	8. Valve-related dysfunction requiring repeat procedure at 30 days, one year, and annually through 10 years 9. Repeat hospitalization for aortic valve disease at 30 days, one year, and annually through 10 years 10. Repeat hospitalization for ascending aorta disease at 30 days, one year, and annually through 10 years 11. Hemodynamic performance metrics by Doppler echocardiography • Mean aortic gradient at baseline, 30 days, one year, annually through 5 years and at years 7 and 10 • Effective orifice area at baseline, 30 days, one year, annually through 5 years and at years 7 and 10 • Degree of total, peri, and transvalvular prosthetic regurgitation at baseline, 30 days, one year, annually through 5 years and at years 7 and 10 12. New York Heart Association (NYHA) functional classification at baseline, 30 days, one year and annually through 5 years and at years 7 and 10 13. Health-related quality of life as assessed by • Kansas City Cardiomyopathy (KCCQ) instrument at baseline, 30 days, one year, annually through 5 years • EQ-5D survey at baseline, 30 days and one year
Study Design	Multi-center, prospective, single arm
Investigation Sites	Up to 40 sites in the United States
Number of Subjects	150 subjects with attempted implant
Patient Population	Severe aortic stenosis subjects with bicuspid aortic anatomy and an indication for SAVR with a bioprosthesis whose predicted risk of mortality at 30 days is <3% per multidisciplinary local heart team assessment
Key Inclusion Criteria	1. Severe aortic stenosis, defined as follows: For symptomatic patients: • Aortic valve area ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **OR** mean gradient ≥40 mmHg, **OR** Maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest For asymptomatic patients: • Very severe aortic stenosis with an aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** maximal aortic velocity ≥5.0 m/sec, or mean gradient ≥60 mmHg by transthoracic echocardiography at rest, **OR** • Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** a mean gradient ≥40 mmHg or maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** an exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia **OR** • Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** mean gradient ≥40 mmHg, or maximal aortic valve

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

5. Study Design

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

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

- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and endpoint-related adverse events. Safety endpoint results will be based on CEC adjudications.
- All sites will follow a standardized protocol for acquisition of echocardiographic endpoint data.
- An Echocardiography Core Laboratory will evaluate all echocardiograms; echocardiographic endpoint results will be based on Core Lab assessments.
- Study sites should follow their institutional procedures for maintenance of imaging and laboratory equipment used for assessing the study variables.

5.1. Duration

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

5.2. Rationale

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

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

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

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

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

30 days (between 30 to 45 days post implant)

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

One Year (between 365 and 395 days post implant)

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

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

- Clinical assessment
- TTE
- Modified Rankin Score
- KCCQ
- Anti-thrombotic medications
- INR. (for subjects on VKA)
- Adverse events

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

- Clinical assessment
- TTE
- Modified Rankin Score
- KCCQ

8.13. Recording Data

8.13.1. Data Collection

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

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

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

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

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

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

8.13.2. Time Windows for Completion and Submission of eCRFs

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

8.13.3. Data Review and Processing

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

(UADE) (21 CFR 812.3)	death has not been previously identified in nature, severity, or degree of incidence in the investigational plan or application, (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (49).

10.2. Reporting of Adverse Events

10.2.1. Evaluation and Documentation of Adverse Events and Device Deficiencies

Investigators are required to evaluate and document in the subject's medical records all adverse events (AE) and device deficiencies (per the definitions in Table 5) observed in study subjects from the time they are enrolled until they are exited from the study. All AE should be followed through their resolution or until subject's study exit.

All AEs that occur during the study need to be reported to Medtronic via the AE eCRF. Documented pre-existing conditions are not considered to be reportable unless there is a change in the nature or severity of the condition. Pre-existing events should be reported as AE in the situation where a new treatment has to be started or an existing treatment has to be changed to treat the adverse event and the event is accompanied with signs and symptoms. In addition, after the subject has completed his/her two-year follow-up visit, only SAEs and device-related AEs need to be reported to Medtronic.

Unavoidable events are conditions which do not fulfill the definition of an Adverse Event, meaning those medical occurrences, clinical signs (including abnormal laboratory findings), diseases or injuries that are not untoward in nature; specifically, those resulting from the intended injury such as the index TAVR procedure. The events listed in Table 6 are expected for patients undergoing TAVR, and do not need to be reported as AE, unless they occur outside of the stated timeframe, are otherwise considered to be an AE according to the treating investigator, or are suspected or confirmed to be device-related.

