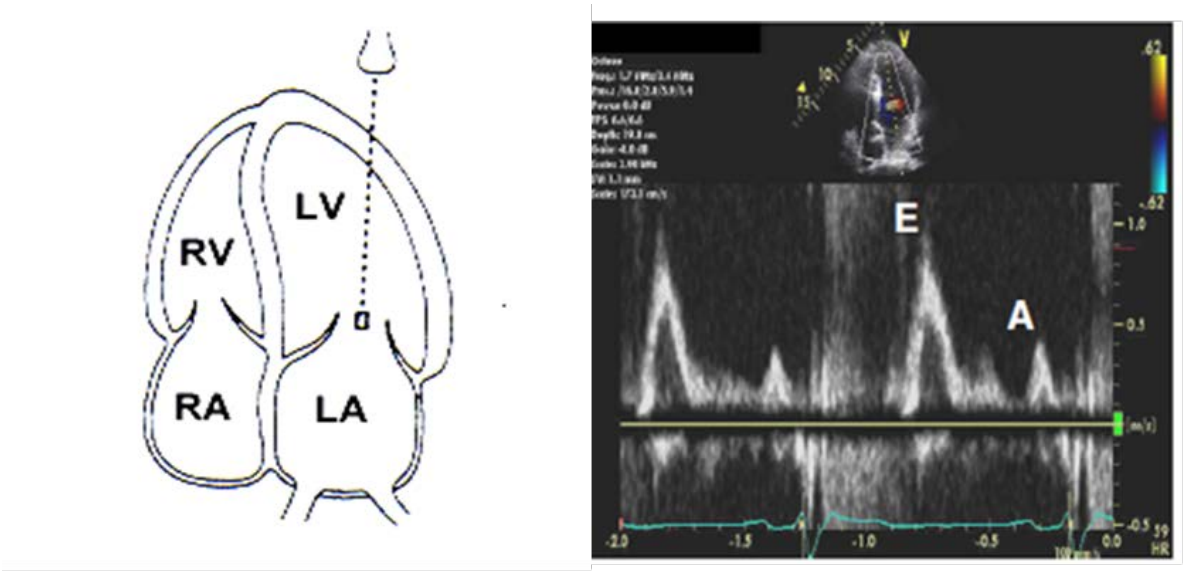

Figure 6. Positioning of the sample volume for recording of mitral inflow velocities.

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)

18.3.6 Core Lab Analysis

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

The Echo Core Lab will report the following variables:

- Heart rate
- Left ventricular outflow tract (LVOT) diameter in mid systole
- Max aortic/prosthetic valve velocity (V_2) by CW Doppler

- Aortic valve velocity time integral (VTI) by CW Doppler
- Mean gradient across aortic valve (MGV_2) by CW Doppler
- LVOT VTI by PW Doppler
- Grade of aortic/prosthetic transvalvular regurgitation (post-implant only)
- Grade of aortic/prosthetic paravalvular regurgitation (post-implant only)
- Grade of prosthetic total (transvalvular plus paravalvular) regurgitation (post-implant only)
- Grade of mitral regurgitation
- Grade of tricuspid regurgitation
- Max tricuspid regurgitant (TR) jet velocity (if TR is present)
- Left ventricular internal dimension at end diastole
- Left ventricular internal dimension at end systole
- Interventricular septal thickness at end diastole
- Left ventricular posterior wall thickness at end diastole
- Left atrial diameter (anterior-posterior linear dimension) at systole
- Left ventricular ejection fraction by visual estimate
- Grade of diastolic dysfunction (if present)
    - 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.[28]

Qualitative grading of valvular regurgitation will be performed using the criteria described in Sections 19.3.5.4 through 19.3.4.8. 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. [26,29]

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 [1]

- Effective Orifice Area (EOA) in cm^2
  EOA = LVOT diameter^2 x 0.785 x (VTI_{V1}/VTI_{V2})
  Where: VTI_{V1} is the velocity time integral of the left ventricular outflow tract in cm, and VTI_{V2} is the velocity time integral of the aortic prosthesis in cm

- Effective Orifice Area Index (EOAI) in cm^2/m^2
  EOAI = EOA/BSA*
  Where: EOA is the effective orifice area in cm^2, and BSA* is the body surface area in m^2

- Doppler Velocity Index (DVI)
  DVI= VTI_{V1}/VTI_{V2}
  Where: VTI_{V1} is the velocity time integral of the left ventricular outflow tract in cm, and VTI_{V2} is the time velocity integral of the prosthetic aortic valve in cm

- Left Ventricular Mass (LVM) in grams
  LVM = 0.83 x [(LVIDD + LVPW + IVS)3 - (LVIDD)3] +0.6
  Where: LVIDD is the left ventricular internal dimension at end diastole in cm, LVPW is the left ventricular posterior wall thickness at end diastole in cm, and IVS is the interventricular wall thickness at end diastole in cm.

