COVER PAGE

Study Official Title: Medtronic CoreValve™ Evolut™ PRO System China Clinical Study (Evolut PRO China Clinical Study)

NCT Number: NCT04982588

Document Type: Clinical Investigation Plan/ Study Protocol

Document Date: 06-OCT-2023

Clinical Investigation Plan (CIP)

Protocol No.:	MDT18065EVR009
Clinical Trial Protocol:	Medtronic CoreValve™ Evolut™ PRO System China Clinical Study (Evolut PRO China Clinical Study)
Name of the investigational medical device:	Medtronic CoreValve™ Evolut™ PRO System
Model/ specification:	The Medtronic CoreValve™ Evolut™ PRO System is comprised of the following three components: 1. CoreValve™ Evolut™ PRO Transcatheter Aortic Valve (TAV) 2. EnVeo™ PRO Delivery Catheter System (DCS) 3. EnVeo™ PRO Loading System (LS)

Component / Material	Model Number/ Customer Facing Number (CFN)	Size	Aortic Annulus Diameter (mm)
CoreValve™ Evolut™ PRO TAV	EVOLUTPRO-23-US	23 mm	18 – 20
	EVOLUTPRO-26-US	26 mm	20 – 23
	EVOLUTPRO-29-US	29 mm	23 – 26
EnVeo™ PRO Delivery Catheter System (16eFr)	ENVPRO-16-US	20 Fr (Outer diameter)	Not applicable
EnVeo™ PRO Loading System (16eFr)	L-ENVPRO-1623-US	Compatible with 23 mm TAV	Not applicable
	L-ENVPRO-16-US	Compatible with 26 and 29 mm TAVs	Not applicable

Category of investigational medical device:	Class III
Class III medical devices requiring clinical trial approval:	Yes ☐ No ☒
Similar product in China:	Yes ☒ None ☐
Protocol version No. and date:	Version 5.0, 06-Oct-2023

Leading Site Clinical trial institution:	The Second Affiliated Hospital of Zhejiang University School of Medicine
Leading Site Investigator:	Professor Wang Jianan
Co-Investigators:	Professor Chen Mao The West China hospital
Sponsor:	Medtronic CoreValve LLC [redacted]
Local Sponsor (Agency):	Medtronic (Shanghai) Management Co., Ltd [redacted]

1. Investigator's Statement

Study Product Name	The **Medtronic CoreValve™ Evolut™ PRO System** is comprised of the following three components: 1. CoreValve™ Evolut™ PRO Transcatheter Aortic Valve (TAV) 2. EnVeo™ PRO Delivery Catheter System (DCS) 3. EnVeo™ PRO Loading System (LS)
Sponsor	Medtronic CoreValve LLC
Local Sponsor/Agent	Medtronic (Shanghai) Management Co., Ltd
Clinical Investigation Plan Identifier	MDT18065EVR009
Version Number/Date	Version 5.0, 06-Oct-2023

I agree that:

1. I will conduct this clinical trial in strict compliance with the Declaration of Helsinki, current laws and regulations of China, and the requirements of the Clinical Investigation Plan;
2. I will record all required data accurately on the Case Report Form (CRF) and assist to complete the final report of the clinical investigation;
3. The investigational medical device will be used only for this clinical trial and the receipt and use of the investigational medical device will be recorded completely and accurately and the records will be retained during the process of the clinical investigation;
4. The monitor and auditor authorized or designated by the Sponsor and the regulatory authorities are allowed to conduct monitoring, audit and inspection for the clinical investigation;
5. The clinical investigation should be conducted in strict compliance with contract/articles of agreement signed by all parties.

I have already read the clinical study protocol, including the above statement and I fully agree all the above requirements.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

Comments of the Sponsor

Signature (Stamp):

Date: MM/DD/YYYY

Comments of the Investigator:

Signature:

Date: MM/DD/YYYY

Comments of Medical Device Clinical Trial Institution

Signature (Stamp):

Date: MM/DD/YYYY

Table of Contents

List of Tables

List of Figures

2. Sponsor's information

2.1. Name of Sponsor

Medtronic CoreValve LLC

2.2. Address of Sponsor

[redacted]

2.3. Contact of Sponsor

The contact of Sponsor will be provided separately in the Investigational Site File (ISF).

2.4. Relevant qualification document(s) of the Sponsor

Relevant qualification document(s) of the sponsor will be provided under a separate cover.

2.5. Name, address, contact information and relevant qualification document(s) of local sponsor(agency)

Medtronic (Shanghai) Management Co., Ltd

[redacted]

Relevant qualification document(s) of the sponsor will be provided under a separate cover.

3. Glossary

Term/Acronym	Definition
2D	Two-dimensional
3D	Three-dimensional
ADE	Adverse device effect
AE	Adverse event
AOA	Alpha-amino oleic acid
AR	Aortic regurgitation
AS	Aortic stenosis
AVA	Aortic valve area
AVAI	Aortic valve area index
AVR	Aortic valve replacement
BAV	Balloon aortic valvuloplasty
BSA	Body surface area
CEC	Clinical Events Committee
CI	Confidence interval
CIP	Clinical Investigation Plan
CMDE	Center for Medical Device Evaluation
CT	Computed tomography
CVA	Cerebrovascular accident
DCS	Delivery catheter system
DD	Device deficiency
DVI	Doppler velocity index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOA	Effective orifice area
EOAI	Effective orifice area index
ERC	Eligibility Review Committee
FDA	(United States) Food and Drug Administration
GCP	Good clinical practice
GI	Gastrointestinal
HIT/HITTS	Heparin-Induced Thrombocytopenia / Heparin-Induced Thrombocytopenia and Thrombosis
IB	Investigator's Brochure
ICF	Informed Consent Form

Term/Acronym	Definition
IFU	Instructions for Use
ILS	EnVeo™ InLine Sheath
IMA	Internal mammary artery
LBBB	Left bundle branch block
LIMA	Left internal mammary artery
LLC	Limited liability company
LS	Loading system
LTFU	Lost-To-Follow-Up
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MDCT/MSCT	Multi-detector computer/computed tomography or Multi-slice computer/computed tomography
MGV_2	Mean gradient across aortic valve
MI	Myocardial infarction
mRS	Modified Rankin score
NMPA	National Medical Product Administration
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PI	Principal Investigator
PROM	Predicted risk of mortality
PW	Pulsed wave
QoL	Quality of Life
RBBB	Right bundle branch block
SADE	Serious adverse device effect
SAE	Serious adverse event
SAVR	Surgical aortic valve replacement
SDV	Source data verification
STS	Society of Thoracic Surgeons
TAV	Transcatheter aortic valve
TAVI	Transcatheter aortic valve implantation
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal echocardiology
TIA	Transient ischemic attack
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiography /echocardiogram

Term/Acronym	Definition
TVT-R	Transcatheter Valve Therapy Registry
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect
V_2	Valve velocity
VARC II	Valve Academic Research Consortium II
VTI	Velocity time integral
WBC	White blood cell

4. Synopsis

Title	The **Medtronic CoreValve™ Evolut™ PRO System** (Transcatheter Aortic Valve Replacement-TAVR) Clinical Study in China (Evolut PRO China Clinical Study)
Clinical Study Type	Interventional, post-market study
Study Design	Prospective, single arm, multi-center, interventional, post-market
Product Name	The **Medtronic CoreValve™ Evolut™ PRO System** is comprised of the following three components: 1. CoreValve™ Evolut™ PRO Transcatheter Aortic Valve (TAV) 2. EnVeo™ PRO Delivery Catheter System (DCS) *3.* EnVeo™ PRO Loading System (LS)
Sponsor	Medtronic CoreValve LLC [redacted]
Local Sponsor	Medtronic (Shanghai) Management Co., Ltd [redacted]
Indication under investigation	Severe, symptomatic aortic stenosis
Product Status	Investigational; the Evolut PRO System (TAV, DCS and LS) involved in this study are labeled “Clinical trial use only” (i.e., investigational device labeling) Note: Effective 24-DEC-2021, National Medical Products Administration (NMPA) approved the Medtronic CoreValve™ Evolut™ PRO System for the treatment of severe aortic stenosis for symptomatic patients in China who are at high or extreme risk for open heart surgery. Overseas clinical data were utilized to support product registration. The Evolut PRO System is commercially available during the Evolut PRO China Clinical Study enrollment period. However, only Evolut PRO System components that are labeled investigational were used in the study. Commercial Evolut PRO System components were not used in the study. After all study attempted implants occurred and the primary endpoint analysis was completed, the Evolut PRO China Study was converted from a pre-market to a post-market study via implementation of Clinical Investigation Plan (CIP) Version 5.0.
Study Objective	To evaluate the safety and efficacy of the Medtronic CoreValve™ Evolut™ PRO System when used by China implanting centers in Chinese patients with severe symptomatic aortic stenosis (AS) who are at high risk for Surgical Aortic Valve Replacement (SAVR).
Primary Endpoints	Safety All-cause mortality at 30 days

	Efficacy Percentage (%) of evaluable echocardiograms with moderate or severe aortic regurgitation at 30 days
Secondary Endpoints	Safety 1) The VARC II[1] Combined Safety Endpoint at 30 days, which includes the following components: • All-cause mortality • All stroke (disabling and non-disabling) • Life-threatening bleeding • Acute kidney injury: stage 2 or 3 (including renal replacement therapy) • Coronary artery obstruction requiring intervention • Major vascular complication • Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR) 2) Event rates of the individual components of the VARC II composite safety endpoint at 30 days 3) New permanent pacemaker at 30 days Efficacy 1) Device success at 24 hours to 7 days per VARC II[1] 2) Valve performance parameters at 30 days by transthoracic echocardiography (TTE): • Mean aortic gradient • Effective orifice area • Degree of aortic regurgitation (transvalvular, paravalvular, total)
Number of Centers	The trial was designed targeting 6 centers with a maximum of 8 in China. Enrollment occurred at 4 centers in China.
Sample Size	The trial was designed estimating 65 subjects with a maximum of up to 70. At completion of the enrollment phase there were 58 subjects in China with an attempted implant, comprised of the following: 1) **Primary study population**: 50 subjects with an attempted implant using the Evolut PRO system 2) **Roll-in population**: The first two attempted subjects at each site were considered "roll-in" subjects. The maximum number of roll-in subjects among site was 20 subjects. There were 8 total roll-in subjects enrolled. The roll-in population will be followed per the same protocol as the primary study population; however, results from the roll-in population will be analyzed separately from the primary study population.
Key Inclusion/ Exclusion Criteria	Key inclusion criteria: 1. Aortic valve area (AVA) < 1.0 cm^2 (or indexed AVA <0.6 cm^2/m^2) OR mean gradient > 40 mmHg, OR max aortic velocity > 4.0 m/sec

	2. High risk for SAVR defined as STS-PROM score ≥ 8% AND ≤ 15%, OR documented Heart Team agreement of high risk for AVR due to frailty or comorbidities 3. Symptoms of aortic stenosis and NYHA ≥ II Key exclusion criteria: 1. Age is less than 65 years old 2. Non-calcified aortic valve 3. Bicuspid aortic valve with no raphe or 2 raphes (Sievers classification type 0 or type 2)[2] *4.* Ascending aortic diameter > 4.5 cm
Study Procedures and Assessments	• Clinical assessment at pre and post-procedure, discharge, 30 days, 6 months, 1 year, and annually through 5 years • Transthoracic echocardiogram (TTE) at pre and post-procedure, 30 days, 1 year, and annually through 5 years • Multi-Detector Computed Tomography (MDCT) at pre-procedure • 12-lead ECG at pre-procedure and 30 days • EQ-5D Quality of Life (QoL) at pre-procedure, 30 days and 1 year

5. Objectives and contents of clinical trial

5.1. Objectives

The objective of this study is to evaluate the safety and efficacy of the Medtronic CoreValve™ Evolut™ PRO System when used by China implanting centers in Chinese patients with severe symptomatic aortic stenosis (AS) who are at high risk for Surgical Aortic Valve Replacement (SAVR).

5.2. Contents

This is a prospective, single arm, multi-center, interventional, post-market study. The study was designed targeting 6 centers with a maximum of 8 centers in China and estimated 65 subjects with a maximum of up to 70 subjects with attempted implants. By completion of the enrollment phase, 58 attempt implant subjects from 4 activated sites were enrolled. In the post-market phase (effective with Clinical Investigation Plan Version 5.0.), the study will continue following subjects enrolled with attempted implants across the 4 activated centers in China. The primary endpoints are all-cause mortality and the percentage of evaluable echocardiograms with moderate or severe prosthetic aortic valve regurgitation at 30 Days. Subjects will be followed up through five-year post-implantation.

5.3. Study Organization

This multi-center clinical study is being conducted at 4 activated centers, including the leading center. Committees were established to provide independent review of the data or assessment of study

parameters based on the services they provide. Additionally, the study sponsor will oversee the execution and management of study. An overview of the study stakeholders and organization is provided in Figure 1.

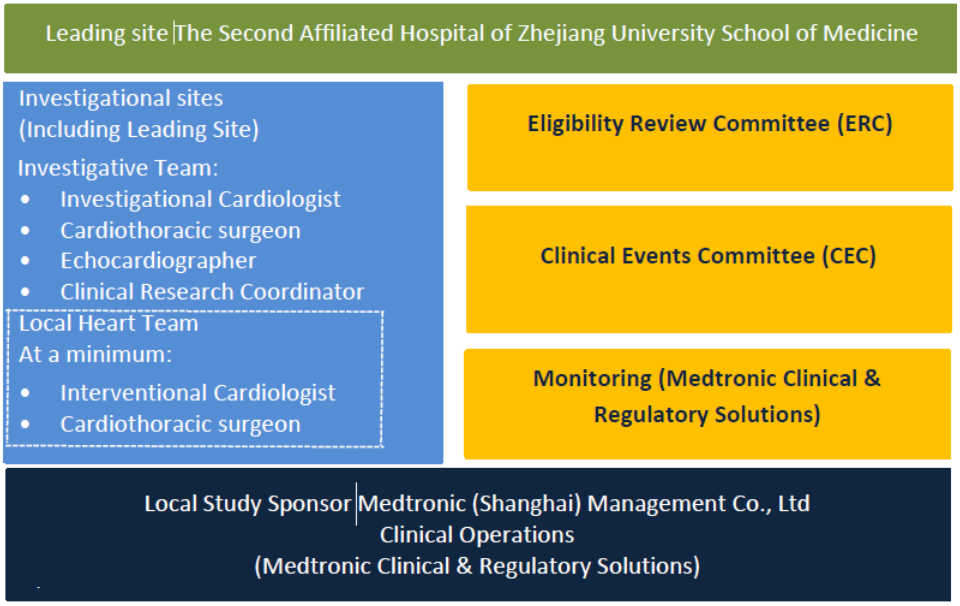


Figure 1. Study organization

6. Background information of the clinical trial

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

The Medtronic CoreValve self-expanding TAVR system received the CE Mark in 2007, and the United States Food and Drug Administration (FDA) approvals for Extreme Risk and High Risk patient populations in 2014. There is extensive published experience demonstrating the CoreValve system is fulfilling its intended role with a favorable risk/benefit ratio, and rigorous clinical trials have established its safety and effectiveness, with improved mortality rate and quality of life compared with medical therapy in extreme risk patients,[4] and even superiority to SAVR among high operative risk patients.[5]

While there have been significant improvements in TAVR outcomes due to better patient selection, increasing operator experience, and iterations in device technology, important issues remain. Clinical challenges where further advances would be desirable include the occurrence of major procedural

complications[6,7,8], stroke[9,10], paravalvular aortic regurgitation[11,12], vascular complications[13,14], and need for new permanent pacemaker implantation[15,16,17,18].

To this end, Medtronic developed modifications to the CoreValve frame and delivery catheter system to enable resheathing or full recapture of the device before it is released from the delivery system. These modifications are incorporated in the CoreValve™ Evolut™ R system (hereafter "Evolut R"). The ability to resheath or recapture the device allows the operator to reposition or remove the bioprosthesis if the initial implant positioning is sub-optimal (too high or too low). This feature is desirable in that it facilitates accurate final positioning which has been shown to mitigate risks associated with sub-optimal positioning such as paravalvular leak[19,20], acute migration[8], and AV-conduction disturbance related to implant depth[15]. In addition, the EnVeo™ PRO Delivery Catheter System with EnVeo™ InLine Sheath provides physicians the option to use a lower profile introducer sheath, which may reduce the risk for major vascular complications.

A comprehensive protocol of bench and animal testing of the Evolut R system has demonstrated its functionality and has confirmed that changes to enable recapture have not impacted the structural integrity, hydrodynamic performance, or durability of the CoreValve bioprosthesis. Beginning in October 2013, clinical studies of the Evolut 23R, 26R and 29R valve sizes involving 301 patients have been conducted in Australia, New Zealand, Europe, and the United States. These clinical studies confirm that TAVR with the Evolut R system can be performed with an acceptable incidence of procedural and device-related complications, that short term safety and clinical efficacy of the Evolut R system are similar to the predicate CoreValve system, and there are no new safety risks associated with the use of the resheath/recapture feature. Results from these studies[21] were used to gain the CE Mark in August 2014 for the 23R valve size and February 2015 for the Evolut 26R and 29R valve sizes, and FDA approval in June of 2015 for the Evolut 23R, 26R and 29R sizes.

In order to further improve the performance of the Evolut R system with respect to paravalvular regurgitation, the Evolut R valve was modified. Specifically, an outer wrap of porcine pericardial tissue was added to cover the first 1.5 cells of the inflow aspect of the frame. The intent of the tissue wrap is to provide a larger surface area contact between the frame and native annulus, intended to improve annular sealing and reduce the potential for paravalvular regurgitation. This iteration of the Evolut R system is known as the Medtronic CoreValve™ Evolut™ PRO system (referred to as the "Evolut PRO system").

In 2016, a 60-patient pre-market clinical study of the Evolut PRO system[i] in the United States demonstrated a reduction in the occurrence of moderate or severe paravalvular regurgitation and an acceptable safety profile consistent with Evolut R system. Data from this study was used to obtain FDA approval in March 2017, and CE Marking in July 2017. Intermediate risk approval was received by FDA in July 2017 and CE Marking August 2016. In addition, in September 2018, the United States FDA approved the removal of a precaution statement in the Evolut PRO labeling relating to the use of the Evolut PRO system in patients with bicuspid aortic valves who are at intermediate, high, or extreme risk for SAVR. This approval was based on clinical data from the Society of Thoracic Surgery/American College of Cardiology Transcatheter Valve Registry (TVT-R) from the commercial experience of the Evolut R and

[i] The Evolut PRO system was initially labeled in the pre-market US clinical study as "Medtronic TAVR 2.0." The TAVR 2.0 devices are identical to the Evolut PRO models proposed for use in the clinical trial in China.

Evolut PRO systems in a post-market real-world environment that reported acceptable clinical outcomes in patients with bicuspid aortic valves and at increased risk for SAVR.[22]

In December 2021, National Medical Products Administration (NMPA) approved the CoreValve™ Evolut™ PRO System for the treatment of severe aortic stenosis for symptomatic patients in China who are at high or extreme risk for open heart surgery, and in April 2023, NMPA approved the indication expansion of CoreValve™ Evolut™ PRO System to intermediate and low risk patients.

With the completion of all Primary Endpoint visits and analyses in the Evolut PRO China Study and considering the product registration status in China, the Evolut PRO China Clinical Study will be transitioned from a pre-market study to a post-market study status effective with Clinical Investigation Plan Version 5.0.

The objective of this clinical study is to confirm that the established safety and efficacy of the Evolut PRO System, inclusive of the system component models outlined in Section 7.1, can be replicated by Chinese implanting centers in Chinese patients with severe symptomatic aortic stenosis, inclusive of both tricuspid and bicuspid anatomy (Sievers classification type 1), who are deemed at high risk for SAVR. Data from this study may be used to support license registration for new generation(s) or expanded indication(s) of the study devices in China.

7. Characteristics, structure and composition, operating principle, mechanism of action and range of trial of the investigational product

For overview of the Medtronic CoreValve™ Evolut™ PRO System, see also the Investigator's Brochure (IB) which includes preclinical testing and clinical data of this investigational product.