Table 6. Non-reportable medical occurrences associated with the index implant procedure

Event	Timeframe (hours) from the Index Procedure
Short transient episode of arrhythmia (including ventricular fibrillation) during index procedure	0
Confusion, anxiety and/or disorientation (other than TIA/stroke) starting within 48 hours with or without medical intervention	120 (5 days)
Temporary change in mental status (other than TIA/stroke) not requiring additional medical interventions or new medical assessments (eg, CT)	72
Dizziness and/or lightheadedness with or without treatment	24
Headache with or without treatment	72
Sleep problems or insomnia with or without treatment	120 (5 days)
Mild dyspnea or cough with or without treatment	72
Oxygen supply after extubation/"forced breathing therapy"	48
Diarrhea with or without treatment	48
Obstipation/Constipation with or without treatment	72
Anesthesia-related nausea and/or vomiting with or without treatment	24
Low-grade fever (<101.3°F or <38.5°C) without confirmed infection	48
Low body temperature	6
Pain (eg, back, shoulder) related to laying on the procedure table with or without treatment	72
Incisional pain (pain at access site) with or without standard treatment and patient not returning to clinic to have additional treatment	No time limit
Pain in throat and/or trachea due to intubation	72
Mild to moderate bruising or ecchymosis	168 (7 days)
Atelectasis/Pleural Effusion not requiring punctuation	168 (7 days)
Edema resulting in weight increase up to 4 kg/9lbs from baseline	168 (7 days)

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

- Date of onset or first observation
- Date of site's first awareness
- AE code number
- Description of the event
- Seriousness of the event
- Causal relationship of the event to the TAV or surgical valve
- Causal relationship of the event to the DCS and/or LS

Event Type	Timeframe for Reporting
Device Deficiency	No later than 72 hours of the investigator's/site's first knowledge of the event

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

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

10.2.4. Documentation and Reporting of Device Deficiencies

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

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

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

11. Data Review Committees

11.1. Clinical Events Committee

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

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

- Cardiac surgery
- Interventional cardiology
- Neurology
- Electrophysiology

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

11.2. Data Safety Monitoring Board

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

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

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

A DSMB charter will be established that describes the Committee roles, responsibilities, and processes. The DSMB will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for safety data review, chairman appointment, and guidelines for study recommendations. The DSMB will meet on a periodic basis to perform a comprehensive data review, including at a minimum, all SAEs and deaths, and will meet more frequently when needed. Safety-related endpoints may also be reviewed at these meetings. DSMB meetings may consist of both open and closed sessions. Medtronic personnel may facilitate the DSMB meeting but will not have voting privileges.

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

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

The DSMB may call additional meetings if, at any time, there is concern about any aspect of the study. All data presented at the meetings will be considered confidential.

12.3. Description of Baseline Variables

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

12.4. Endpoint Analysis

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

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

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

12.6. Primary Efficacy Endpoint #1 – Device Success Rate

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

12.7. Additional Outcome Measures

Additional Outcome Measures are listed as follows:

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

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

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

12.8. Missing Data

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

12.9. Number of Subjects and Investigational Devices, Study Duration

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

Subjects will be consented for follow-up through 10 years. The enrollment period is estimated to be between 12 to 24 months; therefore, the estimated total duration of the study (first subject enrolled to last subject completing his/her last follow-up exam) is estimated to be 12 years. The number of investigational TAVR systems used in the study is estimated to between 150 and 200 (based on sample size).

13. Ethics

13.1. Statement(s) of Compliance

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

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

3.2.1 Reformatting of Images

Reformatting of the images is as follows [53]:

- Site image cross-hairs on aortic root in all windows where it is visible. Lock cross-hairs so they remain orthogonal for all steps.
- In the coronal window, rotate cross-hairs (horizontal line) counter-clockwise to align with virtual basal plane, (Figure 12, upper left panel).
- In the sagittal window, the horizontal line is rotated clockwise or counter-clockwise to align with virtual basal plane (Figure 12, lower left panel).
- On the newly defined double-oblique axial image, scroll up and down through the aortic root until the most caudal attachment points of the three native leaflets come into view (indicated by arrowheads in Figure 13). If one of the leaflets comes into view at a more cranial or caudal slice, adjust the coronal or sagittal cross-hairs until all three leaflets come into view on the same axial slice.
- For confirmation of the correct aortic annulus plane, scroll through the double oblique axial images starting in the mid sinus and ending at the level of the aortic annulus. The sinuses should appear to be relatively the same size at the level of the mid-sinus and the leaflets should all disappear equally at the level of the annulus.