- Left Ventricular Mass Index (LVMI) in g/m^2 body surface area
  LVMI = LVM/BSA*
  Where: LVM is left ventricular mass in g, and BSA* is body surface area in m^2

- Estimated Right Ventricular Systolic Pressure (RVSP) in mmHg
  RVSP = (4 x MVTR jet^2) + 10
  Where: MV TR jet is the max velocity of the tricuspid regurgitant jet, and 10 = the assumed mean right atrial pressure in mmHg

- Body Surface Area* (BSA) in m^2
  BSA = 0.007184 x (height in $cm^{0.725}$ x weight in $kg^{0.425}$)

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

18.4 Recommended MSCT Procedures

Multi-slice Computed Tomography (Cardiac MSCT) is used to evaluate aortic valve anatomy, determine aortic root dimensions for device sizing, and to evaluate peripheral vessel dimensions and anatomy. The

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

following sections are intended as recommended guidelines for acquiring the images for assessing anatomical suitability for implantation.

18.4.1 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)

18.4.2 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 9.

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).

18.4.2.1 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 9. Recommended scan parameters

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.

18.4.2.2 Required aortic root measurements

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

- Aortic valve annulus perimeter (measured at systole if retrospective gating is used)
- Mean sinus of Valsalva diameter (measured at diastole)
- Mean sinus of Valsalva heights (measured at diastole)

Reformatting of Images (21)

- 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 7., upper left panel).
- In the sagittal window, the horizontal line is rotated clockwise or counter-clockwise to align with virtual basal plane (Figure 7, 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 8). 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.

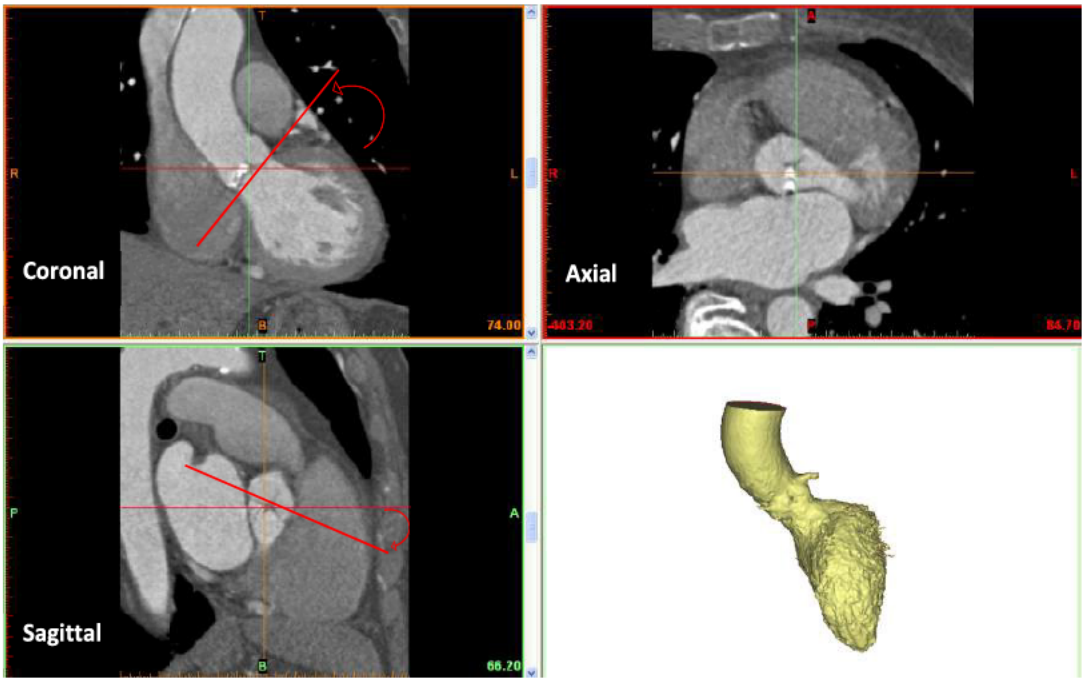

Figure 7: Example images in original orientation (axial, coronal, and sagittal). Red curved arrow and line indicate adjustment of coronal and sagittal planes to align with aortic basal annulus.