7.1. Characteristics of the investigational product

The Medtronic CoreValve™Evolut™ PRO System (hereafter "Evolut PRO system") is a recapturable transcatheter aortic valve replacement (TAVR) system comprised of the following three components:

1. CoreValve™ Evolut™ PRO Transcatheter Aortic Valve (TAV): 23 mm, 26 mm, 29 mm sizes
2. EnVeo™ PRO Delivery Catheter System (DCS)
3. EnVeo™ PRO Loading System (LS)

These components are provided separately for the procedure. A listing of the system components is provided in Table 1. All components are provided sterile and are intended for single use only. The CoreValve™ Evolut™ PRO TAV is loaded into the delivery catheter system using the loading system immediately prior to implantation.

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

Table 1. The Evolut PRO System Components

Component / Material	Description	Model Number/ Customer Facing Number (CFN)	Size	Aortic Annulus Diameter (mm)
CoreValve™ Evolut™ PRO TAV	The bioprosthetic valve manufactured by suturing valve leaflets and skirt, made from porcine pericardium, onto a self-expanding nitinol frame. There are three sizes: 23mm, 26mm, and 29mm.	EVOLUTPRO-23-US	23 mm	18 – 20
		EVOLUTPRO-26-US	26 mm	20 – 23
		EVOLUTPRO-29-US	29 mm	23 – 26
EnVeo™ PRO Delivery Catheter System (16Fr Equivalent)	TAV is loaded onto the distal end of DCS, introduced through the arterial vasculature to the stenotic native aortic valve, and percutaneously delivered and implanted. There is one size of DCS.	ENVPRO-16-US	20 Fr (Outer diameter)	Not applicable
EnVeo™ PRO Loading System (16Fr Equivalent)	Supports loading of a TAV onto the distal end of DCS. There are two sizes of LS: 23mm and 26/29mm.	L-ENVPRO-1623-US	Compatible with 23 mm TAV	Not applicable
		L-ENVPRO-16-US	Compatible with 26 and 29 mm TAVs	Not applicable

7.2. Structure and composition, operating principle and mechanism of action of the investigational product

7.2.1. Evolut PRO Transcatheter Aortic Valve (TAV) Prosthesis

The transcatheter aortic valve (TAV) is a single-use, implantable device. The Evolut PRO TAV is available in three sizes (23 mm, 26 mm and 29 mm), covering an aortic annulus diameter of 18 to 26 mm (Table 1). The TAV is comprised of three leaflets and a sealing skirt constructed from glutaraldehyde-fixated porcine pericardium, sewn to a compressible and self-expandable Nitinol support frame (Figure 2A). An outer wrap made of porcine pericardium, the same material as the inner skirt and leaflets, covers the external frame on the first 1.5 cells of the inflow. The TAV is processed with an anti-mineralization treatment of alpha-amino oleic acid (AOA), a compound derived from oleic acid, a naturally occurring long-chain fatty acid.

7.2.2. EnVeo PRO Delivery Catheter System with InLine Sheath

The delivery catheter system facilitates the placement of the TAV within the annulus of the aortic valve (Figure 2C). The catheter assembly is flexible and compatible with a 0.035 in (0.889 mm) guidewire. The

distal (deployment) end of the system features an atraumatic, radiopaque catheter tip and a capsule that covers and maintains the bioprosthesis in a crimped position. The capsule includes a distal flare to enable full recapture of the bioprosthesis after partial deployment. A stability layer is fixed at the handle and extends down the outside of the catheter shaft. It provides a barrier between the retractable catheter and the introducer sheath and vessel walls, thus enabling the catheter to retract freely.

The EnVeo InLine Sheath (ILS) is assembled over the stability layer, which functions as a hemostatic introducer sheath and minimizes the access site size to the capsule diameter. The InLine Sheath is compatible with a 20 Fr introducer.

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

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

7.2.3. EnVeo PRO Loading System

The loading system facilitates manual loading of the TAV into the deployment sheath capsule of the delivery catheter system by gradually reducing the diameter of the bioprosthesis radially to an optimal diameter (Figure 2B). The manual loading is performed during the procedure prior to implantation. The loading procedure is performed while immersing the loading system, the TAV, and the distal end of the delivery catheter system in cold sterile saline.

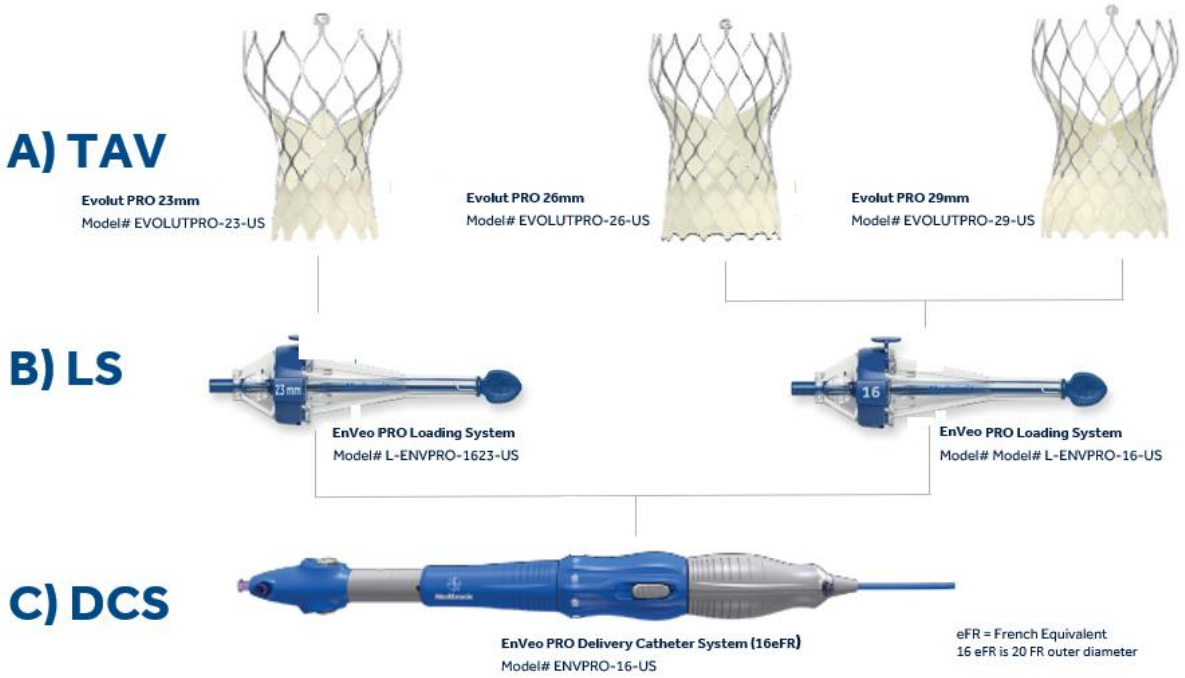


Figure 2. Medtronic CoreValve™ Evolut™ PRO System Components

(A) Evolut PRO TAV (B) EnVeo PRO loading system (LS); (C) EnVeo PRO delivery catheter system (DCS)

7.2.4. Manufacturer

Medtronic CoreValve LLC

[redacted]

7.2.5. Packaging

The Medtronic CoreValve™ Evolut™ PRO system consists of the transcatheter aortic valve (TAV), EnVeo PRO delivery catheter system (DCS) and the EnVeo PRO loading systems (LS). Each of these components is packaged separately and its packaging evaluated individually. The finished TAV, DCS, and LS components were subjected to packaging validation studies to demonstrate packaging integrity and to confirm preservation of product sterility after sterilization, handling, distribution, and storage.

The Instructions for Use (IFU) for the Medtronic Evolut™ PRO system used in this study is provided as a separate document. Product labeling (Chinese) has been developed according to local requirements. All study devices are labeled as per China regulations. Investigational devices are labeled “Clinical trial use only” in accordance with NMPA China GCP 2022.[23]

7.2.6. Equipment

Medtronic will control the supply of investigational devices and study materials (e.g., Investigator Site File, eCRF access). The final study implant using investigational devices occurred in February 2023. First investigational device shipment at each site occurred after the Principal Investigator (PI) and key site personnel who handle storage of the device completed all device training and documented on the Delegated Task List. Medtronic will not provide any study-specific equipment to the sites.

Study sites should follow their institutional procedures for maintenance of echocardiography and laboratory equipment used for assessing the study variables.

7.3. Study trial

The objective of this study is to evaluate the safety and efficacy of the Medtronic CoreValve™ Evolut™ PRO System when used by Chinese implanting centers in patients with severe symptomatic aortic stenosis (AS) who are at high risk for Surgical Aortic Valve Replacement (SAVR).

The study population includes males and females with severe symptomatic aortic stenosis who are considered at high risk for SAVR.[24]

8. Indications, contraindications and precautions of the investigational product

The Medtronic Evolut PRO system is intended for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, to be at high risk for open heart surgery in the evaluation of the Evolut PRO China Clinical Study. The TAV treats aortic stenosis by displacing and functionally replacing the dysfunctional native valve with a bioprosthetic valve delivered on a catheter while the heart is still beating, thus avoiding the risks of cardiopulmonary bypass.[25,26,27,28] Its intended performance is to relieve aortic valve stenosis without inducing significant regurgitation, thereby restoring effective aortic valve function.

Refer to the Investigator's brochure (IB) and Instructions for Use (IFU) document for intended use, indications and contraindications. See IFU also for mechanism of action, manufacturing information, model numbers, device identification, storage and handling requirements, summary of training and experience, description of medical procedures, and list of potential risks and warnings.

9. Overall design

9.1. Study design

This is a prospective, observational, single arm, interventional, multicenter, post-market study. The subjects will continue to be followed through 5 years. The study objective will be assessed by evaluating the primary and secondary endpoints at 30 days.

9.1.1. Study objectives and/or Endpoints

9.1.1.1. Study Objective(s)

The objective of this clinical study is to evaluate the safety and efficacy of the Medtronic CoreValve™ Evolut™ PRO System when used by Chinese implanting centers in patients with severe symptomatic aortic stenosis (AS) who are at high risk for Surgical Aortic Valve Replacement (SAVR).

9.1.1.2. Primary Endpoints

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

Safety

- All-cause mortality at 30 days

Efficacy

- The percentage of evaluable echocardiograms with moderate or severe aortic regurgitation at 30 days by transthoracic echocardiography (TTE).

9.1.1.3. Secondary Endpoints

The following secondary endpoints will be used to evaluate the study objective:

Safety

1) The VARC II[1] Combined Safety Endpoint at 30 days, which includes the following components:

- All-cause mortality
- All stroke (disabling and non-disabling)
- Life-threatening bleeding
- Acute kidney injury: stage 2 or 3 (including renal replacement therapy)
- Coronary artery obstruction requiring intervention
- Major vascular complication
- Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)

2) Event rates of the individual components of the VARC II composite safety endpoint at 30 days

3) New permanent pacemaker at 30 days

Efficacy

1) Device success at 24 hours to seven days, defined as[1]:

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

2) Valve performance parameters at 30 days by transthoracic echocardiography (TTE):

- Mean aortic gradient
- Effective orifice area
- Degree of aortic regurgitation (transvalvular, paravalvular, total)

9.1.1.4. Other Outcome Measures

1) Event rates of the following TAVI-related complications:
   a. change to surgery
   b. need for cardiopulmonary mechanical assistance
   c. coronary occlusion or obstruction
   d. annular rupture or dissection
   e. ventricular perforation
   f. mitral valve damage
   g. prosthetic valve displacement, migration, or embolism
   h. acute kidney injury (up to 7 days post procedure)
2) All-cause mortality at 6 months, one year, and annually through 5 years
3) All stroke (disabling and non-disabling) at 6 months, one year, and annually through 5 years
4) Myocardial infarction at 30 days, 6 months, one year, and annually through 5 years
5) Life-threatening bleeding at 30 days, 6 months, one year, and annually through 5 years
6) New AV-Conduction disturbances (LBBB and RBBB) at 30 days
7) Prosthetic valve endocarditis at 30 days, 6 months, one year, and annually through 5 years
8) Prosthetic valve thrombosis at 30 days, 6 months, one year, and annually through 5 years
9) Valve-related dysfunction, defined as moderate or severe prosthetic valve stenosis, or moderate or severe prosthetic regurgitation (per VARC II) at one year and annually through 5 years
10) Valve-related dysfunction requiring repeat procedure at 30 days, 6 months, one year, and annually through 5 years
11) Valve hemodynamic performance metrics by Doppler echocardiography at one year and annually through 5 years

a. Mean aortic gradient
b. Effective orifice area
c. Degree of aortic regurgitation (transvalvular, paravalvular, total)

12) New York Heart Association (NYHA) functional classification at 30 days, 6 months, one year and annually through 5 years
13) Post-operative EQ-5D quality of life at 30 days and one year

9.1.2. Selection of study method and rationale

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

1) They are clinically relevant and address the most important safety and efficacy aspects of the Evolut PRO and associated implant procedure
2) They are objectively defined and measurable in all subjects
3) They are consistent with current recommendations for endpoints in TAVR clinical studies.[1]
4) They follow the NMPA "Guidelines for Clinical Trials of Trans-catheter Aortic Valve Implantation" (2019-03-01)[29]

Collectively, the 30-day endpoints and all the data collected through 5 years will provide a valid assessment to determine if the established safety and efficacy of the Evolut PRO system can be replicated by Chinese implanting centers in Chinese patients with severe symptomatic aortic stenosis at high risk for SAVR.

9.1.3. Measures for reducing and avoiding deviation

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

1) An Eligibility Review Committee (ERC) confirms subject eligibility and anatomical suitability.
2) An 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.
3) All sites will follow a standardized protocol for acquisition of echocardiographic endpoint data.
4) An independent Echo Core Lab was utilized to evaluate echocardiograms through 30 days.
5) Study sites should follow their institutional procedures for maintenance of echocardiography and laboratory equipment used for assessing the study variables.

9.1.4. Investigational medical device and controlled medical device/diagnosis-therapeutic method (if any)

The Evolut PRO Transcatheter Aortic Valve Replacement (TAVR) System is the investigational device that will be evaluated in this single-arm clinical study.

Note: Effective 24-DEC-2021, National Medical Products Administration (NMPA) approved the Medtronic CoreValve™ Evolut™ PRO System for the treatment of severe aortic stenosis for symptomatic patients in China who are at high or extreme risk for open heart surgery. Overseas clinical data were utilized to support product registration. The Evolut PRO System is commercially available during the Evolut PRO China Clinical Study enrollment period. However, only Evolut PRO System components that are labeled investigational (i.e., "Clinical trial use only") were used in the study. Commercial Evolut PRO System components were not used in the study. After all study attempted implants occurred and the primary endpoint analysis was completed, the Evolut PRO China Study was converted from a pre-market to a post-market study via implementation of Clinical Investigation Plan (CIP) Version 5.0.

9.1.5. Selection of subjects (including selection of control group if necessary)

Subjects who meet the eligibility criteria and sign the informed consent form will participate in this study. Subjects who do not meet all inclusion criteria or meet any one of the exclusion criteria will not be enrolled to participate in the clinical study.

9.1.5.1. Inclusion criteria

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

1. Severe aortic stenosis, defined as aortic valve area of <1.0 cm^2 (or aortic valve area index of <0.6 cm^2/m^2) by the continuity equation, OR mean gradient >40 mmHg OR maximal aortic valve velocity >4.0 m/sec by resting echocardiogram
2. High risk for SAVR defined as STS-PROM score ≥ 8% AND ≤ 15%, OR documented Heart Team agreement of high risk for AVR due to frailty or comorbidities
3. Symptoms of aortic stenosis AND NYHA Functional Class II or greater
4. The subject and the treating physician agree that the subject will return for all required post procedure follow-up visits

9.1.5.2. Exclusion criteria

Exclusion Criteria

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

- Any condition considered a contraindication for placement of a bioprosthetic valve (e.g., subject is indicated for mechanical prosthetic valve)
- Age is less than 65 years
- A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated:
    - aspirin or heparin (HIT/HITTS) and bivalirudin
    - ticlopidine and clopidogrel
    - nitinol (titanium or nickel)
    - contrast media

- Blood dyscrasias as defined: leukopenia (WBC <1000 mm^3), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states
- Untreated clinically significant coronary artery disease requiring revascularization
- Severe left ventricular dysfunction with left ventricular ejection fraction (LVEF) <20% by echocardiography, contrast ventriculography, or radionuclide ventriculography
- End stage renal disease requiring chronic dialysis or creatinine clearance <20 cc/min.
- Ongoing sepsis, including active endocarditis
- Any percutaneous coronary or peripheral interventional procedure with a bare metal or drug eluting stent performed within 30 days prior to study procedure
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 10 weeks of written informed consent signed
- Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
- Recent (within 6 months of Heart Team assessment) cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- Gastrointestinal (GI) bleeding that would preclude anticoagulation
- Subject refuses a blood transfusion
- Severe dementia (resulting in either inability to provide informed consent for the study/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits)
- 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 or adherence to the protocol required follow-up exams
- Currently participating in an investigational drug or another device study (excluding registries)
- Evidence of an acute myocardial infarction ≤30 days before the study procedure
- Need for emergency surgery for any reason
- Liver failure (Child-Pugh class C)
- Patients requiring TAV implantation via carotid aortic access
- Currently undergoing radiation therapy

Anatomical exclusion criteria:

- Pre-existing prosthetic heart valve in any position
- Mixed aortic valve disease (aortic stenosis with severe aortic regurgitation with predominant aortic regurgitation > 3+)
- Severe mitral regurgitation
- Severe tricuspid regurgitation
- Moderate or severe mitral stenosis
- Hypertrophic obstructive cardiomyopathy
- Echocardiographic or Multi-Detector Computed Tomography (MDCT) evidence of intracardiac mass, thrombus, or vegetation

- Non-calcified aortic valve
- Unicuspid valve verified by echocardiography
- Bicuspid aortic valve with no raphe or 2 raphes (Sievers classification type 0 or type 2)
- Sinus of Valsalva diameter unsuitable for placement of the self-expanding bioprosthesis
- Aortic annulus diameter of < 18 or > 26 mm.
- Significant ascending aortopathy requiring surgical repair
- Ascending aorta diameter > 4.5 cm
- For transfemoral access vessel diameter < 5.5 mm or for transaxillary (subclavian) access < 6.0 mm in patients with a patent left internal mammary artery (LIMA)

9.1.5.3. Criteria and procedures for trial/treatment termination

The study enrollment was completed in February 2023, all the enrolled subjects will continue to be followed up for 5 years post procedure.

9.1.5.4. Time of enrollment

If the patient agrees to participate, written informed consent will be obtained. The date of the ERC confirms the subject is eligible will be considered the point of enrollment.

The study enrollment was completed in February 2023.

9.1.5.5. Estimated duration of clinical trial and the reasons for determination

Subjects will be consented for follow-up through 5 years. The enrollment phase of the study was completed; the estimated total duration of the study (first subject enrolled to last subject completing his/her last follow-up visit) is estimated to be 6.5 years, excluding the time required for preparing the study start-up, final report and study closure.

9.1.5.6. Estimated participation duration of each subject

Each implanted subject whether in the roll-in or primary study population will be followed up to 5 years post-procedure. Subjects who are taken to the procedure room for implantation but do not receive an Evolut PRO for any reason will be exited from the study within 30-days post the date of implant procedure unless a study system and/or implant procedure related Adverse Event (AE) is identified. If a study system and/or implant procedure related AE is identified, the subject will be followed until the event is resolved or no further actions need to be taken.

In the rare event the Evolut PRO TAV is explanted from the subject, their participation in the study ends following discharge from the explant hospitalization or 30 days post-explant (whichever comes later) to assess safety and then terminated from the study.

9.1.5.7. Number of subjects required for clinical trial

The study was designed estimating 65 subjects with a maximum of up to 70 subjects in China with an attempted implant. At the completion of enrollment, 58 subjects in China with an attempted implant were enrolled, comprised of the following:

1) **Primary study population**: 50 subjects with an attempted implant using the Evolut PRO system

2) **Roll-in population**: The first two attempted subjects at each site were considered "roll-in" subjects. The maximum number of roll-in subjects among all sites was 20 subjects. At completion of enrollment, there were 8 total roll-in subjects enrolled. The roll-in population will be followed per the same protocol as the primary study population; however, results from the roll-in population will be analyzed separately from the primary study population.