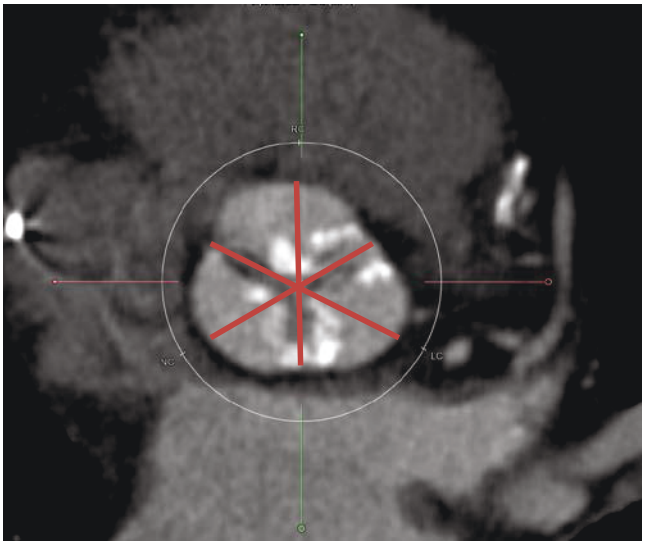

Figure 15. Example of sinus of Valsalva diameters

Sinus of Valsalva Heights

- The sinotubular junction is typically not co-planar with the aortic annulus. Therefore, a sinus of Valsalva height must be measured for each of the three sinuses. This height is defined as the distance between the aortic annular plane and the tallest point in the sinus.
- Choose the double oblique axial image so that it is located at the level of the aortic annulus. The reformatting line representing the double oblique axial image should now be visible in the oblique coronal and oblique sagittal images at the level of the aortic annulus.
- For the left coronary and non-coronary heights, use the oblique coronal image. For the right coronary height, use the oblique sagittal image.
- To complete the measurement, scroll through the oblique coronal or sagittal image (depending on which sinus you are measuring) and locate the heights location of the sinotubular junction. On that image, measure the distance along the path of the aortic root from the aortic annular plane, marked by the reformatting line, to the sinotubular junction (Figure 16).

1.0 STS Factors (continued)

Factor	Definition
Immunocompromise	Indicate whether immunocompromise is present due to immunosuppressive medication therapy within 30 days preceding the operative procedure or existing medical condition. This includes, but is not limited to systemic steroid therapy, anti-rejection medications and chemotherapy. This does not include topical steroid applications, one time systemic therapy, inhaled steroid therapy or preprocedure protocol.
Arrhythmia	History or preoperative arrhythmia (sustained ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial flutter, third degree heart block, second degree heart block, sick sinus syndrome) that has been treated with any of the following modalities: • ablation therapy • AICD • pacemaker • pharmacologic treatment • electrocardioversion, defibrillation
Atrial fibrillation/atral flutter	Presence of atrial fibrillation or flutter within 30 days of the procedure
Myocardial infarction	History of at least one documented myocardial infarction at any time prior this surgery
Endocarditis	Indicate whether the patient has a history of endocarditis. Endocarditis must meet at least 1 of the following criteria: 1. Patient has organisms cultured from valve or vegetation. 2. Patient has 2 or more of the following signs or symptoms: fever (>38°C or >100.4°F), new or changing murmur*, embolic phenomena*, skin manifestations* (ie, petechiae, splinter hemorrhages, painful subcutaneous nodules), congestive heart failure*, or cardiac conduction abnormality. *with no other recognized cause and at least 1 of the following: • organisms cultured from 2 or more blood cultures • organisms seen on Gram's stain of valve when culture is negative or not done • valvular vegetation seen during an invasive procedure or autopsy • positive laboratory test on blood or urine (eg, antigen tests for H mmunocom, S mmunocom, N mmunocompro, or Group B Streptococcus) • evidence of new vegetation seen on echocardiogram and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