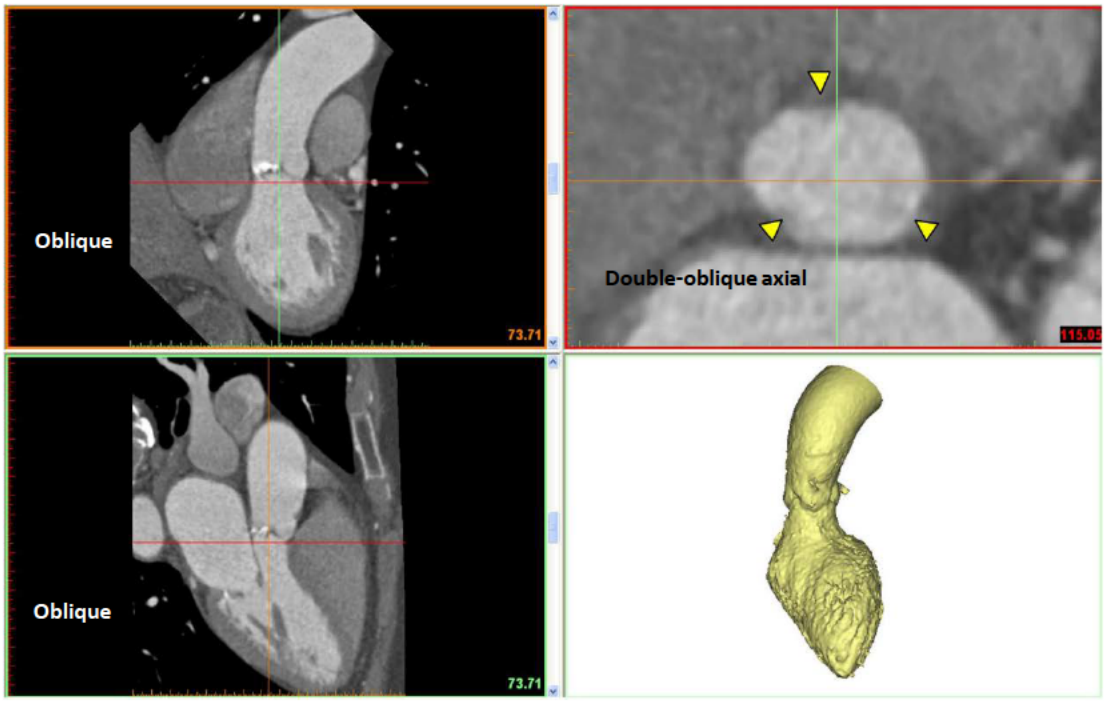

Figure 8. Example images of reformatted oblique coronal (upper left), oblique sagittal (lower left), double oblique axial (upper right), and 3D reconstruction (lower right). Yellow arrowheads indicate most caudal attachment of three leaflets of the aortic valve).

Aortic annulus measurements

- Choose the cleanest systolic images for the aortic annulus measurements, either automatically (e.g., 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.
- Trace the perimeter of the basal annulus (Figure 9, 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 9, right).

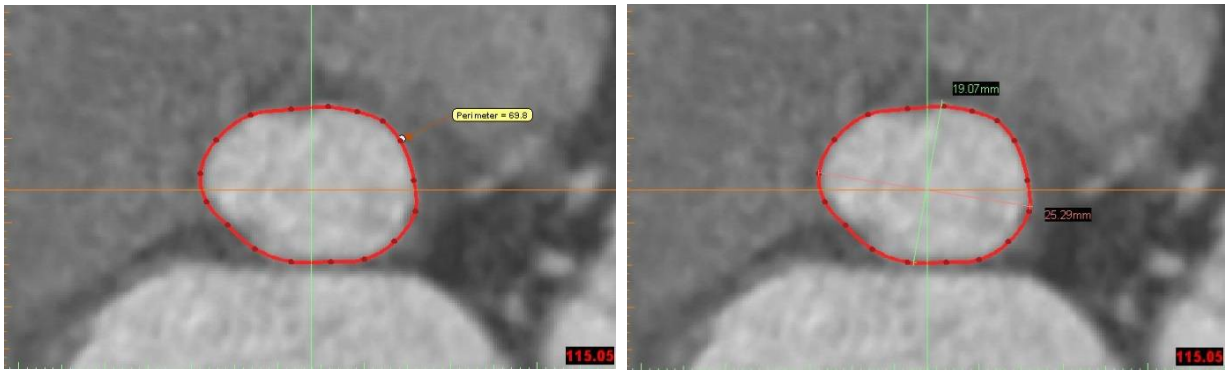

Figure 9. Example of perimeter measurement (left) and major and minor diameter measurements (right).

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 "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 10).