9.1.6. Efficacy evaluation method

The primary and secondary efficacy endpoints were evaluated by quantitative assessment of transthoracic echocardiograms (TTE) by an independent Echo Core Laboratory and determination of the device success composite endpoint per the Valve Academic Research Consortium-2 (VARC II) definition[1]. As the study has transitioned post-market, all other endpoints will be evaluated via quantitative assessment of TTE by each site.

9.1.6.1. Description of the efficacy parameters

The efficacy parameters of aortic regurgitation and hemodynamic performance will be evaluated post-transcatheter aortic valve implantation (TAVI) and at follow-up to assess valve durability and dysfunction. The composite endpoint of device success evaluates procedural mortality, positioning of the prosthetic valve in the proper anatomical location and performance of the prosthetic valve.

9.1.6.2. Selection of method and time for evaluation, recording and analysis of the efficacy parameters

Efficacy is evaluated by the status of primary endpoint and secondary endpoints related with efficacy. The efficacy endpoints were selected per the Valve Academic Research Consortium-2 (VARC II) recommendations[1]. The primary efficacy endpoint is the percentage of evaluable echocardiograms with moderate or severe aortic regurgitation at 30 days. Secondary efficacy endpoints are device success evaluated prior to discharge (at 24 hours to 7 days post-procedure) and hemodynamic performance at 30 days. Statistical analysis of the efficacy parameters were performed when the Implanted set (i.e., subjects who are implanted with the Evolut PRO, defined as the Evolut PRO is placed in the aortic annulus and completely released from the delivery catheter system) completed their 30-day follow-up evaluation. Table 3 outlines the timing of the evaluations to assess the efficacy parameters.

9.1.7. Safety evaluation method

Device and/or index procedure related adverse events (AEs), safety endpoint related AEs and serious adverse events (SAEs) and their outcomes including death will be reported effective with CIP Version 5.0

implementation (i.e., post-market study status transition) at each participating center. Sites should capture or make every effort to collect source material for the safety-related endpoints and obtaining documentation of the cause of death, if available. A Clinical Events Committee (CEC) will provide independent medical review and adjudication of adverse event data used in the safety endpoint assessment of the investigational device. The CEC will review source documentation to assess the clinical context from the implantation procedure leading up to the time of the event.

9.1.7.1. Description of the safety parameters

All-cause mortality adjudicated by the CEC will be categorized as cardiovascular and non-cardiovascular per the VARC II definition.

9.1.7.2. Selection of methods and time for the evaluation, recording and analysis of the safety parameters

Safety will be evaluated by the safety-related endpoints and reported adverse event (AE) and serious adverse event (SAE) data. The primary safety endpoint of all-cause mortality (cardiovascular and non-cardiovascular) was evaluated at 30 days post-implantation per the VARC II definition[1]. The statistical analysis of the primary endpoint was performed when the primary study population (n= 50 subjects with attempted implant, defined as all subjects who are brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, transesophageal echocardiology (TEE) placed, or any monitoring line placed) completed their 30-day follow-up evaluation. Table 3 outlines the timing of the evaluations to assess the safety parameters.

9.2. Trial procedures

9.2.1. Study Site Investigative Team Members

Investigative sites are selected based on the following criteria:

1) Must be a medical institution qualified or filed in the NMPA clinical trial qualification certification system for conducting clinical studies by the regulatory department of NMPA and the Administrative Department of Health under the State Council.
2) The site Principal Investigator will have experience as first or second operator for a minimum of five TAV implantations and/or have successfully completed Medtronic Transcatheter Aortic Valve Replacement (TAVR) operator training program.
3) The site will have the presence or capacity of establishing an investigative team consisting of the following key personnel and their role/responsibilities provided in Table 2.

Table 2. Summary of Site Key Study Personnel

Key Personnel	Role/Responsibilities
Interventional Cardiologist	Each site will have at least one interventional cardiologist and one cardiothoracic surgeon with expertise in aortic valve replacement. The site Principal Investigation (PI) may be an interventional cardiologist or a cardiothoracic surgeon. The PI will undertake all the responsibilities of the investigator as required per NMPA regulations, and clinical trial agreement. In this study, the coordinating investigator of the leading site will coordinate the study with the Sponsor accordingly to the requirements in NMPA GCP[23].
Cardiothoracic surgeon	
Echocardiographer	Each site will have a designated cardiologist whose primary responsibilities are to assure the required echocardiograms are performed in compliance with the CIP, and for reviewing and approving the site echocardiography eCRFs, if authorized by the PI. The designated echocardiographer may also serve as a member of the local Heart Team.
Clinical Research Coordinator	Each site will have a designated study coordinator whose responsibilities include coordination of study activities, follow-up evaluations, and maintaining the records defined in the CIP.
Heart Team	Each site will utilize a local Heart Team to make determinations regarding eligibility of the prospective subject for the study. In addition, the local Heart Team will confirm each enrolled subject meets the high-risk criteria for SAVR. At a minimum, the local Heart Team should include the following members: • A cardiothoracic surgeon • An interventional cardiologist The PI may serve as a member of the Heart Team.

9.2.2. Trial flow chart

An overview of the study flow is shown in Figure 3:

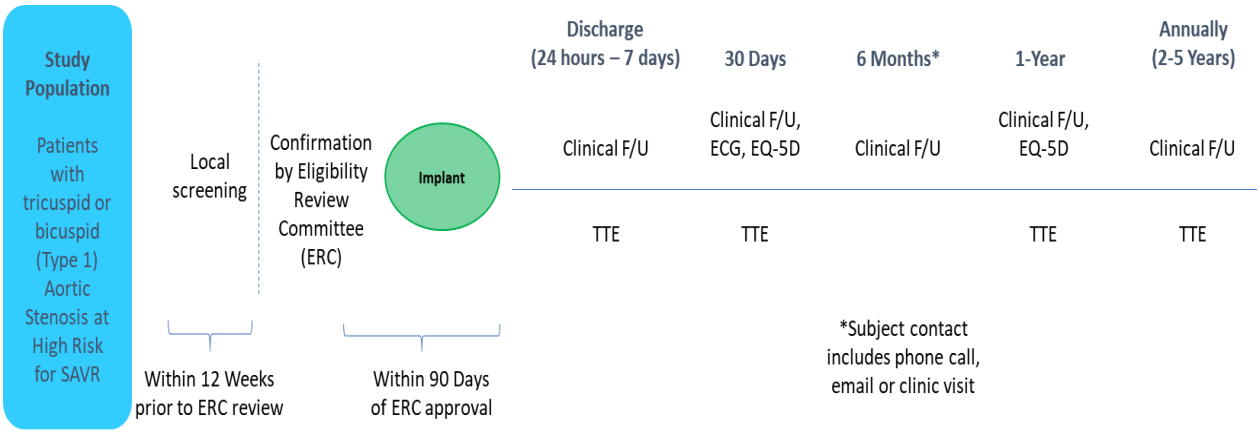


Figure 3. Study flow chart

9.2.3. Subject Screening and Enrollment

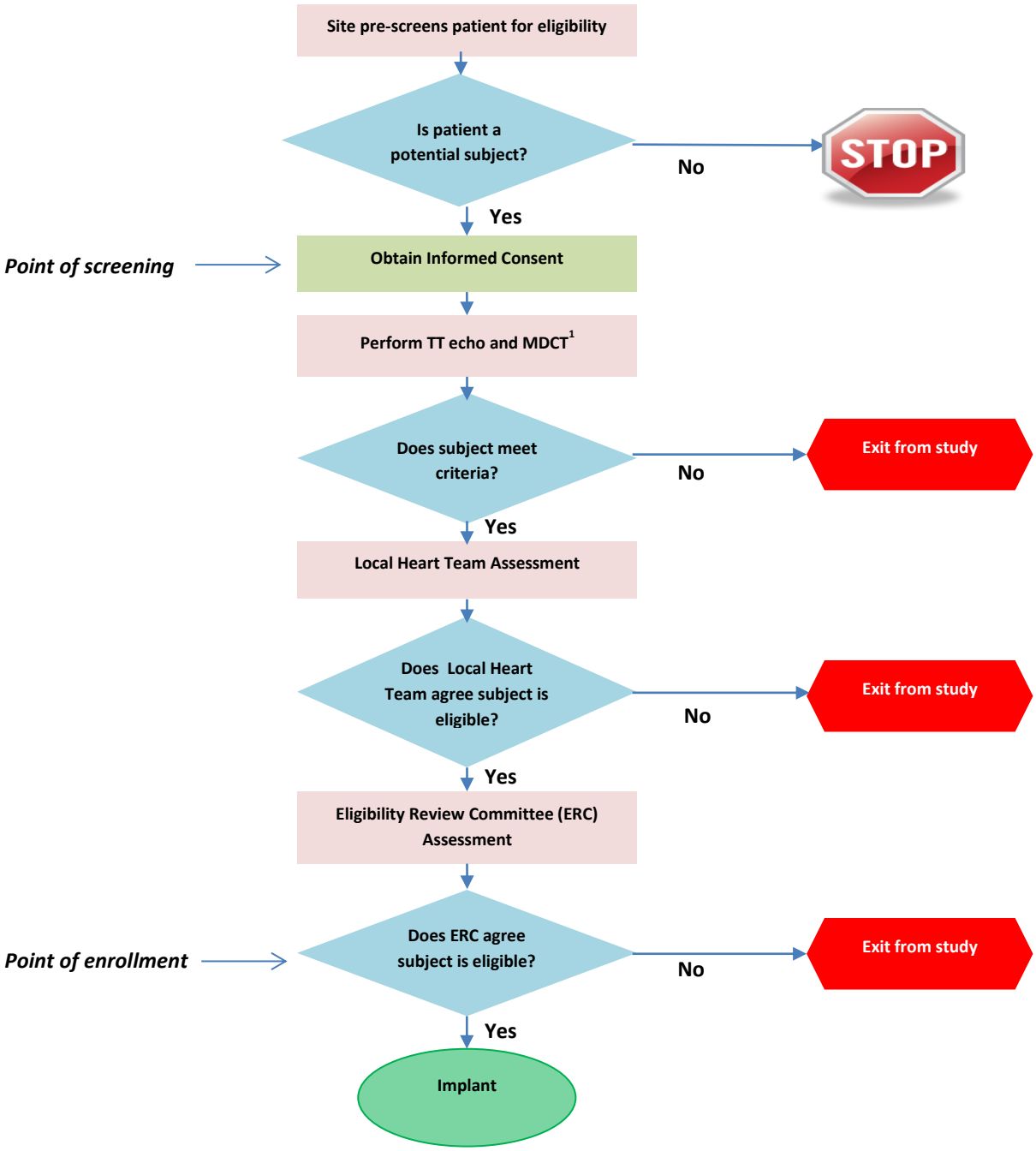
The study enrollment was completed in February 2023, the process of patient screening and subject enrollment is as follows:

1. Patients identified by the study site to have symptomatic aortic stenosis will be pre-screened by the investigative team for the criteria described in Section 9.1.5, Selection of Subjects, using available medical records, including relevant imaging studies that may have been previously performed for diagnostic purposes.
2. If, based on the review of available information, the patient is deemed to be a potential candidate for the study, the investigational status of the Evolut PRO system and all aspects of the study will be explained to the patient. The patient will then be invited to participate in the study.
3. If the patient agrees to participate, written informed consent will be obtained prior to undergoing any study-specific tests/procedures. The date of the signed informed consent will be considered the point of screening. The informed consent process should be documented in the patient's medical record, and the subject shall be provided with a copy of the signed informed consent document.
4. If the subject does not have a transthoracic echocardiography (TTE) available within 12 weeks of the submission to the Eligibility Review Committee (ERC), the subject will undergo a TTE. If all echocardiographic criteria are met, the subject is eligible for further screening.
5. Subjects that meet the echocardiographic criteria will undergo: 1) MDCT of their peripheral vasculature and aortic annulus to assess anatomic suitability for Evolut PRO implantation[ii], and 2) Heart Team assessment to determine their operative risk profile for SAVR.

[ii] Anatomical suitability will be also be assessed by Medtronic Imaging Services Lab. Information on MDCT procedures and sizing recommendations is provided in Appendix III.

6. If the local Heart Team considers the subject to be suitable for implantation and at high risk for SAVR, the subjects' clinical information will be submitted to the ERC. The following information should be submitted to the ERC:
   - Clinical assessments including STS-PROM, medical history and co-morbidities
   - TTE data on degree of aortic stenosis
   - MDCT data on anatomical suitability[ii]
7. The ERC will review clinical information to confirm the eligibility of the subject for implantation. If the ERC confirms the subject is eligible, the date of the ERC confirms the subject eligibility will be considered the point of enrollment, and implantation should be performed within 90 days of ERC approval.
8. Sites will maintain a log of patients consented, attempted, and implanted, as well as the Subject ID numbers assigned to each patient. Subjects who are consented but do not go forward to attempted implantation will be exited from the study.

Figure 4 is a flow chart of subject screening and eligibility confirmation process leading up to the study implant procedure.



Note

1. TTE or MDCT performed for diagnostic purposes prior to consent may be used, provided they are within window and contain the necessary data.

Figure 4. Flow chart of the study entry process

9.2.3.1. Heart Team Risk Assessment

Each screened subject is evaluated by the local Heart Team to confirm they are considered to be high risk for SAVR according to the following definition:

- STS-PROM ≥ 8% AND ≤ 15%, OR documented Heart Team agreement of high risk for AVR due to frailty or comorbidities

Categorization of high risk is based on the subject's STS-PROM as well as additional risk factors not captured by STS-PROM, including:

- porcelain aorta or severely atherosclerotic aorta
- frailty
- severe liver disease/cirrhosis
- hostile chest
- Internal mammary artery (IMA) or other critical conduit(s) crossing midline and/or adherent to posterior table of sternum
- severe pulmonary hypertension
- severe right ventricular dysfunction

9.2.4. Required Evaluations

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

Baseline/Pre-implant Required prior to Eligibility Review Committee (ERC) submission (within 12 weeks prior to review by the ERC; except for MDCT)[iii]

- Clinical assessment and history (e.g., clinical history, STS-PROM, co-morbidities, NYHA, symptoms, etc.)[iv]
- Transthoracic echocardiogram (TTE)
- Cardiac Multi-detector Computed Tomography (MDCT; peripheral vasculature and aortic annulus)
- Heart Team assessment
- Adverse Events

Baseline/Pre-implant (performed upon ERC approval to Implant procedure)

- 12-lead ECG
- Modified Rankin score (mRS)
- EQ-5D Quality of Life survey
- Adverse Events

Implant Procedure

[iii] Pre-implant MDCT must be performed within 365 days of planned implant date

[iv] Definitions of STS and other co-morbidities are provided in Appendix III

- Post deployment left ventricular and aortic pressures (hemodynamics) and aortography (final result)
- Adverse Events
- Device Deficiencies

24 hours to 7 days Post Procedure (prior to Discharge)

- TTE (for device success)
- Adverse Events
- Device Deficiencies

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

- Clinical assessment (NYHA not assessed at discharge)
- Adverse Events
- Device Deficiencies

30 days (between 30 to 45 days post procedure)

- Clinical assessment
- TTE
- 12-lead ECG
- EQ-5D Quality of Life survey
- Adverse Events
- Device Deficiencies

6 months (between 183 to 210 days post procedure)

- Clinical assessment
- Adverse Events
- Device Deficiencies

One Year (between 365 and 395 days post procedure)

- Clinical assessment
- TTE
- EQ-5D Quality of Life survey
- Adverse Events
- Device Deficiencies

Annual through 5 years (between implant anniversary date and 30 days after)

- Clinical assessment
- TTE
- Adverse Events
- Device Deficiencies

Other Evaluations

- Modified Rankin score assessment should be conducted at 1 and 3 months following the date of a stroke event.[1]

Table 3. Summary of visit schedule and required evaluations

Event	Screening		Index Hospitalization			Follow-up Assessments			
	Baseline (Local screening 12 weeks prior to ERC)	Baseline (ERC approval to Implant)	Implant	24 Hours to 7 Days	Discharge	30 Days	6 Months	1 Year	2-5 Years Annually
						Clinic Visit	Subject Contact[1]	Clinic Visit	Clinic Visit
Clinical assessment	X				X[2]	X	X	X	X
Adverse Event[3]	X	X	X	X	X	X	X	X	X
Device Deficiencies			X	X	X	X	X	X	X
MDCT	X[4]								
TTE	X			X[5]		X		X	X
Heart Team Assessment	X								
12-lead ECG		X				X			
Modified Rankin score[6]		X							
Aortography			X						
EQ-5D		X				X		X	

[1] Subject contact includes phone call, email or clinic visit
[2] NYHA assessment is not required at discharge
[3] Events are collected after the time of written informed consent signed. Refer to Section 16 for reportable adverse events.
[4] Pre-implant MDCT must be within 365 days of planned implant date
[5] TTE for device success should be performed within 24 hours to 7 days post procedure
[6] Modified Rankin score assessment should be conducted at 1 and 3 months following the date of a stroke event

Visit Windows

Baseline	Within 12 weeks prior to Eligibility Review Committee review
Discharge	Discharge from index procedure or 7 days post implant, whichever comes first
30 Days	Between 30 and 45 days post implant
6 Months	Between 183 and 210 days post implant
1 Year	Between 365 and 395 days post implant
2-5 Years	Between implant anniversary date and 30 days after

9.2.5. Recording Data

Subject Disposition

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

Subjects who are taken to the procedure room for implantation but do not receive an Evolut PRO for any reason will be exited from the study within 30-days post the date of implant procedure unless a study system and/or implant procedure related Adverse Event (AE) is identified. For subjects that have their Evolut PRO TAV explanted, their participation in the study ends following discharge from the explant hospitalization or 30 days post-explant (whichever comes later).

Implant Procedure

The implantation procedure was performed according to the standard procedures of the implanting physicians. Procedural aspects specific to the Evolut PRO system was performed according to the Instructions for Use (IFU). Valve size selection should be based on the anatomical dimension criteria described in Appendix III, Section 4.0.

Data to be acquired during the implantation procedure included the following:

- Name of the primary operator
- Anesthesia type (general or local)
- Delivery catheter access site and vessel diameter of access site
- Pre-deployment BAV (yes/no)
- Use of rapid or controlled pacing during BAV and deployment (yes/no)
- Size of Evolut PRO TAV implanted
- Post implant dilation (yes/no)
- Post implant pressures at final result (LV systolic and end-diastolic, aortic systolic and diastolic, LV aortic peak-to-peak or mean gradient)
- Implantation of Evolut PRO TAV within the desired location (yes/no)
- Post implant severity of prosthetic regurgitation by angiography (none, 1+, 2+, 3+, 4+) by Sellers criteria[30]
- Post implant severity of prosthetic paravalvular regurgitation by TEE, if performed
- Post implant severity of prosthetic transvalvular regurgitation by TEE, if performed
- More than one TAV implanted (yes/no)
- Patency of coronary arteries post implant (yes/no)
- Estimated contrast volume used
- Total procedural time(minutes): time in procedure room to exit from procedure room
- Occurrence of adverse events
- If Evolut PRO implantation was not attempted, reason why

Echocardiography

Transthoracic echocardiography (TTE) is required at the following intervals: pre-implant, 24 hours to 7 days (for device success), 30 days, 1 year, and annually through 5 years. Echocardiographic study endpoint results within 30 days visits were based on core lab assessments, and the Echo Core Lab results will not be utilized for any echocardiograms collected after the 30 day follow-up visit interval. . Further details of the echocardiography methods are provided in APPENDIX II: ECHOCARDIOGRAPHY PROCEDURES.

Sites will obtain the necessary views and measurements to document the following variables at each protocol-required exam:

- Height[v] and weight
- Left ventricular outflow tract (LVOT) diameter in mid systole
- Max aortic/prosthetic valve velocity (V_2) by CW Doppler
- Aortic valve velocity time integral (VTI) by CW Doppler
- Mean gradient across aortic valve (MGV_2) by CW Doppler
- LVOT VTI by PW Doppler
- Grade of aortic/prosthetic transvalvular regurgitation
- Grade of 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

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

- Body surface area (Dubois and Dubois)[31]
- Body mass index
- Peak aortic pressure gradient
- Aortic valve area (AVA)/effective orifice area (EOA) by continuity equation
- Aortic valve area index (AVAI)/effective orifice area index (EOAI)
- Doppler Velocity Index (DVI)

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

Clinical Assessment

[v] Height will be collected at the baseline (pre-implant) exam only. Height for the post-implant exams will be derived from the baseline height.