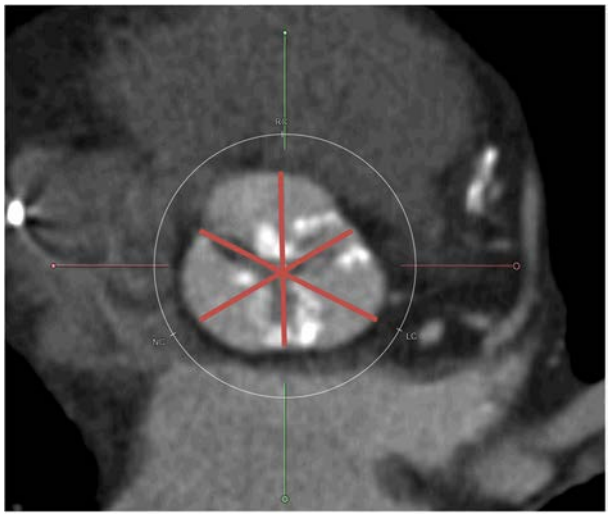

Figure 30. Example of sinus of Valsalva diameters

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 11).

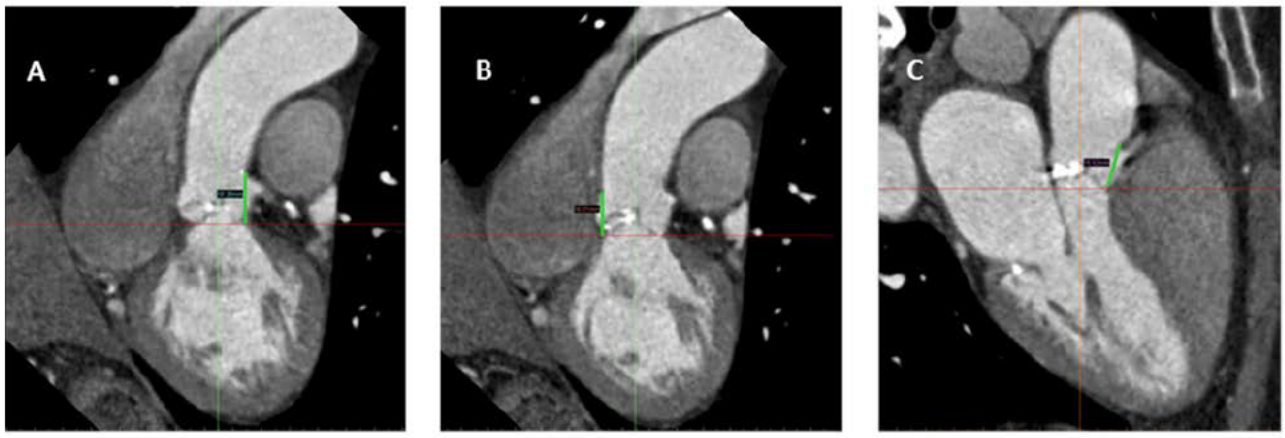

Figure 41. Examples of sinus of Valsalva heights; (A) left coronary; (B) non-coronary; (C) right coronary

18.4.3 Anatomic suitability and valve size selection

Device size	Aortic annulus		Sinus of Valsalva		Minimal Lumen Diameter (mm)
	Perimeter (mm)	Mean diameter (mm)	Mean diameter (mm)	Mean height (mm)	
23 mm	56.5 – 62.8	18 – 20	≥ 25	≥ 15	Evolut PRO: ≥ 5.5 Evolut PRO+: ≥ 5.0
26 mm	62.8 – 72.3	20 – 23	≥ 27	≥ 15	
29 mm	72.3 – 81.7	23 – 26	≥ 29	≥ 15	
34 mm	81.7 – 94.2	26-30	≥ 31	≥ 16	≥ 6.0

18.5 Resheath and Recapture Definitions

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

Resheath attempt	An attempt to intentionally resheath only a portion of the Evolut™ PRO or Evolut™ PRO+ TAV (including the frame) into the capsule of the delivery catheter (e.g. with the intent to reposition of the valve during deployment).

Recapture attempt	An attempt to intentionally fully resheath the entire Evolut™ PRO or Evolut™ PRO+ TAV (including the frame) into the capsule of the delivery catheter until there is no gap between capsule and the tip (e.g. with the intent to enable re-crossing of the aortic valve or retrieval of the system).

18.6 Endpoint Definitions

Mortality	
Cardiovascular mortality	Any of the following criteria: 1) Death due to proximate cardiac cause (e.g. 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 (e.g. trauma, cancer, suicide).