Clinical assessment will be performed at the following intervals: pre-implant, discharge, 30 days, 6 months, 1 year, and annually up to 5 years.

The following variables will be documented at each protocol-required assessment:

- Follow-up status
- NYHA functional classification (except hospital discharge)
- EQ-5D (at baseline, 30 days and one year only)
- Documentation of adverse events and device deficiencies

Missed Follow-up Visits

Every effort should be made to ensure subjects return to the clinic for all protocol required follow-ups except for the 6-month subject contact (may be conducted by phone call, email or clinic visit). If the subject is unable to return for an in-person clinic visit, the Investigator, or designee, should document in the patient record the reason the subject was unable to complete the visit and, if applicable, follow the requirements for deviation reporting as outlined in Section 17.1.

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

Unscheduled Follow-up Visits

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

9.2.6. Subject Withdrawal or Discontinuation

All subjects will be encouraged to remain in the study through the last follow-up visit at 5 years. Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of total study subjects. If a study subject is discontinued from the study before study completion (including subjects with explants), the reason for discontinuation should be documented in the subject file and a Study Exit eCRF must be completed.

The study site will make every effort to have all subjects complete the follow up visit schedule.

Subject Lost-To-Follow-Up (LTFU) should be avoided as much as possible and investigators are urged to do their utmost best to maintain subject follow-up compliance. Continuous attempts throughout the five-year follow-up period should be made to contact the subject, the subject's family or referring physician before documenting a subject LTFU. It is highly recommended to document each attempt to contact the subject and the method used (e.g. telephone contacts, registered letters) in the subject's records.

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. In case a subject cannot be reached, all contact efforts to obtain follow-up must be documented in both the study files and on the study eCRFs.

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

In addition, there is no post-study access of the investigational device for participants as study treatments are complete and there is no need for additional investigational devices.

9.2.7. Norms for using device

9.2.7.1. Product and Study Training Requirements

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

Prior to each site's first use, Medtronic provides training to implanting physicians on the use of the investigational device following a similar training procedure applied to investigational studies conducted worldwide.

9.2.7.2. Product Receipt and Tracking

In this study, the Evolut PRO system including the Transcatheter Aortic Valve (TAV), Delivery Catheter System (DCS) and Loading System (LS) are considered investigational devices in China. Sites are responsible for maintaining records for product delivery, receipt and tracking and product disposition to allow for traceability during and after the clinical investigation.. Sites are required to maintain investigational device records that contains the following information:

- Investigational device name
- Serial number / Lot number
- Quantity of devices received
- Date of receipt of device
- Name of person receiving the device
- Name of person using the device

- Date of implant or use
- ID number of subjects receiving or using the device
- Disposition (implanted, disposed of, or returned to Medtronic)

9.2.7.3. Product Storage

The Evolut PRO system was labelled and stored in a secure location during the enrollment period, and no use of these investigational devices for other applications than mentioned in this CIP are permitted.

9.2.7.4. Product Accountability

Device accountability records are maintained at the study site. The quantity of devices received by the study site, those returned, and those devices used at the study site are recorded in device accountability records. The Investigator or an authorized designee must explain in writing the reasons for any discrepancy noted in device accountability. The study enrollment was completed in February 2023, and all sites have returned unused, opened or unopened devices to Medtronic.

Medtronic and/or its designee has trained the Investigator and appropriate site personnel on device-tracking instructions and requirements, which included the site's record keeping responsibilities of receipt and disposition of all investigational devices shipped to and returned by the site.

Note: for additional information on shipment, receipt, and return of study devices refer to the device tracking instructions.

9.2.7.5. Product Return

The study enrollment was closed in February 2023, the Investigators have returned unused devices to Medtronic along with a copy of the completed device inventory. The investigator's copy of the device reconciliation records must document any unused devices that have been returned to Medtronic as well as all product usage including opened but non-implanted devices.

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

- The device serial numbers / Lot numbers
- The quantity and reason for the device being returned to Medtronic or disposed of
- Name of the person who returned or disposed of each device
- Date of shipment back to Medtronic

9.2.7.6. 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 a TAV is explanted after implant, the TAV and/or affected components should be disposed at study site according to hospital requirements.

9.3. Monitoring plan

Monitoring visits and/or remote reviews were and will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. Investigational sites will be monitored to ensure compliance with the study protocol (including the informed consent process), adherence to applicable regulations, accuracy of study data, and to ensure the safety and wellbeing of the subjects is preserved. Prior to subject enrollment, an initiation visit was completed with each site. Monitoring visits will also be used to verify that study data submitted on case report forms are complete and accurate with respect to the subject records and to verify device accountability.

Site personnel will complete electronic case report forms (eCRFs) following each subject study schedule. Study data submitted will be reviewed against subject charts and other sources containing original records of subject data.

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

Monitoring will be provided by representatives of Medtronic, including but not limited to, Medtronic Clinical & Regulatory Solutions (MCRS) with oversight from the Medtronic clinical project manager and study team. Representatives of Medtronic (i.e. contractors and designees) may act as the study monitors or co-monitors to the site.

Prior to the first site activation a monitoring plan is established outlining the activities, as well as study site training, the process for corrective and preventive actions, audit preparation and inspection support. Source data verification (SDV) will be performed and the extent of SDV will be described in the monitoring plan.

The principal investigator(s), his/her delegate(s) and the study coordinator(s) are expected to be present and available during the monitoring visit to discuss monitoring outcomes. This accessibility is of particular importance for reviewing data in the eCRF. Direct access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

10. Statistical consideration

10.1. Statistical design, method and analysis procedures

This is a prospective, single arm, multi-center, interventional, post-market study. The primary endpoints are all-cause mortality and the percentage of evaluable echocardiograms with moderate or severe prosthetic aortic valve regurgitation at 30 Days. As this is not a powered hypothesis-driven study, the sample size was not determined by statistical methods. The sample size is consistent with the 50 subject minimum as outlined NMPA TAVI Clinical Trial Guideline[29].

Subjects who are taken to the procedure room and attempt the implantation will comprise the study population evaluated for the study objectives and associated endpoints. Data from subjects enrolled as roll-ins will not be combined with the primary analysis cohort and will be analyzed separately. The analysis subsets for the study endpoints are shown in Figure 5.

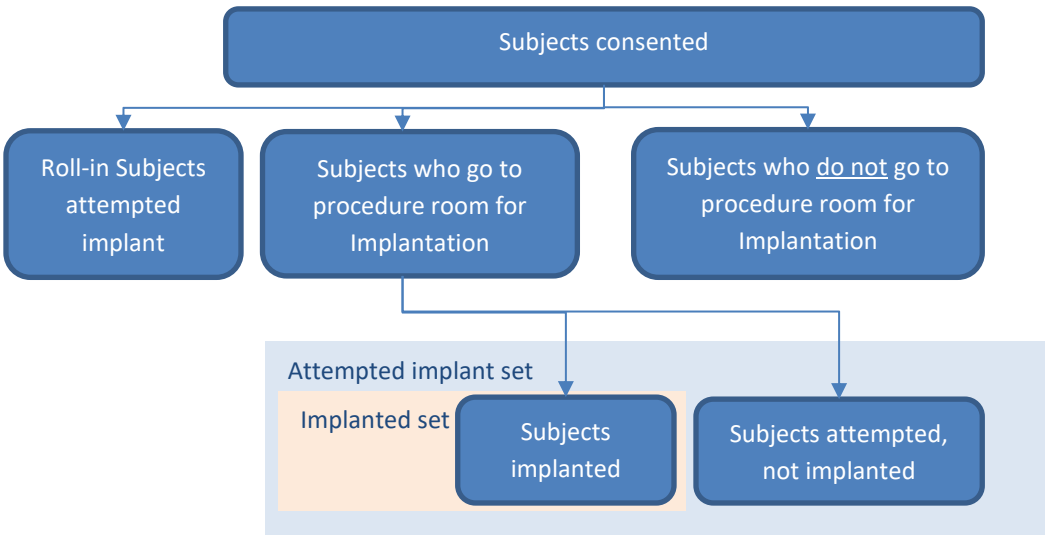


Figure 5. Analysis sets for the study endpoints

There are 2 main analysis sets for the primary study population:

1. **Attempted implant set.** Includes all subjects who are brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed, or any monitoring line placed.
2. **Implanted set.** Includes all subjects who are implanted with the Evolut PRO, defined as the Evolut PRO is placed in the aortic annulus and completely released from the delivery catheter system.

Statistical analysis of primary and secondary endpoints was performed when the primary study population (n= 50 subjects with attempted implant, exclusive of "roll-in" patients) were followed for 30 days. Results for the baseline characteristics and the primary and secondary endpoints from the 60-subject TAVR 2.0 US Clinical Study (Evolut PRO) will be provided for descriptive comparison. In addition, results will be descriptively compared to available results for other commercially approved TAVR systems in China.

Data will be analyzed and Clinical Study Reports (CSRs) will be prepared for the primary endpoint (at 30 days) and for the final analysis. The final analysis will be performed when all implanted subjects have completed their 5-year follow-up. Annual CSRs may also be prepared after the primary endpoint and prior to the final analysis CSRs, per the discretion of the Sponsor.

10.1.1. Primary Endpoint Analyses

The analysis of the primary endpoints was completed according to the pre-market protocol (i.e., CIP Version 4.0) when the primary study population were followed for 30 days. The primary safety endpoint of all-cause Mortality at 30 Days was analyzed for the Attempted implant set. The Kaplan-Meier rate and a 95% two-sided confidence interval was calculated.

The primary efficacy endpoint of aortic regurgitation at 30 Days was analyzed for the Implanted set. The number and percentage of subjects with evaluable echocardiograms with moderate or severe total (paravalvular plus transvalvular) aortic regurgitation was calculated. A 95% two-sided confidence interval for aortic regurgitation was calculated.

10.1.2. Secondary Endpoint Analyses

The analysis of the secondary endpoints was completed according to the pre-market protocol (i.e., CIP Version 4.0) when the primary study population were followed for 30 days. The secondary safety endpoints of VARC II Combined and Individual Safety Components and new permanent pacemaker at 30 days was analyzed for the Attempted implant set. The Kaplan-Meier rates and 95% two-sided confidence intervals was calculated.

The secondary efficacy endpoint of Device Success was analyzed for the Attempted implant set. The number and percentage of subjects that meet device success criteria was calculated. A 95% two-sided confidence interval for the device success rate was calculated.

The secondary efficacy endpoint of valve performance parameters at 30 Days was analyzed for the Implanted set. Descriptive statistics for the following hemodynamic variables were planned:

- Mean aortic gradient
- Effective orifice area
- Degree of aortic valve regurgitation (transvalvular, paravalvular, total)

For continuous variables the number of subjects, means, medians, standard deviations, and ranges were presented. For categorical variables the number of subjects, total number of subjects, and percentages were presented.

10.2. Calculation of sample size

As this is not a powered hypothesis-driven study, the sample size of 50 attempted subjects was not determined by statistical methods. Rather, it was based on adherence to the NMPA TAVI Clinical Trial Guideline[29] and was confirmed during the NMPA consultation meetings and protocol synopsis submitted with no further objections/feedback (October 2018 through March 2019).

10.2.1. Total sample size

The total sample size of the primary study population is 50 attempted implants, exclusive of the roll-in population.

10.2.2. Case number for each disease in clinical trial and reasons for determination

All 50 attempted implants that made up the primary study population were categorized as high risk for surgical aortic valve replacement (SAVR). The sample size is consistent with the 50 subject minimum as outlined NMPA TAVI Clinical Trial Guideline[29].

10.2.3. Minimum and maximum number of subjects for each clinical trial institution in multicenter clinical trial

The site enrollment was completed in February 2023. There is no minimum number of subjects required for each clinical institution. No site was to implant more than 20 subjects, excluding the roll-in subjects, without prior authorization from Medtronic.

10.3. Significance level and study power of clinical trial

As this is not a powered hypothesis-driven study, formal hypothesis testing will not be performed.

10.4. Estimated drop-out rate

Since the study primary safety and efficacy endpoints are at 30 days, a minimal amount of missing data is anticipated for the primary endpoints. The estimated clinical attrition and lost to follow-up rate is less than 20% for the 5-year follow-up duration.

10.5. Criteria for acceptability/unacceptability of clinical trial results

Statistical analysis was performed by the leading site with collaboration support and oversight from the Sponsor for primary and secondary endpoint analysis . Statistical analysis of the primary endpoints was performed when the primary study population (n= 50 subjects with attempted implant, exclusive of "roll-in" patients) were followed for 30 days. Results for the baseline characteristics and the primary and secondary endpoints from the 60-subject TAVR 2.0 US Clinical Study (Evolut PRO) will be provided for descriptive comparison. Criteria for acceptability/unacceptability is not applicable as this is not a powered hypothesis-driven study. At the time of the primary endpoint analysis, the leading site was consulted to review the clinical trial results for acceptability/unacceptability.

10.6. Criteria and reasons for trial termination based on statistics

Interim analysis and corresponding early termination criteria are not planned for this trial. Hence, this section is not applicable. All statistical analysis will be performed after completing data collection, data review and data cleaning is confirmed.

10.7. Statistical methods for all data, and processing of missing, unused, wrong (including withdrawal and drop out) or abnormal data

Every effort will be undertaken to minimize missing data. In time-to-event outcomes, drop-outs will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach.

Unless otherwise specified in each objective, no statistical techniques will be used to impute missing data for continuous or categorical outcomes. If a subject's data are missing for any reason, that subject

will not be included in that portion of the analysis. Erroneous (i.e., wrong including withdrawal and drop out) and abnormal data will be cleaned prior to performing the database snapshot for the statistical analyses. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

10.8. Reporting of procedure deviations from the original statistical plan

The statistical analysis plan (SAP) will be confirmed by the sponsor and finalized before a database snapshot is performed for analysis. The coordinating investigator/leading site confirmed the analysis plan prior to the database snapshot for the primary endpoint analysis. The SAP may be modified to consider actual scenarios observed during the study phase before final approval. In principle, major analysis methods or analysis sets will not be changed. All revisions will be recorded.

10.9. Criteria for selection of the subjects for analysis set and reasons

Statistical analysis sets should be clearly defined prior to the time when analysis is carried out. The two main analysis sets for this study are defined as follows:

1. **Attempted implant set.** Includes all subjects who are brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed, or any monitoring line placed.
2. **Implanted set.** Includes all subjects who are implanted with the Evolut PRO, defined as the Evolut PRO is placed in the aortic annulus and completely released from the delivery catheter system.

Statistical analysis of the primary endpoints and secondary endpoints at 30 days was performed when the primary study population (n= 50 subjects with attempted implant, exclusive of “roll-in” patients) were followed for 30 days.

The final statistical analysis will be performed when all implanted subjects have completed their 5-year follow-up. Annual statistical analysis may also be prepared after the primary endpoint and prior to the final analysis, per the discretion of the Sponsor.

10.10. Exclusion of special information during assumption validation and reasons thereof (if applicable)

There is no hypothesis testing in this study, hence it is not applicable to require excluded information for hypothesis testing. If there are special information observed in the study, it will be evaluated on a case by case basis and documented in the report.

11. Data management

11.1. Data Collection

11.1.1. Electronic Case Report Forms (eCRFs)

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, and filed in the patient medical file.

Only authorized persons can complete eCRFs. eCRFs shall be signed by investigational center staff as specified on the Delegation of Authority Log included in the Investigator Site Binder. The study Electronic Data Capture (EDC) system maintains an audit trail on entries, changes and corrections in eCRFs.

A copy of the eCRFs to be used in this clinical study is available under a separate cover, upon request to the sponsor and in the Investigator Site Binder.

Investigational center will be trained for use of the eCRF prior, or at latest during, investigational center initiation visit, on a training database. Access to final eCRFs for study conduct will be granted after training is performed.

11.1.2. Subject Questionnaires

Subject questionnaires will be collected on paper that will be kept at the investigational center. The investigator, or designated investigational center staff, will then enter the answers of the subject on the paper questionnaires into EDC system. It is important that the investigator or designated investigational center staff verifies questionnaires for completeness.

11.1.3. Time Windows For Completion and Submission of eCRFs

It is expected that eCRFs are completed in a timely manner with the exception of all AEs (see Section 16.7), which need to be recorded within 24 hours in the eCRF after awareness of the investigator or investigational center staff to the event. After data entry, eCRFs should be submitted (i.e. saved) so that Monitors can proceed with data verification without delay.

11.1.4. Data Review and Processing

The leading investigational center is accountable for data management and analysis about the data from each clinical research institution in a centralized manner according to local regulations and study requirements for primary and secondary endpoint analysis. After that, the Sponsor will be accountable for the data management and analysis.

Collected data will be reviewed for completeness, correctness and consistency, as per the Monitoring Plan and Data Management Plan. In case of issues, queries will be entered on the respective eCRF for the investigator or authorized designee to complete, correct or comment on the data.

12. Feasibility analysis

12.1. Probability analysis of success

The Medtronic manufacturing system is established, governed by quality system procedures and regularly audited by various auditing bodies from around the world. The quality of the investigational device is carefully examined and verified before delivery. The investigational device has been commercially available globally, including in the United States, Europe, China and other countries. The Evolut PRO system has been studied in pre-market and post-market follow-up clinical studies. The basic principles, structure composition, and materials either comply with the international and/or domestic standards or have been carefully examined and verified by Medtronic. Additionally, Evolut PRO testing has been completed by an NMPA-certificated medical device testing organization.

The study design of this study complies with related NMPA instructions and requirements of ethical review, and all potential subjects will be strictly selected according to indications of the investigational device.

As this is not a powered hypothesis-driven study, the probability of success is not applicable. However, it is anticipated that the safety and efficacy profile will be similar to the overseas Evolut PRO data.

12.2. Probability analysis of failure

Although regulatory, ethical, scientific and medical requirements have been fully taken into consideration, the unanticipated risk in the clinical application of investigational device could lead to failure of this study. Potential risks could be reduced with well-trained study staff and strict protocol compliance.

As this is not a powered hypothesis-driven study, the probability of failure is not applicable. However, we anticipate the safety and efficacy profile will be similar to the overseas Evolut PRO data.

13. Risks and Benefits

The results of risk analysis, balancing benefits against risks associated with both the device system itself and procedures involved in its use, are included in the Investigator's Brochure (IB) and the Instructions for Use (IFU). Based on the risk assessments performed, the overall residual risk based on the potential Evolut PRO system design and use related risks have been determined to be acceptable and is exceeded by the benefits of TAVR to the patient.

13.1. Potential Risks

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

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

- Death
- Cardiac arrest
- Coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)
- Urgent surgery (e.g., coronary artery bypass, heart valve replacement, valve explant)
- Multi-organ failure
- Heart failure or low cardiac output
- Myocardial infarction
- Cardiogenic shock
- Respiratory insufficiency or respiratory failure
- Cardiovascular injury (including rupture, perforation, or dissection of vessels, ventricles, myocardium, or valvular structures that may require intervention)
- Perforation of the myocardium or a vessel
- Stroke (ischemic or hemorrhagic) or other neurological deficits
- Transient ischemic attack
- Permanent disability
- Urgent need for balloon valvuloplasty (note that BAV during implantation is expected)
- Urgent need for Percutaneous Coronary Intervention (PCI)
- Major or minor bleeding that may or may not require transfusion or intervention (including life-threatening or disabling bleeding)
- Cardiac tamponade
- Ascending aorta trauma
- Disturbances in the electrical system of the heart that may result in the permanent placement of a device (pacemaker)
  - Atrio-ventricular node block
  - Bundle branch block
  - Asystole
- Cardiac arrhythmias
- Thrombosis (including valve thrombosis)
- Valve migration/embolization
- Ancillary device migration/embolization (including components of the delivery catheter system)
- Prosthetic valve dysfunction including but not limited to:
  - Fracture
  - Bending (out-of-round configuration) of the valve frame
  - Under-expansion of the valve frame
  - Calcification
  - Pannus
  - Wear, tear, prolapse or retraction in the valve leaflet
  - Poor valve coaptation
  - Suture breaks or disruption
  - Leak

  - Mal-sizing (prosthesis-patient mismatch)
  - Malposition (either too high or too low)
  - Valve regurgitation (paravalvular or transvalvular)
  - Valve stenosis
- Mitral valve regurgitation or injury
- Hypotension or hypertension
- Renal insufficiency or renal failure (including acute kidney injury)
- Allergic reaction to antiplatelet agents, contrast medium, or anesthesia
- Infection (including septicemia; bioprosthetic or native valve endocarditis)
- Vascular access site or access related complications, including but not limited to:
  - Dissection
  - Perforation
  - Pain
  - Bleeding
  - Hematoma
  - Pseudoaneurysm
  - Irreversible nerve injury
  - Compartment syndrome
  - Arteriovenous fistula
  - Stenosis
- Tissue erosion
- Encephalopathy
- Pulmonary edema
- Pericardial effusion
- Pleural effusion
- Myocardial ischemia
- Peripheral ischemia
- Bowel ischemia
- Heart murmur
- Hemolysis
- Cerebral infarction-asymptomatic
- Non-emergent reoperation
- Inflammation
- Fever
- Syncope
- Dyspnea
- Anemia
- Angina
- Abnormal lab values (including electrolyte imbalance)
- Exposure to radiation through fluoroscopy and angiography
- Delivery catheter malfunction resulting in need for additional re-crossing of the aortic valve and prolonged procedural time

13.2. Potential Benefits

The Medtronic CoreValve™ Evolut™ PRO system has been approved in the United States (i.e., Country of Origin) for indication of use in patients with symptomatic severe aortic stenosis who are at high risk or greater for operative mortality with SAVR. The primary potential benefit to subjects participating in the study is to restore function of their diseased (stenotic) native aortic valve. Other potential benefits include avoiding the risks of open-heart surgery and cardiopulmonary bypass and an earlier return to normal activities than after open heart surgery.

13.3. Risk-Benefit Rationale

The Evolut PRO system has been studied in pre-market and post-market clinical studies in the United States, Europe and other countries. TAVR with the Evolut PRO system has been shown to be a safe and effective treatment for patients with severe aortic stenosis who are at high risk or greater for operative mortality with surgical aortic valve replacement (SAVR).

Available pre-market and real-world clinical evidence on TAVR in tricuspid and bicuspid patients has demonstrated that implantation of the Evolut R and Evolut PRO transcatheter aortic valves can be accomplished by multiple operators with a high degree of technical success and with an acceptably low level of procedural complications. Results demonstrated comparable outcomes for bicuspid patients as compared to tricuspid patients who were deemed at increased risk for SAVR (intermediate and above). This study is designed to confirm the safety and efficacy of the Evolut PRO system in the Chinese patient population. Although there are risks to the study subjects for participation in the study, they are anticipated to be similar to the risks of undergoing TAVR outside of the study. The study endpoints are clinically relevant and consistent with the study objectives. The overall study design is confirmed with the NMPA TAVI Guideline[29] was confirmed during the NMPA consultation meetings and protocol synopsis submitted with no further objections/feedback (October 2018 through March 2019). Therefore, the study as described is justified.

Measures to Mitigate Risks to Study Subjects

The following measures were and will be implemented to minimize risks to the study subjects:

- Implanting physicians had experience with TAVR
- Implanting physicians underwent didactic and simulator training prior to the study start at each site
- Patients will be rigorously followed over the course of the study

Alternatives

Presently, therapeutic alternatives for patients with the clinical indication targeted for the Evolut PRO system include the following:

- Medical therapy
- Balloon aortic valvuloplasty
- Surgical aortic valve replacement
- TAVI with another device approved in China

14. Quality control of clinical trial

Per NMPA GCP (China GCP 2022) [23], before site activation, Medtronic reached a written agreement with clinical trial institutions and investigators on trial quality control. Medtronic has developed standard operating procedures related to quality control of clinical trials, such as the transportation, receiving, storage, distribution, disposal and return of investigational medical devices, which shall be followed by clinical trial institutions and investigators. These should also be covered in the written agreement.

15. Ethical issues and informed consent of clinical trial

15.1. Ethical considerations

15.1.1. Statement of Compliance

This study is a post-market clinical trial to evaluate the safety and efficacy of the Medtronic CoreValve™ Evolut™ PRO System when used by China implanting centers in Chinese patients with severe symptomatic aortic stenosis (AS) who are at high risk for Surgical Aortic Valve Replacement (SAVR). The study will be conducted in accordance with the laws and regulations of China, including any future applicable laws and regulations in China.

This protocol, any subsequent amendments to this protocol, the Informed Consent/Assent form, subject material and any form of subject recruitment information (e.g. advertisements) relating to this study will be approved by the responsible EC in accordance with local regulatory requirements as applicable. The study will not start until EC approval has been granted, the sponsor has cleared the investigational center to begin the study, and the investigational center staff has been appropriately trained to conduct the study. Copies of all relevant correspondence between the investigational center and the EC will be retained at investigational center with copies forwarded to the sponsor for their files.

Regulatory Compliance

To protect the rights and welfare of patients, this clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki, the Clinical Trial Agreement and CIP, the laws and regulations of China including, Announcement of NMPA on Filing of Medical Device Clinical Trial (2015, No. 87) and also including applicable data protection laws, this study will continue to follow China GCP 2022 as regulatory compliance guidance during a post market setting, except on AE collection, reportable events please refer to Section 16 for details . Investigational centers will also comply with any additional EC requirements applicable.

The principles of the Declaration of Helsinki have been implemented through the patient informed consent process, EC approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

Regulatory Submission

Study Filing to Shanghai Municipal Food and Drug Administration after EC approval in a post market study is not required, but as this is a transition to a post-market study, Sponsor will continue to submit the current version of the CIP and fully executed Clinical Trial Agreement to Shanghai Municipal Food and Drug Administration.

Sponsor's Support

The sponsor shall avoid improper influence on, or inducement to, the subject, monitor, any investigator(s) or other parties participating in or contributing to this study.

Sponsor representatives may provide support as required for the study, including technical support at investigational center. Sponsor representatives may provide technical support as required for the study under supervision of the PI, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities.
- Technical support will be provided during study period.
- Technical support will be under the supervision of a study investigator, but no data entry on the eCRF shall be performed by Medtronic personnel or their representatives at investigational centers.
- Technical support to conduct device interrogations.

15.1.2. Investigator's Responsibilities

This study will be conducted at the investigational centers where all study-related activities will be performed and will be led by a PI. An investigator is an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

The investigator's responsibilities include but are not limited to:

- Conduct of the investigation in accordance with the CIP, the regulations as outlined in NMPA that apply to this study and other applicable regulations, and any conditions of approval imposed by the reviewing EC
- Conduct of investigation in accordance to regulations from NMPA to meet responsibilities with respect to protect human subjects and ensuring the integrity of the data from clinical investigations. The regulations are also intended to clarify NMPA's expectations concerning the investigator's responsibility:
    - to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and
    - to protect the rights, safety, and welfare of study subjects.
- Supervision of all testing of the device involving human subjects
- Ensuring that the requirements for obtaining informed consent are met in accordance with NMPA
- Allowing study devices to be used only with subjects under the investigator's supervision and to supply study devices only to persons authorized to receive it
- Ensuring that investigational center staff are adequately trained to perform their assigned duties
- Maintenance of accurate, complete, and current records relating to the investigator's part of an investigation, to include
    - all relevant correspondence with Medtronic and EC
    - records of receipt, use, or disposition of a device
    - records of each subject's case history and exposure to the device
    - the CIP, with documents showing the dates of and reasons for each deviation from the CIP
- Preparation and submission to Medtronic and, when required, the reviewing EC, the following complete, accurate, and timely reports:
    - AEs (see Section 16.7 for reportable AEs) occurring during an investigation
    - progress reports on the investigation as required by the EC
    - protocol deviation that may affect the subjects' rights and interests, safety, health or the scientific integrity of clinical trials, including deviation regarding requests and reports
    - any use of the device without obtaining informed consent
    - any further information requested by the EC about any aspect of the investigation
- Meeting with the monitor to discuss study progress and findings
- Ensuring that investigational center resources are adequate to fulfill the obligations of the study

- Ensuring completion of eCRF to include: entry and addressing discrepancies in a timely fashion and approving selected eCRFs. It is expected that data is entered into RDC. Failure to keep up with entry of study data may result in study payment delay.

Only authorized study personnel, as listed on the Delegation of Authority Log, are permitted to consent subjects, receive, dispense, dispose of and return investigational products, conduct subject visits, insert devices and enter data on eCRFs. These tasks may be delegated by the investigator; however, the investigator is ultimately responsible to ensure investigational center staff are qualified and perform the tasks that have been delegated to them. In addition, the investigator is responsible for the conduct of investigational center in the execution of the clinical trial.

The investigator's signature on the Investigator Statement and Signature Page confirms that the investigator is familiar with the CIP in its entirety and agrees to conduct this study in accordance with the provisions of the CIP and all applicable regulations. The investigator, prior to the initiation of any study related activity, will sign the Investigator Statement and Signature Page. If the sponsor discovers that an investigator is not complying with the Investigator Statement and Signature Page, CIP, or other regulatory requirements, the sponsor shall promptly secure compliance or discontinue that investigator's participation in the study.

15.2. Examination and approval of study protocol

The study will be conducted in accordance with the requirements of local Ethics Committees. The responsible Ethics Committee (EC) at each investigational site must approve the study protocol and consent. Study activities will not commence prior to receipt of documentation of EC approval by the site and Medtronic. The Investigator and study site staff must comply with the requirements of their EC.

Prior to enrolling subjects, each investigational site's EC will be required to approve all necessary study documents including the CIP, the Informed Consent Form (ICF) and any other written information to be provided to the subjects. EC approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the study at an investigational site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. If the EC approval letter is not in English, the Medtronic clinical study team must ensure documented review of the letter in English, or a translation to English must be obtained. In addition, the approval letter needs to be accompanied by an EC roster or letter of compliance, to allow verification that the investigator, other site study staff, and/or Medtronic personnel are not members of the EC. If they are members of the EC, written documentation is required stating that he/she did not participate in the approval process. Medtronic will prepare the required documents and send them to the investigator for reporting to the EC. Investigators must inform Medtronic of any change in status of EC approval once the investigational site has started enrollment. If any action is taken by an EC with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

15.3.Informed consent process and informed consent form

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

Prior to the patient or legal representative signing the ICF, the investigator or authorized designee will fully explain to the patient or legal representative the nature of the research, study procedures, anticipated benefits, and potential risks of participation in the study. The language used shall be in the patient's native language, as non-technical as possible and must be understandable to the patient and legal representative, where applicable. The investigator or delegate will allow adequate time for the patient or legal representative to read and review the consent form and to ask questions.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a subject to participate or to continue to participate in the clinical study. The informed consent process shall not appear to waive the subject's rights.

Signing the ICF serves to document the written and verbal information that the investigator or authorized delegate provides to the patient or legal representative, the patient or legal representative's understanding of the information, and their agreement to participate. The ICF must be signed and personally dated by the subject and investigator or authorized designee. The investigator or authorized delegate must document in the patient's medical records that the patient was consented and the date on which the consent was obtained. The original signed consent form will be retained in the patient's study records and a copy of the informed consent will be provided to the patient or legal representative.

The principal investigator or his/her authorized designee will provide a patient with a patient study ID card during the informed consent process. The patient shall use the card to inform doctors/nurses who are not involved in the clinical study in case of unscheduled visits or an emergency treatment.

No patients from a vulnerable population will be included into the study. In addition, due to the nature of the eligibility criteria of the study, waiver of prior informed consent process due to emergency treatments is not applicable in this study.

Revision for Informed Consent Form

As directed by the regulatory authorities, EC or Medtronic, subjects may have to be re-consented to new revisions of the informed consent throughout the duration of the study.

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the study. The investigator or his/her designee should inform the subject in a timely manner.

Medtronic will revise the written ICF whenever new information becomes available that may be relevant to the subject's confirmed participation in the study. The revised information will be sent to the

investigator for EC approval. After approval by the EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

16. Provisions for reporting of adverse event and equipment deficiencies

Throughout the course of the study, investigational centers will make all efforts to remain alert to possible reportable adverse events (AEs) or untoward findings. The study personnel will elicit reports of AEs from the subject at each visit (including phone calls) documenting the medical diagnosis, date of event start and end, causality (relationship to device or procedure), treatment, outcome, and description that includes the details of the event. The Investigator will determine if an adverse event is serious and device/procedure related.

Pre-existing medical conditions or symptoms reported prior to written informed consent signed are not an adverse event (AE), therefore they will be recorded in medical history form. After written informed consent signed, if there is no worsening in the pre-existing medical conditions or symptoms, the out-patient visit for regular follow up and/or medication replenishment or adjustment will not be reported as an AE. Investigators will be responsible for the clinical assessment/medical judgment and document the none worsening conditions or symptoms for each visit. In this post-market study, investigators need to report all SAEs, index procedure and/or device related AEs, and safety endpoint AEs (Refer to Appendix V Safety Endpoint Definitions).

In the post-market study, Medtronic uses the definitions provided in National Medical Products Administration (NMPA, formerly CFDA) China GCP 2022[23], ISO 14155:2011, 21 CFR 812 for AE definitions. ISO14155:2011 definitions are used for AE classifications while expedited reporting to local authorities/EC should be done based on local definitions of local regulations.) Medtronic follows MEDDEV 2.3/3 revision 3 guidelines for classifying causality levels; but will apply these causality definitions across all events, not only serious adverse events and definitions have been adapted accordingly.

16.1. Adverse event (AE)

Adverse Event (AE) (ISO 14155-2011)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Event (AE) (China GCP 2022 Article 64)

Untoward medical occurrence during the clinical study, whether or not related to investigational medical devices.

Adverse Device Effect (ADE) (ISO 14155-2011)

Adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device.

Note 2: This definition includes any event that is a result of a use error or intentional misuse of the investigational device.

16.2.Serious adverse event (SAE)

Serious Adverse Event (SAE) (ISO 14155-2011)

An adverse event that

- Led to a death
- Led to a serious deterioration in the health of the subject, that either resulted in
  1. life threatening illness or injury,
  2. a permanent impairment of a body structure or a body function
  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
- Led to fetal distress, fetal death or a congenital abnormality or birth defect *Inpatient Hospitalization is defined as: admission to the hospital for a period of 24 hours or more based on urgent medical need rather than elective admission.

Note 1: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be a serious adverse event.

Note 2: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. (ICH Topic E 2 A Clinical Safety Data Management: Definitions & Standards for Expedited Reporting. EMEA 2006)

Serious Adverse Event (SAE) (China GCP 2022 Article 64)

Any untoward medical occurrence during the clinical study: results in death or serious deterioration in health; life-threatening diseases or injuries; causing permanent damage to the body structure or function; requires hospitalization or prolongation of hospitalization; requires medical measures to prevent from persistent or significant disability/incapacity; results in fetal distress, fetal death, or congenital anomaly/birth defect.

Serious Adverse Device Effect (SADE) (ISO 14155-2011)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

Unanticipated Adverse Device Effect (UADE) (21 CFR 812.3(s))

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unexpected Serous Adverse Device Effect (USADE) (ISO 14155-2011)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

16.3. Device Deficiency (DD)

Device Deficiency (ISO 14155-2011)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device Deficiency (China GCP 2022 No.28 Article 64)

Any unreasonable risk caused by a medical device in normal use during clinical trial that may endanger human health or life safety, such as label error, quality issues, malfunction and etc.

16.4. Causality Assessment

An event is not automatically related to the study device or procedure simply because the subject is wearing the device and participating in the study. The event should be reviewed to determine if the device or study procedure could have possibly caused the event and therefore is related to the study device or procedure.

Causality assessment is the determination of the relationship between an event and the device being studied. It is expected that the investigational center will review all elements surrounding the event to properly assess the causality of the event to the study device (TAV), the TAVR delivery system, the loading system or to a study TAVI implant procedure.

Guidelines for classifying causal relationships between the event and the TAV, the delivery catheter system and the TAVR implant procedure is provided in APPENDIX V: DEFINITIONS: SAFETY ENDPOINTS AND EFFICACY EVENTS, Section 4.0 Classification of Causal Relationships. In addition to classifying causal relationships, sites are to provide a cause analysis for each event.

16.5. Anticipated or Unanticipated

If the SAE is determined to be related to the study device or procedure, the sponsor will then assess the event to determine if it is anticipated or unanticipated.

- **Anticipated:** the event is identified in the CIP; labeling; IB or IFU.
- **Unanticipated:** the event has not been previously identified in the CIP; labeling; IB or IFU.

16.6. Evaluation and Documentation of Adverse Events

Investigators are required to evaluate and document all adverse events (AE) and device deficiencies (per the definitions above) observed in study subjects throughout the study duration, starting at the time of written informed consent signed. All SAEs, index procedure and/or device related AEs, and safety endpoint AEs (Refer to Appendix V Safety Endpoint Definitions) that occur during the study need to be reported to Medtronic via the AE eCRF and should be followed through their resolution or until subject's study exit.

Medical occurrences that are inherent to a TAVR procedure and expected to occur in the majority of subjects for a projected duration may be considered unavoidable. The events listed in Table 4 are expected for patients undergoing TAVR, and do not need to be reported as AE; unless they occur outside of the stated timeframe, are otherwise considered need to be reported according to the treating investigator, or are suspected or confirmed to be device-related.

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

Event	Timeframe (hours) from the Index Procedure
Short transient episode of arrhythmia (including ventricular fibrillation) during index procedure	0
Confusion, anxiety and/or disorientation (other than TIA/stroke) starting within 48 hours with or without medical intervention	120 (5 days)
Temporary change in mental status (other than TIA/stroke) not requiring additional medical interventions or new medical assessments (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	72
Pain in throat and/or trachea due to intubation	72
Mild to moderate bruising or ecchymosis at access site(s) as determined by physician	168 (7 days)

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

- Date of onset or first observation
- AE code number
- AE term
- Description of the event
- Date of site's first knowledge of the event
- Seriousness of the event
- Causal relationship of the event to the Evolut PRO TAV
- Causal relationship of the event to the DCS
- Causal relationship of the event to the LS

- Causal relationship of the event to the implant procedure
- Event cause analysis
- Treatment required
- Outcome or status of the event
- Date of resolution

In addition, sites should submit relevant source documents to Medtronic for the Clinical Events Committee (CEC) members to use in their adjudication for all surgical or catheter-based intervention on the Evolut PRO, deaths, and safety endpoint events. Definitions of safety endpoints, and guidelines for accessing causal relationships are provided in APPENDIX V: DEFINITIONS: SAFETY ENDPOINTS AND EFFICACY EVENTS. The AE code list will be provided under a separate cover.

16.7. Reporting procedures and information of contact

16.7.1. Reporting of Adverse Events

The Investigator or designee will record all AEs since the time of written informed consent signed in the clinical study. Each AE needs to be assessed for its device or procedure relatedness. Investigators should provide continuous monitoring, assessment and documentation of the events throughout the duration of the study.

Adverse events will be documented in the subject source file and only SAEs, index procedure and/or device related AEs, safety endpoint AEs (Refer to Appendix V Safety Endpoint Definitions) need to be reported to sponsor on an eCRF. The investigational center is responsible for documentation of AEs including obtaining source documents related to the event, such as hospital records (admission summary; lab results, test results, discharge summary) or device operation reports to support the event if possible. Source documents will be reviewed to determine if additional AEs have occurred and require reporting.

How long to follow an AE *(AEs should be followed until one of these criteria is met)*:

- Until the AE resolves
- Until no further action can be taken for an ongoing AE
- Until the subject exits the study, or
- Until study closure

NOTE: In the case of permanent impairment, continue to follow the event until it stabilizes, and the overall clinical outcome has been ascertained.

Adverse events that have not resolved at the time of the subject's discontinuation or completion of the study should have an "outcome" of Not Recovered/Not Resolved at study end in subject source and on an eCRF. The investigator should ensure that subject is aware of any follow-up or additional treatment that is required for any ongoing AE at end of study participation; however, there will be no eCRF entry for the ongoing follow-up.