Myocardial Infarction	
Periprocedural MI (≤72 h after the index procedure)	New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. 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	Any of the following criteria:

(>72 h after the index procedure)	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 • 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 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. • Pathological findings of an acute myocardial infarction

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 (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated 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 Classification	• **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

Hospitalization (or rehospitalization)	
Definition Any admission after the index hospitalization or study enrollment to an inpatient unit or hospital ward for at least 24hours (including an emergency department stay), or as measured by a change in calendar date. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition.	
Cardiovascular Hospitalization	Includes hospitalizations for heart failure, stroke or TIA, vascular or access-site related, unstable angina, myocardial infarction, cardiogenic shock, conduction disturbances and arrythmias, or other hospitalizations.
Non-Cardiovascular Hospitalization	Includes hospitalizations not due to cardiovascular causes as mentioned above.

Bleeding Complications	
Life-threatening or disabling bleeding	Fatal bleeding *(BARC type 5)* OR • 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 • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* OR • 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 (e.g. 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 hemoglobin will be calculated; BARC: Bleeding Academic Research Consortium; RBC: red blood cell	

Notes:

1. 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.
2. Pre-operative hemoglobin will be used to determine severity of bleeding events

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% 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

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, pseudoaneurysms, 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)

Note: Refer to VARC-2 bleeding definitions

Valve Dysfunction Requiring Repeat Procedure
Any valve dysfunction that requires repeat procedure (e.g. balloon valvuloplasty, TAVR, or surgical AVR)

Note: Repeat procedures are reported on the appropriate e-CRF

Other TAVR Related Complications	
Conversion to open surgery	Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications Conversions to open surgery will be considered serious adverse events regardless of reason for the surgical conversion.
Unplanned use of cardiopulmonary bypass	Unplanned use of CPB for hemodynamic support at any time during the TAVR procedure
Coronary artery obstruction	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the Evolut™ PRO or PRO+ 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 (e.g. restrictions due to the Evolut™ PRO or PRO+) 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 TAVR procedure

Valve Thrombosis (Clinical)	Any thrombus not caused by infection attached to or near the trial valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment which is associated with any of the following clinical sequelae.:
	• Thromboembolic complications including
	  ○ Any ischemic stroke
	  ○ Any peripheral embolic event
	  ○ ST segment elevation or Non-ST elevation myocardial infarction
	• Hemodynamic impairment associated with a worsening of heart failure
	
	Note: valve thrombus found at autopsy in a subject whose cause of death was not valve-related or found at operation for an unrelated indication should not be reported as valve thrombosis

Valve Thrombosis (Sub-Clinical)	Any thrombus not caused by infection attached to or near the trial valve that occludes part of the blood flow path or interferes with valve function, without evident clinical sequelae, causing a hemodynamic impediment meeting the following criteria: • Increase in aortic regurgitation to moderate to severe. An increase by more than 50% of discharge mean aortic valve gradient (with the post discharge mean gradient being ≥ 20 mmHg) or a decrease in the Doppler Velocity Index (DVI) by more than 50%
Leaflet Motion Abnormality (With Treatment)	Possible leaflet motion abnormality identified by any imaging modality with medical therapy (e.g. anticoagulation therapy, fibrinolytic therapy or valve-related medical intervention) initiated and without significant negative change in valve function (i.e. increasing obstruction or central regurgitation).
Leaflet Motion Abnormality (Without Treatment)	Possible leaflet motion abnormality identified by any imaging modality without medical therapy (e.g. anticoagulation therapy, fibrinolytic therapy or valve-related medical intervention) initiated but without significant negative change in valve function (i.e. increasing obstruction or central

	regurgitation).
Valve migration	After initial correct positioning, any observed movement (upward or downward) of the Evolut™ PRO or PRO+ within the aortic annulus from its initial position, with or without consequences.
Valve embolization	The Evolut™ PRO or PRO+ moves during or after deployment such that it loses contact within the aortic annulus*
Ectopic valve deployment	Permanent deployment of the Evolut™ PRO or PRO+ in a location other than the aortic root
Valve in Valve deployment	Additional valve prosthesis is implanted within a previously implanted Evolut™ PRO or PRO+ because of sub-optimal device position and/or function, during or after the index procedure.
Hemolysis	Red cell destruction as evidenced by plasma free hemoglobin >50 mg/dl **Minor hemolysis:** No intervention required **Major hemolysis:** Requires intervention (e.g. 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 (e.g. reoperation, catheter re-intervention) or is associated with prosthetic valve dysfunction
TAVR Conversion to Other Percutaneous Procedure	Any conversion of the intended TAVR procedure, prior to closure to other percutaneous intervention due to technical challenges, technical contraindications to the intended procedure identified intra-procedurally or complications.
Aborted Procedure	Termination of the procedure prior to implantation of the valve due to identification of a technical contraindication, intraprocedural complications of a concomitant procedure prior to valve implantation or radiation dosage. Aborted procedures will be considered serious adverse events regardless of reason for termination of the procedure.
Reintervention – Surgical or Percutaneous	Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical reoperations, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered

	reinterventions. Reintervention is further subdivided into surgical and percutaneous. Relationship to the study valve will be assessed for the most current valve implanted or attempted to be implanted.