16.7.2. Notification of Adverse Events

Sponsor Notification:

Initial reporting may be done by phone, fax, e-mail, or on the eCRF completing as much information as is available. The original fully completed AE eCRF must be submitted to Medtronic as soon as possible.

As soon as possible (desired within 24 hours of investigator or study coordinator awareness), the investigational center staff must report all SAE, and SADE to Medtronic. For the previously mentioned events, the AE eCRF will be completed with all known details as soon as possible, this will serve as notification to Medtronic. If the study database cannot be accessed due to technical problems, contact the sponsor via email, phone, fax and provide the known details of the event. Once the access issue has been corrected, the event should be entered onto an AE eCRF.

16.7.3. Expedited Safety Reporting Requirements

Documentation of GCP office and EC notification of any safety event must be kept at the investigational center and a copy sent to the sponsor.

It is the responsibility of the investigator to follow their EC reporting requirements.

Timeframes and mechanisms for the clinical site reporting adverse events to EC, and Medtronic will still refer to NMPA GCP for Medical Devices[23] (China GCP 2022) listed in Table 5.

Table 5. Investigator Reporting Requirements for AE and Device Deficiencies

For the following events, reporting requirements are: • **Serious Adverse Events (SAE)**	
Investigators shall report to (China GCP 2022 Article 32):	
Medtronic	Within 24 hours
GCP office	Within 24 hours
EC	Within 24 hours
For the following events, reporting requirements are: • **All other AEs related with index procedure and/or device.** • **All other safety endpoint AEs** (Refer to Appendix V Safety Endpoint Definitions) • **All Device Deficiencies**	
Investigators shall record adverse events and device deficiencies identified during clinical trials of medical devices. (China GCP 2022 Article 31)	
To Medtronic	Submit AE and DD in a timely manner after the investigator first learns of the event.
To EC and GCP office	Submit event analysis report per EC's requirements

NOTE: In case there is/are additional AE reporting requirement(s) and/or process(es) (e.g. internal hospital policy or province regulatory authority instruction, etc.), these specific AE reporting requirement and process must be documented in a separate cover.

Timeframes and mechanisms for the sponsor submitting adverse events to local regulatory authorities and other clinical Research institutions and investigators participating in the study per the NMPA GCP for Medical Devices[23] (China GCP 2022) are listed in Table 6.

Table 6. Sponsor Reporting Requirements for AE and Other Serious Safety Issues

For the following events, reporting requirements are: • **Investigational device related Serious Adverse Events (SAE)** • **Other serious safety issues that led to clinical study suspension or termination.**	
Medtronic submits to: (China GCP 2022 Article 44)	
The drug regulatory departments in the province, autonomous region or municipality directly under the Central Government where the sponsor is located	Within 7 days after learning that serious adverse events related to death or life-threatening serious adverse events occur on the medical device under clinical trial. Within 15 days after learning that serious adverse events not related to death or non-life-threatening serious adverse events occur on the medical device under clinical trial and the medical device under clinical trial may have other serious safety risks.

For the following events, reporting requirements are: • **Investigational device related Serious Adverse Events (SAE)** • **Other serious safety issues that led to clinical study suspension or termination.**	
	Submit Large scale investigational device related SAEs or other serious safety issues that led to clinical study suspension or termination.
The drug regulatory departments and health administration departments in the provinces, autonomous regions or municipalities directly under the Central Government where the clinical trial institutions of the medical device are located	Within 7 days after learning that serious adverse events related to death or life-threatening serious adverse events occur on the medical device under clinical trial. Within 15 days after learning that serious adverse events not related to death or non-life-threatening serious adverse events occur on the medical device under clinical trial and the medical device under clinical trial may have other serious safety risks. Submit Large scale investigational device related SAEs or other serious safety issues that led to clinical study suspension or termination.
Other clinical trial institutions of the medical device involved in the clinical trial	Within 7 days after learning that serious adverse events related to death or life-threatening serious adverse events occur on the medical device under clinical trial. Within 15 days after learning that serious adverse events not related to death or non-life-threatening serious adverse events occur on the medical device under clinical trial and the medical device under clinical trial may have other serious safety risks. Submit Large scale investigational device related SAEs or other serious safety issues that led to clinical study suspension or termination.
Other Ethics Committees involved in the clinical trial	Within 7 days after learning that serious adverse events related to death or life-threatening serious adverse events occur on the medical device under clinical trial. Within 15 days after learning that serious adverse events not related to death or non-life-threatening serious adverse events occur on the medical device under clinical trial and the medical device under clinical trial may have other serious safety risks. Submit Large scale investigational device related SAEs or other serious safety issues that led to clinical study suspension or termination.
Other principal investigators involved in the clinical trial	Within 7 days after learning that serious adverse events related to death or life-threatening serious adverse events occur on the medical device under clinical trial. Within 15 days after learning that serious adverse events not related to death or non-life-threatening serious adverse events

For the following events, reporting requirements are: • **Investigational device related Serious Adverse Events (SAE)** • **Other serious safety issues that led to clinical study suspension or termination.**	
	occur on the medical device under clinical trial and the medical device under clinical trial may have other serious safety risks. Submit Large scale investigational device related SAEs or other serious safety issues that led to clinical study suspension or termination.

NOTE: In case there is/are additional AE reporting requirement(s) and/or process(es) (e.g. internal hospital policy or province regulatory authority instruction, etc.), these specific AE reporting requirement and process must be documented in a separate cover.

Documentation and Reporting of Device Deficiencies

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

Device deficiencies that did not lead to an adverse event but might have led to a SADE if:

- a suitable action had not been taken, or
- an intervention had not been made, or
- circumstances had been less fortunate,

should be reported to Medtronic as soon as possible after the investigator first learns of the event. Initial reporting may be done by phone, fax, e-mail, or on the eCRF completing as much information as is available. The original fully completed Device Deficiency eCRF must be submitted to Medtronic as soon as possible.

Emergency Contact Details for Reporting SAE, SADE and Device Deficiencies

Investigators should contact their Medtronic clinical study monitor if they have any questions regarding reportable AEs or DDs. Medtronic will provide and maintain a listing of current contact details for each site. In case the investigator requires information from Medtronic in an emergency situation, the investigator may contact Medtronic. A list of contact information will be kept separately.

16.7.4. Product Complaint Handling

The device is market released, therefore, product complaint reporting and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the study and should be done in addition to the AE reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

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 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

17. Provisions for clinical study protocol deviation and the revision of clinical study protocol

17.1. Protocol Deviations

A deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. It is expected that the investigator will conduct this clinical trial in compliance with the CIP and all applicable regulations governing the conduct of clinical research involving human subjects. Failure to do so could result in one or all of the following:

- Investigational center disqualification
- Notification to the regulatory authorities/EC depending on the severity of the deviation and reporting requirements

Examples of protocol deviations include but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain EC approval before the start of the study
- Implanted subject did not meet inclusion or met exclusion criteria[vi]
- Required testing and/or measurements not done or incorrectly done
- Subject does not attend follow-up visit or follow-up visit performed outside window
- Unauthorized use of investigational devices
- Adverse events not reported in the required time frame as required by regulation, the site's EC, or as specified in the Clinical Investigation Plan (CIP)
- Control of study devices not maintained
- Source data permanently lost
- Enrollment of patients during lapse of 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 wellbeing 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).

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

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

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

[vi] Subjects must meet all inclusion/exclusion criteria to be eligible for implantation. However, it will not be considered a protocol deviation if study related testing (e.g., echo, MDCT, Heart Team Assessment) of a consented patient identifies implantation eligibility criteria that are not met.

In addition, investigators are required to adhere to their 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.

17.2. Revisions or Amendments to the Clinical Investigational Plan

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

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

18. Record Retention

The sponsor and investigator will retain all records and documents pertaining to this study in compliance with local regulations. They will be available for inspection by the appropriate regulatory agencies. In addition, the investigator will retain the source documents from which the information entered on the eCRF was derived. These records are to be retained in a secure storage facility maintained by the investigational center for 10 years after completion of the study or termination of the study, whichever is longer. The investigator should not dispose of these records without the approval of the sponsor. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials. The sponsor shall keep the clinical data indefinitely and till no such medical device is used.

In addition, the Medtronic Clinical Research Department should be contacted if the Principal Investigator plans to leave the investigational site.

Investigator may withdraw responsibility to maintain records for the time required by the study protocol by transferring custody to another qualified person willing to accept responsibility for them. Medtronic will report this change within 10 days to the relevant regulatory authorities as necessary.

Medtronic will maintain study records under its responsibility until Evolut PRO is no longer commercially used, or at least 15 years, whichever is longer.

19. Suspension or Early Termination

19.1. Investigational Center Suspension or Termination

Medtronic, EC, or a regulatory authority may decide to suspend or prematurely terminate an investigational center (e.g. if information becomes available that the risk to study subject is higher than initially indicated, business decision, in case of expiring approval of the reviewing EC, non-compliance to the CIP or lack of enrollment). The medical device clinical trial management departments of clinical trial institutions should be notified within 5 days with the rationale in writing. If an investigational center 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 EC and the study subjects.

Clinical study institutions and the researchers discover that risks outweigh potential benefits or have obtained sufficient results to determine the safety and effectiveness of the testing medical devices, when it is required to suspend or terminate clinical studies, they shall inform the testing subjects, and assure them with proper treatment and follow-ups, meanwhile report as required, and provide detailed written explanation. When necessary, they shall report to the department of NMPA of the concerned province, autonomous region and municipality.

Upon receiving notifications that the applicant or ethics committee need to suspend or terminate clinical studies, the researchers shall timely notify the testing subjects, and assure them with proper treatment and follow-ups.

The suspended clinical studies cannot be resumed without permission from EC. Upon completion of clinical studies, the applicant shall send written notice to the management of food and drug administration of the concerned province, autonomous region and municipality.

Medtronic shall ensure that all investigators who conduct the clinical study comply with the clinical investigation plan. In case a clinical research institution and an investigator are found failed to comply with relevant laws and regulations, China NMPA Good Clinical Practice for Medical Devices (China GCP 2022) [23] and this clinical investigation plan, Medtronic shall identify it and implement a course of corrective actions. For serious case or continued case without rectification, Medtronic should terminate the study at this clinical research institution and notify the local Food and Drug Administration (province, autonomous region or municipality as appropriate) where this clinical research institution locates and NMPA.

19.2. Subject Follow-Up In Case of Termination

In case of early investigational center suspension or termination, all subjects should be contacted to plan an early Termination visit at the investigational center. All efforts will be made to complete and report all study observations at the time of termination. The subject will receive appropriate treatment and follow-up as per local standard of care.

20. Direct access to source data/documents

Source Data/Document Access

Entered data must be traceable to source documents. Source documentation is defined as the first time the data appear and may include clinical records, hospital records, procedural reports, autopsy reports, and any other material that contains original information used for study data collection or adverse event reporting.

The eCRFs may not serve as source documents. Source documentation for data elements not routinely captured in medical records (e.g., echocardiography variables, Modified Rankin Score) may vary from site to site: the site may use technical worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. Direct access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

20.1. Investigator Records

At a minimum, the following records must be kept by the investigator:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Investigator's Brochure and/or user guide
- Medtronic and EC-approved Patient ICF
- EC and Regulatory authority approval or notification
- Fully signed clinical study agreements (i.e. including Investigator Statement and Signature Page, Clinical Trial Agreement and Confidential Disclosure Agreement)
- Completed Delegation of Authority Log
- Training documentation of all investigational center staff
- Subject screening log and/or subject identification (SID) log
- Signed, dated and fully executed ICFs
- Source document requirements
- Fully executed eCRFs and corrections
- Report of AEs and Device Deficiencies
- Device accountability records
- CIP Deviation/ CIP Non Compliance, if any
- Clinical Bulletins- A brief official update or summary of current study news on a matter of immediate interest and high importance to investigational center surrounding the CIP.
- Current signed and dated curriculum vitae (CV) of PI (and key study team members if required per local requirements)
- Site-specific summary or Clinical Study Reports (CSRs)

20.2. Investigator Reporting Responsibilities

The Investigator reporting requirements are listed in Table 7.

Table 7. Investigator Reporting Requirements

Report	Submit to	Description/Constraints
Protocol deviation	Sponsor, Management department of medical device clinical study (if required), EC	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Protocol deviation that may affect the subjects' rights and interests, safety, health or the scientificity of clinical trials, including deviation regarding requests and reports. Principal investigators shall report any deviation from the clinical trial protocol in time. (China GCP 2022 Article 34)
Failure to obtain informed consent	Sponsor and EC	Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (ISO 14155:2011)
Progress report	EC and Management department of medical device clinical study (if required)	Principal investigators shall report the progress of clinical trials of medical devices to the Ethics Committee on time. (China GCP 2022 Article 34)
Site-specific summary	Sponsor, EC (if needed per EC requirements)	For multi-center studies: The site-specific summary of each sub-center shall be signed and dated by the principal investigator of the center, reviewed and signed by the clinical trial institution of medical device of the center, and then submitted to the sponsor. The site-specific summary of clinical trials in sub-centers mainly includes personnel information, information of investigational medical devices and control medical devices (if applicable), trial overview, case inclusion, implementation of clinical trial protocol, summary and descriptive analysis of trial data, quality management of clinical trials of medical devices, occurrence and treatment of adverse events and device deficiencies, description of deviation from the protocol, etc. (China GCP 2022 Article 56)
Other	EC and NMPA	An investigator shall, upon request by a reviewing EC, NMPA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation.

20.3.Audits and Inspections

Medtronic may conduct audits at participating clinical sites. The purpose of an audit is to assess clinical study activities independently of the personnel directly involved in the study. Regulatory authorities, such as the NMPA, and ECs may also perform inspections at participating sites. The investigator and/or institution shall permit Medtronic and Regulatory Authority direct access to source data and documents. Any Regulatory Authority inspection announcements shall be forwarded immediately to the Medtronic Clinical Study Manager of this study. A list of contact information will be kept separately.

21. Finance and insurance

If subjects are physically injured as a result of participation in this study, reasonable and appropriate medical treatment will be provided by Medtronic, if such treatment is not already covered by subject's medical insurance according to the local requirements. The sponsor shall undertake treatment expenses and corresponding economic compensation for injuries or death related to clinical studies occurred to testing subjects, except the damage due to mistakes of the medical institutions and their medical staff during diagnosis and treatment, if not addressed in a separate agreement.

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable laws and customs concerning specific insurance coverage. If required, a Clinical Study Insurance statement/certificate will be provided to the EC.

21.1. Clinical Investigation Agreement

A Clinical Investigation Agreement shall be entered into effect by the participating site and/or the principal clinical investigator at each site as per the local legal requirements and returned to Medtronic prior to the commencement of any study activities. The investigator is indicating approval of the Protocol and subsequent amendments, by signing and dating the agreement. Amendments to this protocol shall be agreed upon between Medtronic and clinical investigator(s) and be recorded with a justification for the amendments.

Funding for the study will be defined according to the local regulations and must be agreed upon in writing by the clinical research institution and Medtronic before the study commences. The payments for the study should be appropriate relative to the number of subjects enrolled. The Evolut PRO System will be provided by Medtronic free of charge for use in this clinical study. A reasonable amount of the travel expense for the annual clinic follow-up will be reimbursed. The cost of the medical check-ups which are required by the study will be reimbursed as well. No other compensation for the participation in this study will be provided by Medtronic.

22. Contents included in the clinical study report

The Clinical Study Reports (CSR) shall reflect the clinical trial results comprehensively, completely and accurately, and the data of safety and effectiveness of the clinical trial report shall be consistent with the source data of the clinical trial as described in NMPA China GCP 2022[23] and compliant with NMPA China GCP 2022 Appendix 2 "Template of Clinical Study Report of Medical Devices". Any deviations from original statistical plan and the rationale will be described in the Clinical Study Report. Primary endpoint CSR and subsequent CSRs, along with the CIP, may support the new generation(s) of study devices being commercially available.

23. Confidentiality principle

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

Study data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published.

24. Agreement on trial results publication

This clinical study will be registered in a public clinical trials registry, ClinicalTrials.gov. Study information and study results will be posted. Medtronic is committed to the widespread dissemination of all primary and secondary endpoint results. A Publication Plan will be implemented and followed. During the course of or at the conclusion of the study, a multisite abstract reporting the primary results may be prepared by the Principal Investigators (in collaboration with others including but not limited to the Clinical Events Committee (CEC)). A multisite publication may similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single site experience within the study is not allowed until both the preparation and publication of the multisite results, and then only with written permission from Medtronic.

25. Responsibilities of all parties

Investigator responsibilities will be included in clinical trial agreement and subject responsibilities will be available in Informed Consent Form (ICF). Sponsor will undertake all the responsibilities of the sponsor as required per NMPA regulations.

26. Data Review Committees

26.1. Clinical Events Committee

A Clinical Events Committee (CEC) will provide independent medical review and adjudication of adverse event data used in the endpoint assessment of the investigational device. The CEC will adjudicate all deaths, and all endpoint related events reported by the investigators. The analysis of the study endpoint data will be based on CEC adjudicated events. Endpoint definitions are provided in APPENDIX V: DEFINITIONS: SAFETY ENDPOINTS AND EFFICACY EVENTS.

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

- Cardiac surgery
- Interventional cardiology
- Neurology
- Electrophysiology

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

27. Appendices

I. Names and Addresses of Investigational Centers
II. Echocardiography Procedures
III. MDCT Acquisition Guidelines
IV. STS Calculator and Risk Factors
V. Definitions: Safety Endpoints and Efficacy Events
VI. Study contacts
VII. Sample informed consent form

APPENDIX I: NAMES AND ADDRESSES OF INVESTIGATIONAL CENTERS

List of all clinical trial institutions and investigators for multicenter clinical trial:

Code of clinical trial institution	Name of clinical trial institution	Investigator	Title	Contact information
The list of all clinical trial institutions and investigators will be provided separately in the Investigational Site File (ISF).				

APPENDIX II: ECHOCARDIOGRAPHY PROCEDURES

1.0 Required Exams

Transthoracic echocardiography is required at the following intervals:

Interval	Time Window
Baseline (Pre-implant)	Within 12 weeks prior to Eligibility Review Committee review
Device Success	Between 24 hours and 7 days post procedure
30 days	Between 30 and 45 days post procedure
1 year	Between 365 and 395 days post procedure
Annual up to 5 years	Between implant anniversary date and 30 days after

2.0 General Imaging and Recording Procedures

- A list of recommended images is provided in Section 2.1.
- 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. 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 storage and transmission if necessary.
- The following information was documented on CD-R disks and sent to the Echo Core Lab for evaluation during the pre-market setting. Echo core lab will not be utilized via implementation of Clinical Investigation Plan (CIP) Version 5.0 :
  - Study site ID number
  - Subject ID number
  - Exam date
  - Study interval

2.1 List of Recommended Images

Parasternal long-axis window

- 2D gray scale standard view (LV in a sagittal section)

- 2D color Doppler for mitral regurgitation (MR)
- 2D color Doppler of aortic (or prosthetic) regurgitation (AR)
- If AR is present, ZOOM & narrow sector with focus on vena contracta of regurgitant jet
- 2D gray scale ZOOM for LV outflow tract diameter (LVOT)
- Frozen image of measured LVOT diameter
- 2D gray scale; ZOOM at an intercostal space higher for aortic root / aortic prosthesis

Parasternal short-axis window

- 2D grayscale LV at mitral valve level
- 2D grayscale LV at papillary muscle level
- 2D grayscale-guided M-mode at LV minor axis (LV dimensions, avoid papillary muscles)
- Frozen image of measured LV dimensions (without measurements)
- 2D grayscale LV at apical level
- 2D grayscale aortic valve level (post TAVI the native annulus is usually identified by maximal calcification)
- 2D color Doppler of AR: post TAVI 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)

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

Apical 4-Chamber window

- 2D grayscale standard view
- 2D color Doppler of MR
- If MR is present, ZOOM & narrow sector, shift Nyquist 35-40 for PISA measurements
- If MR is present, CW Doppler of MR jet (frozen image)
- 2D color Doppler of TR
- If TR is present, CW Doppler of TR jet (frozen image without measurement)
- Frozen image of TR jet velocity with measurements
- 2D grayscale focussed on LV with decreased depth
- PW Doppler of transmitral flow at mitral valve tips (frozen image)

Apical long–axis view

- 2D grayscale standard view
- 2D color Doppler of AR
- If AR is present, ZOOM & narrow sector, shift Nyquist 35-40 for PISA measurements
- If AR is present, CW Doppler of AR jet (frozen image without measurement)
- Frozen image of CW Doppler of AR jet (with measurements)
- CW Doppler of aortic/prosthetic valve (frozen image without measurement)
- Frozen image of measured aortic/prosthetic valve velocity
- PW Doppler LVOT (native aortic valve): within 0.5 – 1 cm below native aortic valve (frozen image without measurements

- PW Doppler LVOT (post –implant) immediately proximal to inflow of stent (frozen image without measurements)
- Frozen image: measured LVOT velocity

Apical 2-Chamber view

- 2D grayscale standard view
- 2D grayscale focused on LV with decreased depth

Sub-costal Position

- 2D grayscale; long-axis view
- 2D grayscale; short-axis view
- 2D grayscale: IVC and hepatic vein
- IF AR mild by color Doppler, PW Doppler from descending aorta (frozen image)

Supra-Sternal Position

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

Right Parasternal Position

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

Results Reporting

- Screen prints of all results pages

3.0 Data Requirements

Sites should obtain the appropriate images and Doppler recordings and keep in site, reportable variables are listed below. Procedures for acquiring key variables are described in Section 4, Acquisition of Key Variables.