*Valve embolizations are not applicable to valves that move during the procedure but are able to be recaptured and repositioned.

Prosthetic Valve Endocarditis
Any of the following: 1) Fulfillment of the following Duke criteria (22) for definite endocarditis: • Histologic and/or microbiologic evidence of infection at surgery or autopsy, or • 2 major criteria, or • 1 major criterion 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 Evolut™ PRO or PRO+ at autopsy

Prosthetic Valve Dysfunction	
Stenosis: mild	**For subjects with BSA ≥ 1.6 m^2:** Mean aortic gradient ≥ 20 and ≤40 mmHg, EOA ≥ 0.8 and ≤ 1.1 cm^2 AND/OR DVI ≥ 0.25 and ≤ 0.35 **For subjects with BSA < 1.6 m^2:** Mean aortic gradient ≥ 20 and ≤40 mmHg, EOA ≥ 0.6 cm^2 and ≤ 0.9 cm^2 AND/OR DVI ≥ 0.25 and ≤ 0.35
Stenosis: moderate/severe	**For subjects with BSA ≥ 1.6 m^2:** Mean aortic gradient > 40 mmHg, EOA < 0.8 cm^2 AND/OR DVI < 0.25 **For subjects with BSA < 1.6 m^2:** Mean aortic gradient > 40 mmHg, EOA < 0.6 cm^2 AND/OR DVI < 0.25
Paravalvular regurgitation: moderate	Moderate paravalvular regurgitation (per echo criteria in CIP)
Paravalvular regurgitation: severe	Severe paravalvular regurgitation (per echo criteria in CIP)
Transvalvular regurgitation: moderate	Moderate transvalvular regurgitation (per echo criteria in CIP)
Transvalvular regurgitation: severe	Severe transvalvular regurgitation (per echo criteria in CIP)

Notes:

- DVI = Doppler Velocity Index (LVOT VTI/valve VTI)
- For subjects LVOT diameter > 2.5 cm, the DVI criteria for significant (moderate or severe) stenosis is 0.2

- Reporting of prosthetic valve dysfunction will be based on core lab values (if available).
- 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.

19 Version History

Version	Summary of Changes	Author(s)/Title
1.0	New Document	[redacted]
2.0	• Added statements regarding compliance to the TAVR Clinical Pathway and Conduction Disturbance Appendix • Updated all references from "TAVI" to "TAVR" • Clarified Operator 1 and 2 minimum requirements in Participating Sites section • Revised Heart Team composition in Heart Team section • Removed Heart Team eligibility assessment in Summary of Visit Schedule and Required Evaluations section • Modified the enrollment rate in the Duration and Sample Size sections • Removed requirement of subject meeting inclusion / exclusion criteria prior to consent in the Enrollment section • Added definition for signs and symptoms of aortic valve disease in Endpoints Definitions section	[redacted]
3.0	• Update secondary endpoint to say Percentage of subjects with ≥ moderate aortic regurgitation (AR) at discharge • Subject Enrollment: Added Roll-In Subject Section: o For all participating centers, the first three subjects implanted will be considered "roll-in" subjects. The purpose of the roll-in subjects is to provide Investigators the time for training and familiarization with the protocolized implant technique. The Training and Education team will review recommendations made by the Steering Committee for transition of sites from roll-in phase to attempted implant analysis phase.	[redacted]