- Height[vii] and Weight
- Left ventricular outflow tract (LVOT) diameter in mid systole
- Max aortic/prosthetic valve velocity (V_2) by CW Doppler
- Aortic valve velocity time integral (VTI) by CW Doppler
- Mean gradient across aortic valve (MGV_2) by CW Doppler
- LVOT VTI by PW Doppler
- Grade of aortic/prosthetic transvalvular regurgitation
- Grade of 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

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)[31]
- Body mass index
- Peak aortic pressure gradient
- Aortic valve area (AVA)/effective orifice area (EOA) by continuity equation
- Aortic valve area/effective orifice area index
- Doppler Velocity Index

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

4.0 Acquisition of Key Variables

[vii] Height will be collected at the baseline (pre-implant) exam only. Height for the post-implant exams will be derived from the baseline height

4.1 LVOT Diameter

Pre-implant LVOT diameter is measured from the inner edge to inner edge of the septal endocardium, and the anterior mitral leaflet in mid-systole (Figure 6A and B).[32,33] Following implantation, LVOT diameter is measured from the parasternal long-axis view, immediately proximal to the inflow aspect of the stent, and in mid systole (Figure 6C and Figure 6D).[32,33,34]

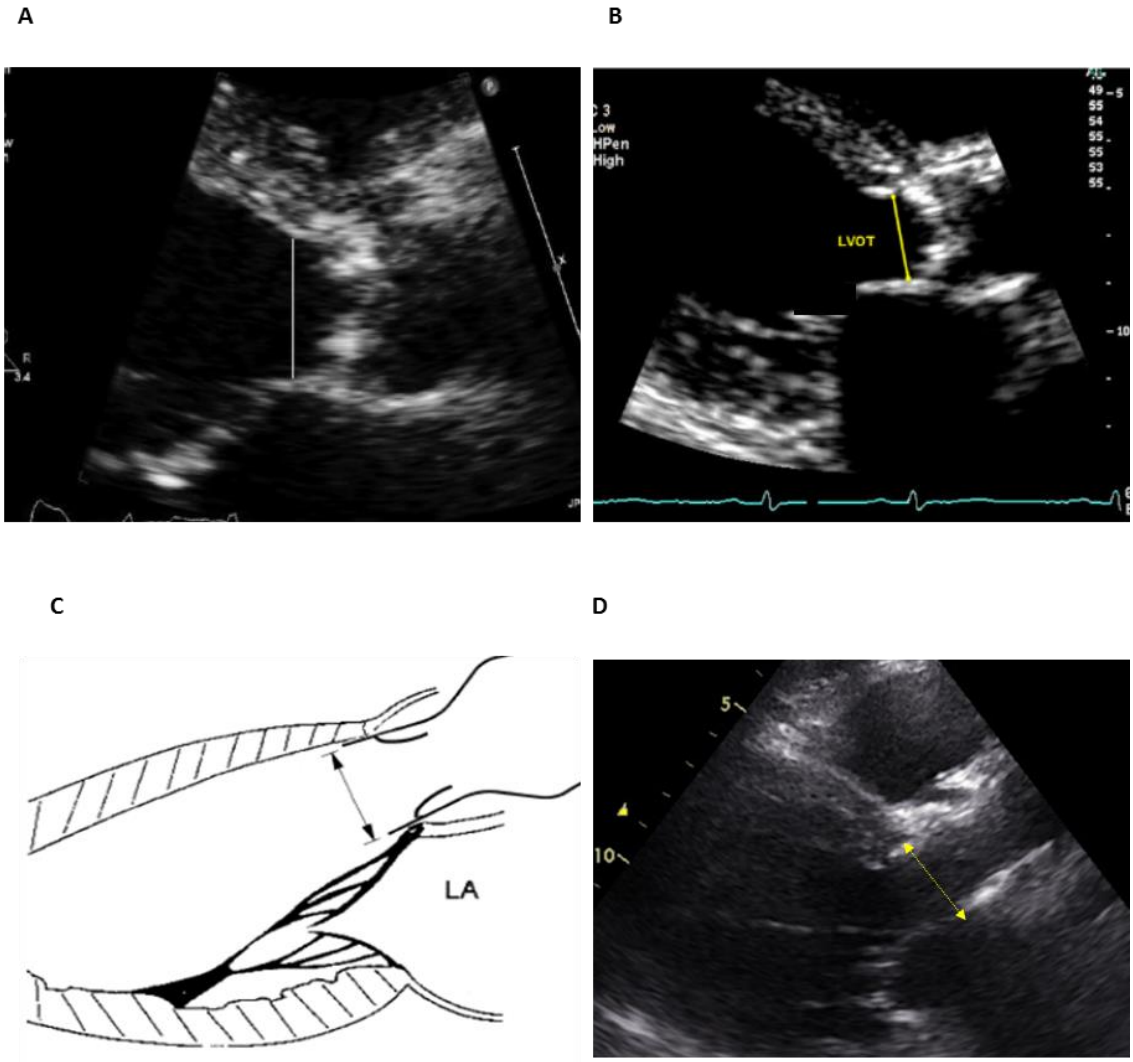


Figure 6. Left ventricular outflow tract (LVOT) diameter measurements

(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 implantation, LVOT diameter measurement is from outer edge to outer edge of the inflow aspect of the stent.

4.2 LVOT Velocity

LVOT velocity is recorded with PW Doppler from the apical position, in either the apical long-axis view or in the anteriorly angulated four-chamber view (or "5-chamber view"). For pre-implant exams, the PW sample volume should be positioned just proximal to the aortic valve, with care to avoid the zone of pre-valve acceleration (usually 0.5 to 1.0 cm proximal to the cusps, Figure 7A).[32]

Post TAV implantation, the sample volume should be placed proximal to the inflow aspect of the stent.[33] Full-screen imaging of the Evolut PRO TAV should be used to verify positioning of the sample volume below the stent before switching to spectral Doppler mode (Figure 7C and Figure 7D).[34,35] The LVOT VTI is measured by tracing the modal velocity (middle of the dense signal) for use in the continuity equation.[32]

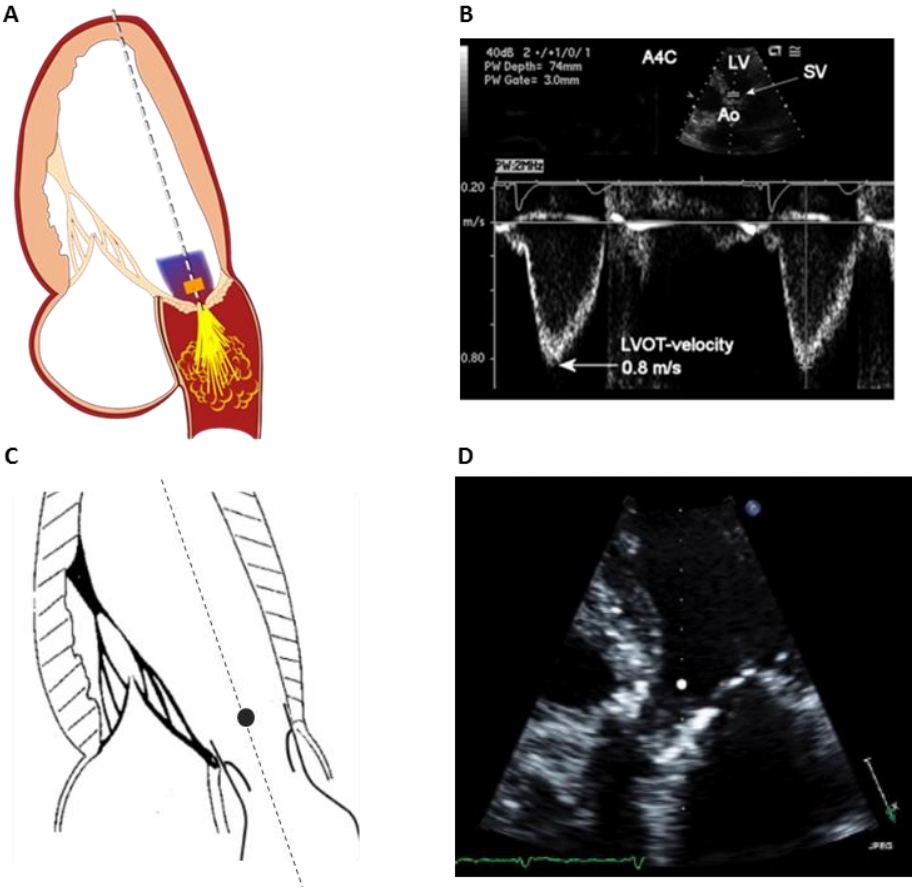


Figure 7. LVOT velocity recording

(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 stent; **(D)** Full-screen imaging of stent to ensure positioning of sample volume below the stent.

4.3 Aortic Valve Velocities

The 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 8).[32]

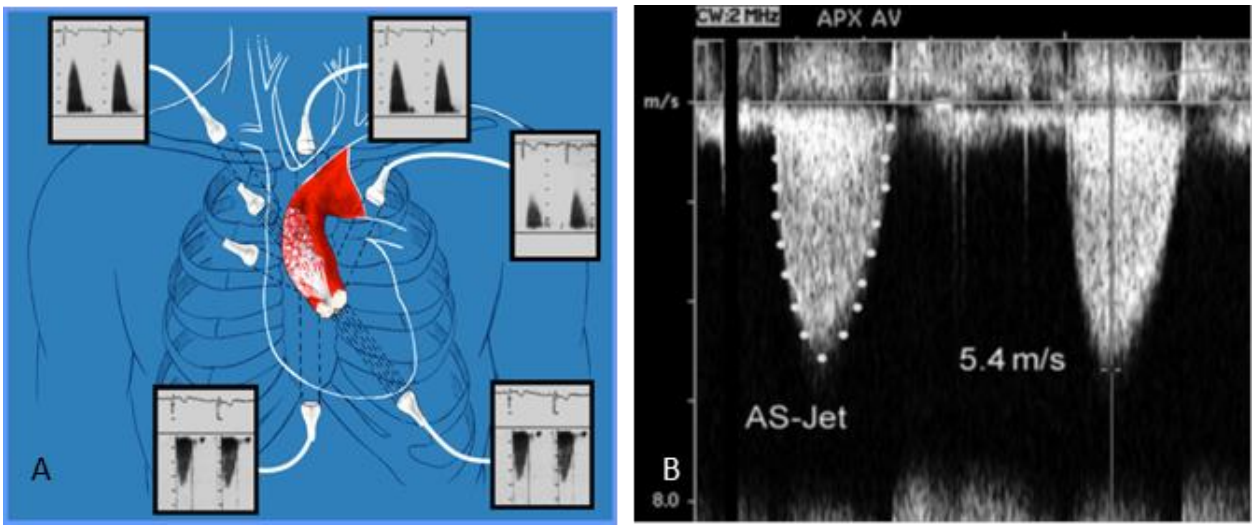


Figure 8. Aortic valve velocities

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

4.4 Assessment of Prosthetic Aortic Regurgitation

An integrated exam approach using color flow, pulsed-wave (PW), and continuous-wave (CW) Doppler is used to assess the severity of transvalvular and paravalvular aortic regurgitation (AR). Color flow Doppler imaging should be performed from the parasternal long and short-axis views, and the apical long-axis and/or 5-chamber views. In the short axis view, color imaging should be performed at multiple levels (from level of the leaflets to below the skirt and frame to assess paravalvular regurgitation, and at the coaptation point of the leaflets for transvalvular (central) regurgitation.[36,37]

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 8.[37] 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 8. 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 semi-quantitative)						
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	Usually present	Present	
Proximal flow convergence visible	Absent	Absent	Absent	Possible	Often present	Often present
Vena contract width (mm)	<2	<2	2-4	4-5	5-6	>6
Vena contract 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 (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	Holodiastolic (end-diast. Vel. >20 cm/s)	Holodiastolic (end-diast. Vel. >25 cm/s)	
Circumferential extent of PVR (%)	<10	<10	10-20	20-30	>30	>30
Doppler parameters (quantitative)						
Regurgitant volume (ml/beat)	<15	<15	15-30	30-45	45-60	>60
Regurgitant fraction (%)	<15	<15	5-10	10-20	20-30	>30
Effective regurgitant orifice area (mm^2)	<5	<5	5-10	10-20	20-30	>30

4.5 Assessment of Mitral Regurgitation

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

Mitral regurgitant (MR) jets should be recorded with CW Doppler using a velocity scale that allows assessment of the density, shape, duration, and peak velocity of the MR jet. If the severity appears moderate or greater by visual assessment, pulmonary vein velocities should be recorded with PW Doppler to assess for the presence of systolic flow reversal. Grading of the severity of mitral regurgitation should be integrative using the parameters in Table 9.[38]

Table 9. Parameters for evaluation of the severity of mitral regurgitation

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

4.6 Assessment of Tricuspid Regurgitation

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

Tricuspid regurgitant (TR) jets should be recorded with CW Doppler using a velocity scale that allows assessment of the density, shape, duration, and peak velocity of the TR jet. If the severity appears moderate or greater by visual assessment, hepatic vein velocities should be recorded with PW Doppler to assess for the presence of systolic flow reversal. Grading of the severity of tricuspid regurgitation should be integrative using the parameters in Table 10.[38]

Table 10. Parameters for evaluation of the severity of tricuspid regurgitation

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

4.7 Assessment of Left Ventricular Function and Left Atrial Size

Dimensions of the left ventricle and left atrium should be obtained by either 2-D linear measurements or using 2-D guided m-mode from either the parasternal long or short axis views (Figure 9). Left ventricular chamber dimensions, septal thickness, and posterior wall thickness are measured using the American Society of Echocardiography (ASE) measurement convention[37] (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.

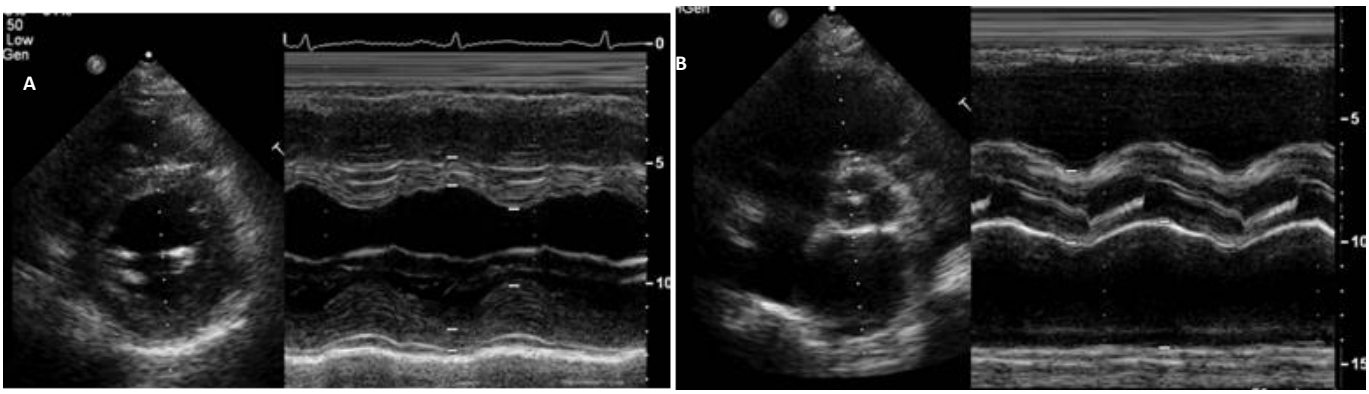


Figure 9. Left ventricle and left atrium measurements

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

5.0 Core Lab Analysis

Protocol-required echocardiograms were required to sent to the Echo Core lab for assessment during the pre-market setting (i.e., through CIP Version 4.0): the data generated by the Echo Core Lab was the primary data used for analysis and reporting. Received echocardiograms were logged in and analyzed by the Echo Core Lab according to their procedures determined for this study. Echo core lab will not be utilized via implementation of Clinical Investigation Plan (CIP) Version 5.0.

The Echo Core Lab was required to 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
- 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

Qualitative grading of valvular regurgitation will be performed using the criteria described in Sections 4.4 through 4.6. 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.[39]

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[viii]

- 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

- 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 $kg^{0.425}$)

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

APPENDIX III: MULTI-SLICE COMPUTED TOMOGRAPHY ACQUISTION GUIDELINES

1.0 Introduction

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

2.0 General Requirements

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

3.0 ECG-gated Contrast Enhanced Scan of Aortic Root

Retrospective ECG-gated scans are recommended, which allows for reconstruction in various phases of the cardiac cycle and optimal evaluation of anatomic dimensions and valve morphology. Recommended scan parameters are listed in Table 11.

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

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

3.1 Post processing

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

Table 11.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.

3.2 Required Aortic Root Measurements

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

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

3.2.1 Reformatting of Images[40]

- 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 10, upper left panel).
- In the sagittal window, the horizontal line is rotated clockwise or counter-clockwise to align with virtual basal plane (Figure 10, 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 11). 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.

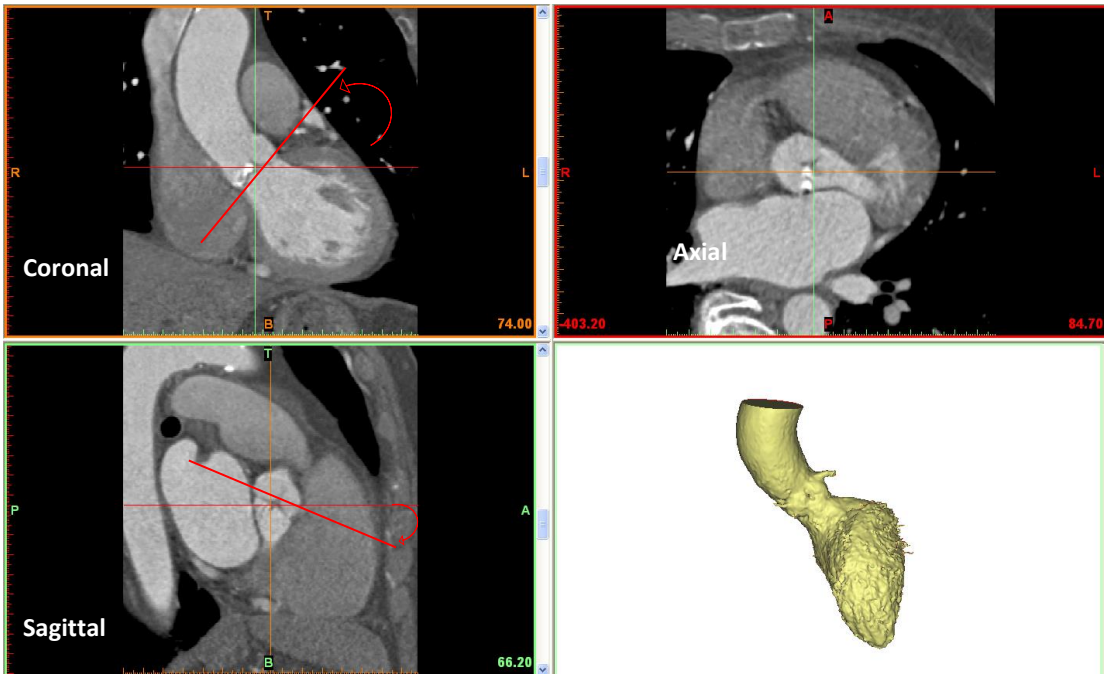


Figure 10. Example images in original orientation (axial, coronal, and sagittal)

Red curved arrow and line indicate adjustment of coronal and sagittal planes to align with aortic basal annulus.

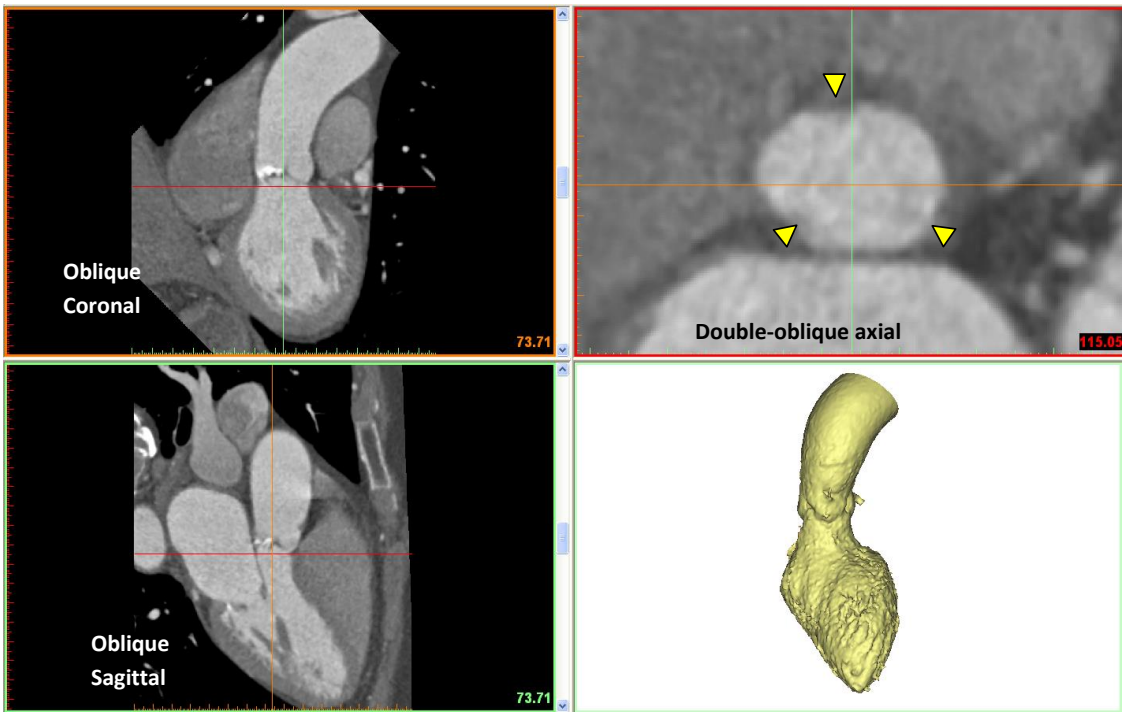


Figure 11. Example images of reformatted oblique coronal, oblique sagittal, double oblique axial, and 3D reconstruction

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

3.2.2 Aortic Annulus Measurements

- Choose the cleanest systolic images for the aortic annulus measurements, either automatically (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, as described in Section 3.2.1, Reformatting of Images.
- Trace the perimeter of the basal annulus (Figure 12, 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 12, right).

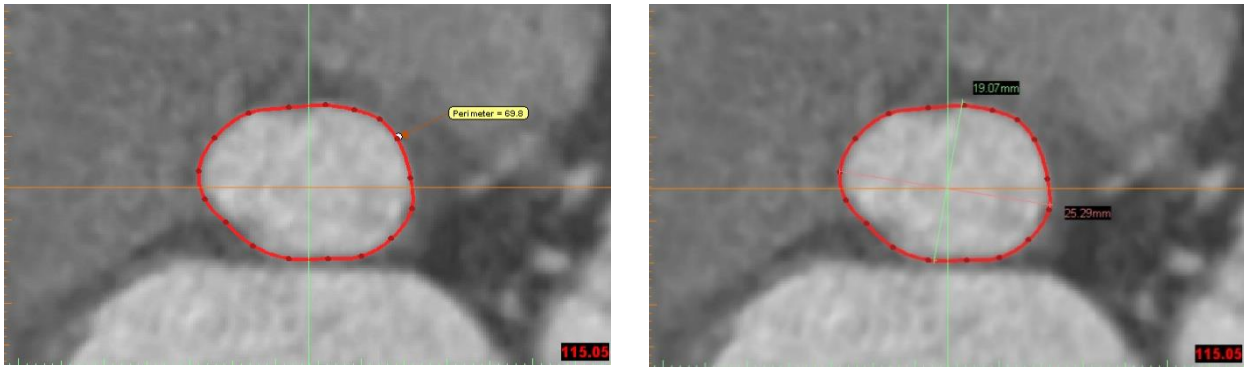


Figure 12. Aortic annulus measurements

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

3.2.3 Sinus of Valsalva Measurements

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

Sinus of Valsalva Diameters

- Select the double oblique axial image where the widest portion of the three sinuses is visible.
- For tricuspid aortic valves, measure a diameter from each commissure through the site of the root to the opposite sinus. Complete for all three sinuses (Figure 13, left). For Sievers Type 1 bicuspid aortic valves, measure the commissure to opposing sinus using a single line measurement tool; complete for all three sinuses (Figure 13, right).

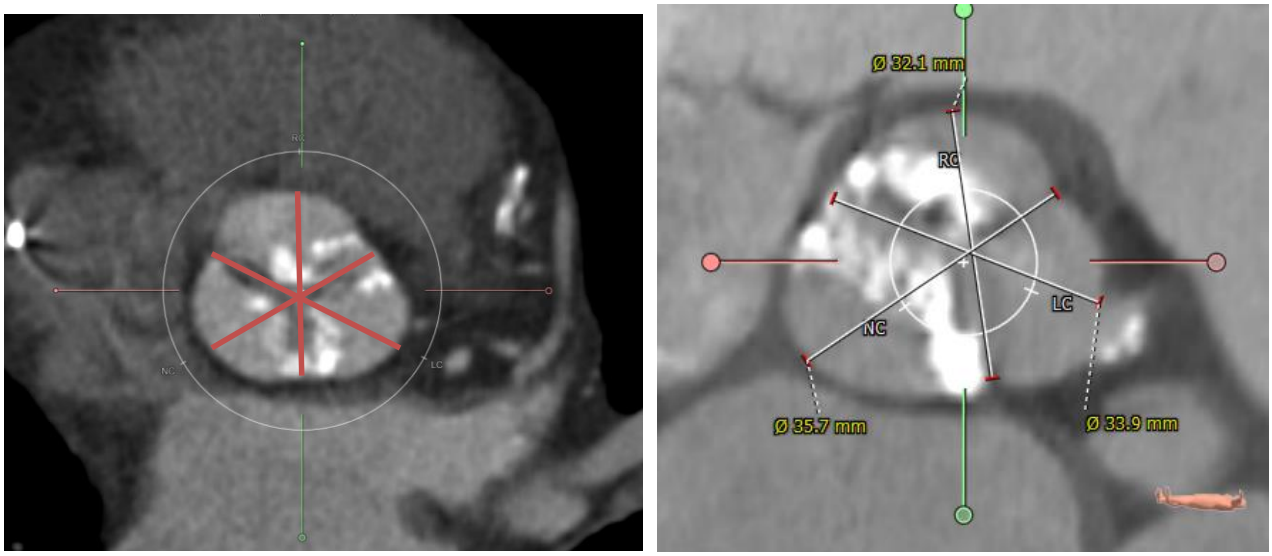


Figure 13. Examples of Sinus of Valsalva diameters

Examples of tricuspid valves (left) and Sievers Type I bicuspid valves (right).

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 14).

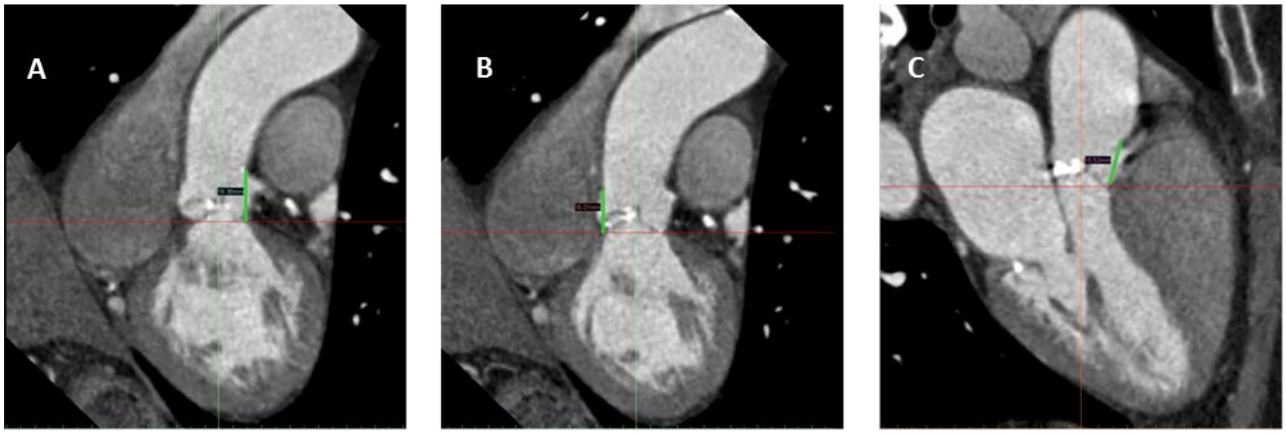


Figure 14. Examples of Sinus of Valsalva heights

(A) left coronary; (B) non-coronary; (C) right coronary

4.0 Anatomic Suitability and Valve Size Selection

TAV Size	Aortic Annulus		Sinus of Valsalva	
	Perimeter (mm)	Mean Diameter (mm)	Mean Diameter (mm)	Mean Height (mm)
23 mm	56.5 – 62.8	18 – 20	≥ 25	≥ 15
26 mm	62.8 – 72.3	20 – 23	≥ 27	≥ 15
29 mm	72.3 – 81.7	23 – 26	≥ 29	≥ 15

APPENDIX IV: STS CALCULATOR AND RISK FACTORS

1.0 STS Calculator

STS-PROM scores are to be calculated using the current Risk Model and Variables – STS Adult Cardiac Surgery Database at http://riskcalc.sts.org/stswebriskcalc/#/calculate. The risk model and variable definitions are provided within the database[41].

2.0 Other Factors Not Captured by Traditional Risk Score[1]

Co-morbidity	Definition/Criteria
Porcelain aorta or severely atherosclerotic aorta	Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible.
Frailty	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence Criteria: • 5-meter walking time • Grip strength* • BMI <20 kg/m2 and/or weight loss 5 kg/yr • Serum albumin <3.5 g/dL • Cognitive impairment or dementia
Sever liver disease/cirrhosis	Any of the following: • Child-Pugh class C • MELD score ≥10 • Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt • Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction
Hostile chest	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications from prior surgery • Evidence of severe radiation damage (e.g., skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) • History of multiple recurrent pleural effusions causing internal adhesions
IMA or other critical conduit(s) crossing midline and/or adherent to posterior table of sternum	A patent IMA graft that is adherent to the sternum such that injuring it during re-operation is likely. A patient may be considered extreme risk if any of the following are present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. • The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3 mm of the posterior table.
Severe pulmonary hypertension	Primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure

Co-morbidity	Definition/Criteria
Severe right ventricular dysfunction	Criteria as defined by the guidelines (e.g., TAPSE <15mm, RV end-systolic area >20 cm^2, etc.)

APPENDIX V: DEFINITIONS: SAFETY ENDPOINTS AND EFFICACY EVENTS

Definitions of adverse events to be evaluated as clinical safety endpoints, other TAVI-related complications, and efficacy events are provided in Sections 1.0, 2.0, and 3.0, respectively. Site investigators will classify the causal relationships between the event and the TAV, the delivery catheter system, and the TAVR implant procedure according to the definitions provided on Section 4.0.

1.0 Safety 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 (>72 h after the index procedure)	Any of the following criteria: 1) Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least 1 of the following: • Symptoms of ischemia • ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)] • New pathological Q-waves in at least 2 contiguous leads

Myocardial Infarction	
	• Imaging evidence of a new loss of viable myocardium or new wall motion abnormality 2) Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. 3) Pathological findings of an acute myocardial infarction

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 Classifications

Stroke and TIA
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

Bleeding Complications	
Life-threatening or disabling bleeding	1) Fatal bleeding *(BARC type 5)* OR 2) Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome *(BARC type 3b and 3c)* OR 3) Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* OR 4) Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* *(BARC type 3b)*
Major bleeding *(BARC type 3a)*	1) Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND 2) Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding *(BARC type 2 or 3a, depending on the severity)*	Any bleeding worthy of clinical mention (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 Consortium29; RBC: red blood cell	

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

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

Acute Kidney Injury (up to 7 days post procedure)	
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, pseudoaneuysms, hematomas, percutaneous closure device failure) *not leading to* death, life-threatening or major bleeding*, visceral ischemia, or neurological impairment OR 2) Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR 3) Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR 4) Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)
Percutaneous closure device failure	Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

*Refer to VARC bleeding definitions[1]

VALVE DYSFUNCTION REQUIRING REPEAT PROCEDURE
Any valve dysfunction that requires repeat procedure (e.g., balloon valvuloplasty, TAVI, or surgical AVR)

2.0 Other TAVI Related Complications

Complication	Definition
Conversion to open surgery	Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications
Unplanned use of cardiopulmonary bypass	Unplanned use of CPB for hemodynamic support at any time during the TAVI procedure
Coronary artery obstruction	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the CoreValve™ Evolut™ PRO prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVI procedure.
Ventricular septal perforation	Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI 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 CoreValve™ Evolut™ PRO) of the mitral valve during or after the TAVI procedure
Cardiac tamponade	Evidence of new pericardial effusion associated with hemodynamic instability and clearly related to the TAVI procedure
Prosthetic valve thrombosis	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. **Valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve related should not be reported as valve thrombosis*.
Valve migration	After initial correct positioning, any observed movement (upward or downward) of the Evolut PRO within the aortic annulus from its initial position, with or without consequences.
Valve embolization	The Evolut PRO moves during or after deployment such that it loses contact within the aortic annulus **Note:** Valve embolizations are not applicable to valve that move during the procedure but are able to be recaptured and repositioned.
Ectopic valve deployment	Permanent deployment of the Evolut PRO in a location other than the aortic root
TAV in TAV deployment	Additional valve prosthesis is implanted within a previously implanted CoreValve™ Evolut™ PRO because of sub-optimal device position and/or function, during or after the index procedure. Note: TAV in TAV deployment is not a reintervention as it captures valve in valve deployment during the index procedure and Percutaneous Reintervention – TAV in TAV Deployment captures valve in valve deployment 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).

Complication	Definition
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
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).
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.
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.

PROSTHETIC VALVE ENDOCARDITIS
Any of the following: 1) Fulfillment of the following Duke criteria[42] for definite endocarditis:

PROSTHETIC VALVE ENDOCARDITIS
• Histologic and/or microbiologic evidence of infection at surgery or autopsy, or • 2 major criteria, or • 1 major criteria and 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 CoreValve™ Evolut™ PRO at autopsy

3.0 Efficacy Event Definitions

PROSTHETIC VALVE DYSFUNCTION	
Stenosis: moderate/severe	Any of the following 1) Peak aortic velocity >4 m/s OR mean aortic gradient >40 mmHg, AND EOA <0.8 cm^2.

PROSTHETIC VALVE DYSFUNCTION	
	2) Peak aortic velocity >4 m/s OR mean aortic gradient >40 mmHg, AND EOA ≥0.8 cm^2, and DVI <0.25, 3) Peak aortic velocity ≤4 m/s and mean aortic gradient ≤ 40 mmHg, AND EOA <0.8 cm^2, and DVI <0.25
Paravalvular regurgitation: moderate	Moderate paravalvular regurgitation (per echo criteria in CIP, Table 8)
Paravalvular regurgitation: severe	Severe paravalvular regurgitation (per echo criteria in CIP, Table 8)
Transvalvular regurgitation: moderate	Moderate transvalvular regurgitation (per echo criteria in CIP, Table 8)
Transvalvular regurgitation: severe	Moderate or severe transvalvular regurgitation (per echo criteria in CIP, Table 8)
Total regurgitation: moderate	Moderate total regurgitation (per echo criteria in CIP, Table 8)
Total regurgitation: severe	Severe total regurgitation (per echo in CIP, Table 8)

Notes:

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

4.0 Classification of Causal Relationships

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

Causal relationships between event and the TAV

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

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

Causal relationships between event and the TAVR delivery system

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

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

Causal relationships between event and the TAVR implant procedure

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

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

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

APPENDIX VI: STUDY CONTACTS

Sponsor:	Medtronic CoreValve LLC [redacted]
Local Sponsor (Project & Site Management):	Medtronic (Shanghai) Management Co., Ltd [redacted]
Monitoring & Site Management	Medtronic Clinical & Regulatory Solutions (MCRS)
Clinical Events Committee:	Baim Institute for Clinical Research [redacted]

The detailed contact list will be kept separate from the CIP and provided to the investigators. Medtronic will maintain an updated list. For specific contact information of the core members (e.g. Medical expert) refer to the detailed list.

For the relevant qualification documents of Medtronic refer to the EC review document package.

APPENDIX VII: SAMPLE INFORMED CONSENT FORM

Sample Informed Consent Form will be provided in a separate cover.

28. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted]
2.0	• Sections 6.0 and 7.2.1: Revised to correct outer wrap description from 2.0 to 1.5 cells. Rationale: align with engineering documents and IB. • Section 7.2.3 Figure 2: Corrected loading system name from Evolut PRO to EnVeo PRO • Section 16.6: Removed reference to "AE code list' and added 'The AE code list will be provided under a separate cover.' • Section 16.7.3, Table 5: Removed 'with SADE potential' as the Investigator should submit all AEs and DDs to Medtronic • Section 21.1: Added 'The cost of the medical check-ups which are required by the study will be reimbursed as well.' for consistency with the Patient Informed Consent Form • Minor formatting changes throughout	[redacted]
3.0	• Cover and Content: Updated lead site name, lead site investigator, the co-investigator • Section 5.3: deleted "vendor". • Section 9.1.1.4: Other Outcome Measures • Added New York Heart Association (NYHA) functional classification at 30days. • Section 9.2.7.5 and 9.2.7.6: Revised the paragraph for Device Malfunction or Explant.	[redacted]

	• Section 9 (including fig.4): Added the point of screening and revised the point of enrollment and the related sections. • Content: Revised “AE” to “Ae”, “Ec” to “EC”. • Fig1 and Appendix VI: STUDY CONTACTS: Delete Pathology Core Laboratory; Update Monitoring & Site Management. • Appendix V: revised “Moderate paravalvular regurgitation” to “Moderate transvalvular regurgitation”.	
4.0	• Investigational Product Registration Approval Status Update • Device Success Analysis Cohort Correction • Supplemental Definitions for CIP Appendix V, Section 2.0- Other TAVI-related Complications • Updated all relevant sections to align with requirements of new NMPA GCP for Medical Devices • Fig1 and Appendix VI: STUDY CONTACTS: Delete Wuxi Clinical Development Services and replace with Medtronic Core Clinical Solutions. • Miscellaneous administrative updates/corrections throughout	[redacted]
5.0	• Study design transferred from a pre-market to a post-market study • Deleted Echo Core lab • Safety reporting update from collecting all AEs to only collect SAEs, index procedure and/or device related AEs and safety endpoint AEs (Refer to Appendix V Safety Endpoint Definitions Safety Endpoint Definitions)	[redacted]

	• Added 16.7.4 Product Complaint Handling pursuant to current product market release status • Updated Appendix IX V: TAV in TAV deployment definition to add note and Endocarditis definition error typo correction. • Miscellaneous administrative updates/corrections throughout	

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