	○ Roll-in subjects will complete in-clinical follow-up evaluations as noted in section 9.1.5 Follow-Up Evaluations however the results for the roll-in population will be analyzed separately from the primary analysis cohorts. • Heart Team: added language stating the Heart Team should assess eligibility of the subject according to the site's standard process and payer requirements. • Trial Organization: updated Publication Committee members to include steering committee members • Inclusion/Exclusion Criteria: Added exclusion criteria: ○ Subjects with pre-existing permanent pacemaker ○ Previous aortic valve replacement ○ Exclude subjects with horizontal aorta (aortic angulation > 70 degrees per the IFU) ○ Prohibitive left ventricular outflow tract calcification • Implant Procedure: Added statement in introduction of section. ○ In addition, the valve deployment will be completed in accordance to the cusp overlap technique via procedural angiography. • Follow-Up Evaluations: Added procedural angiography during TAVR procedure in Summary of Visit Schedule and Required Evaluations table. • Adverse Events and Definitions: ○ Added in AE definition table: "Ballooning as needed during the implant procedure is standard practice and should not be considered a reintervention." ○ Clarified that Serious Adverse Events and Device Deficiencies will be collected from the time of enrollment • Statistical Design and Methods: Added potential for interim analysis in Primary Analysis. • Sample size: ○ Updated rationale for sample size ○ Updated sample size to include roll-in subjects • Conduction Disturbance Management Appendix: Updates to introduction section ○ Removed statement: An occurrence or recurrence of high-degree atrioventricular block (HAVB) or third-degree atrioventricular block (complete heart block [CHB]) (see definitions of conduction	

	disturbances section) at any time between procedure and discharge is an indication for permanent pacemaker implantation (PPI) (refer to HAVB during the TAVR procedure section). ○ Removed reference to subjects with pre-existing pacemakers. ○ Added statement: Subjects with pre-existing conduction disturbances (eg RBBB) or new conduction disturbances may be discharged prior to the recommended timeframes with continuous ECG monitoring. Pacing wires may be removed prior to recommended timeframe and telemetry may be discontinued prior to the recommended timeframe to allow for early discharge. ○ Revised instruction for the following cohorts: ▪ ECG changes (48 hours post op QRS remains > 150 ms, PR remains > 240 ms, or further increase of ≥ 20 ms PR compared to 24-hour post-op ECG) and ▪ New LBBB (48 hours post op continuing QRS > 150 ms or PR > 240 ms): ▪ Revised instruction: consider EP study to further evaluate if the subject should be implanted with a permanent pacemaker or discharge with continuous ECG monitoring system until 30-day follow-up visit. • Endpoint Definitions: Clarified valve thrombus found at autopsy in a subject whose cause of death was not valve-related or found at operation for an unrelated indication should not be reported as valve thrombosis.	
4.0	• Added the Evolut PRO+ 23, 26, 29, and 34mm TAVs, DCSs, and LSs to the commercially available devices able to be used in the study • Added guidewires and sheaths to the device list in the Synopsis • Added requirement to report non-serious VARC-2 adverse events from the time of enrollment until the completion of follow-up • Section 8.2.2 Updated to say the Training and Education Committee will provide recommendations for transition of	[redacted]

	sites from roll-in phase to attempted implant analysis phase. • Section 9.1.1 Screening Procedures: moved the ECG done at 48 hours pre-procedure from the screening procedures to the pre-procedure visit • Section 9.1.3 Implant procedure (TAVR): updated language under Peri-Procedure to say "General anesthesia should be avoided unless deemed necessary (e.g. for placement of a transesophageal echo), and it is believed that its use will not impede an early discharge • Added section 9.1.3.1 Procedural Angiogram instructions • Section 9.1.4 Prior to Discharge: added requirement to collect weight in the physical exam • Section 9.1.5 Follow-Up Evaluations: removed requirement to collect height • Section 9.1.5 Follow-Up Evaluations: changed collection of summary bills and itemized hospital bills to 'may be collected' instead of 'will be collected' • Section 9.1.8 Core Labs: removed statement saying external Holter monitor data will be sent to a core lab • Added section 9.5 Device Malfunction or Explant • Section 13.1.1 Enrolled Population – Per protocol set: removed 'treated with conscious sedation' • Section 13.7 Missing Data: removed "The reasons for missing data will be described and evaluated for assessment of possible bias. The distribution of prognostic factors between subjects with data and those without data will be examined to evaluate any potential sources of bias." • Section 16 Other Institutions and Professional Services: added Pathology Core Lab • Appendix 19.1 Conduction Disturbance Management: Updates to the pathways based	
5.0	• Changed CIP template to current version B • Changed all references from MDCT to MSCT throughout CIP for consistency • Section 2: Added Device Deficiency (DD), Unanticipated Serious Adverse Device Effect (USADE), and Europe, Middle East, and Africa (EMEA) to the glossary • Section 3: Synopsis: Added 'Product Status' • Included EMEA study participation throughout CIP	[redacted]

	• Up to 15 sites with at least 200 subjects • Increased enrollment period to 36 months and study duration to 4 years • Updated inclusion criterion #1 to say: Acceptable candidate for treatment with the Evolut™ PRO or Evolut™ PRO+ system in accordance with the commercial Instructions for Use and local regulations • Removed exclusion criteria: Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to enrollment • Added Section 6.2 Study Oversight • Section 7: removed EnVeo R Delivery System and Loading System since they are no longer being used in the geographies part of this study • Section 7.1.1: added European/Israeli device model numbers to Table 2 and Table 3 • Section 9.2.1: Included that Medtronic will provide correspondence to sites when they are approved to move into the as-treated analysis phase • Section 9.3: changed word from “randomization” to “participation” • Section 10.1. 2: Updated duration from enrollment to TAVR procedure from 30 days to 90 days • Section 10.1.5: Added clarification in Table 4 on when ECGs must be collected within the study and removed statement regarding collection of UB-04 billing statements • Section 12.1: updated SAE and Device Deficiency definition to be current and added Serious Adverse Device Effect and Unanticipated Serious Adverse Device Effect definitions. In addition, added language on assessing SAE relatedness • Added Section 12.4: Product Complaint Reporting • Section 13.3: Included pacemaker implantation analysis required by BSI and referenced the TAVR Low Risk Post Market Clinical Follow-Up Plan • Section 13.1.1: updated the Per Protocol sets (1 and 2) • Section 14: Added that EU centers will follow EU MDR and GDPR	

	• Section 16: Added angiogram Core Lab and membranous septum Core Lab • Section 18.1: Clarified when a subject is required to be discharged with continuous ECG monitoring if they are in the new onset LBBB group • Section 18.3.1: Updated echo requirement to say one needs to be done within 10 weeks prior to procedure as this was an error in the previous CIP version • Section 18.4.3: added valve size information for the PRO+ 34mm TAV and Minimal Lumen Diameter information for all valve sizes	
6.0	• Added "EU Legal Representative" to the Bakken Research Center for local sponsor • Added ANZ as a local sponsor • Local Sponsor: Changed Canada address to ULC from LTD. • Added up to 7 sites in Australia and New Zealand with approximately 50 subjects • Updated overall sponsor to "Medtronic Structural Heart Clinical Research" and removed "Coronary" • Updated references to tables throughout document for accuracy • Changed 'as treated' to 'attempted implant' in sections 9.2.1 and 13.1 to align with the statistical analysis set • Section 2: added ANZ (Australia, New Zealand) and VARC (Valve Academic Research Consortium) to the glossary • Added roll-in Sample Size to the Study Synopsis • Section 3 & Section 5: Updated Primary Objective to Study Objective and updated language to say: The study objective is to collect post-market clinical evidence on valve performance and procedural outcomes associated with an "optimized" TAVR care pathway and post-TAVR conduction disturbance pathway while using the Evolut™ PRO and Evolut™ PRO+ devices. In addition, added primary, secondary, and exploratory objectives to align with the primary, secondary, and exploratory endpoints • Section 7.1.1: Corrected the US Model Numbers for the DCS and LS as they were previously listed incorrectly. Added Australia, New Zealand, & Israeli Model Numbers for all devices	[redacted]

	• Section 9.2: added additional 50 patients and 7 sites in ANZ. Stated study will include approximately 650 subjects instead of 'up to 650 subjects'
	• Section 10.1.3.1: Added all steps included in the cusp-overlap procedural technique
	• Section 10.2: Updated language to say that new information would be provided to subjects in an updated informed consent
	• Section 10.6.1: Added definition of source data
	• Section 12.1: Added definition of Adverse Event and Adverse Device Effect
	• Section 13.1.1: removed 's' from "Roll-ins subjects" in the "Roll-in" description
	• Section 13.1.1: Clarified the primary analysis will be based off the endpoints, not the objectives
	• Section 13.3:
	  ○ Removed language stating another interim analysis will occur after 400 subjects are enrolled in the attempted implant set.
	  ○ Modified language to state that pacemaker implantation rates at 30 days will be compared by region (US/CAN, EMEA, and ANZ).
	• Section 13.4:
	  ○ Added additional 50 patients and 7 sites in ANZ to make the entire study population 854 (including roll-ins)
	  ○ Removed the words "up to" from the total combined sample size with all analysis sets is 854 subjects
	• Section 14.1:
	  ○ Updated to say the study will comply to ICH E6 R2 GCP
	  ○ Clarified that each site must fulfill all local regulatory requirements prior to enrolling subjects and throughout the duration of the study, as applicable and updated regulations for Europe.	

	• Section 15.6: Added language that Medtronic will maintain a list of internal CIP approvers separate from this document.
	• Section 18.6:
	  ○ Added Evolut PRO+ throughout where applicable with Evolut PRO
	  ○ Removed the table with Signs and Symptoms of Aortic Valve Disease and added a new table that has the definition for Hospitalization and Rehospitalization	