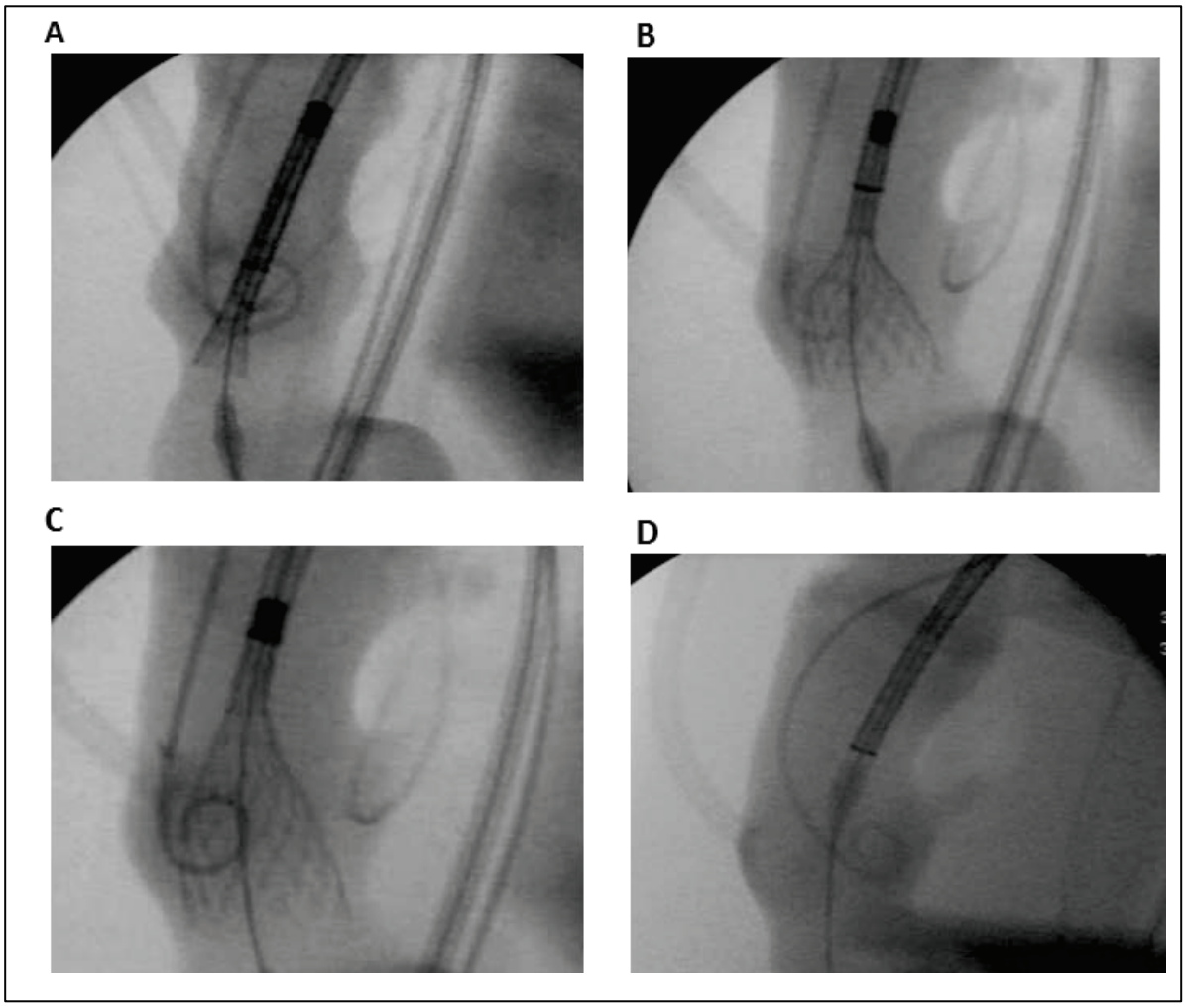

Figure 17. (A) Between 0 and 1/3 of the valve length outside of the capsule **(B)** between 1/3 and 2/3 of the valve length outside of the capsule **(C)** Point of no return: capsule marker in alignment with the spindle marker **(D)** Full recapture: entire valve resheathed into the capsule until there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

1.0 Safety Endpoints (continued)

Stroke and TIA
Diagnostic criteria 1) Acute episode of a focal or global neurological deficit with at least 1 of the following: • change in the level of consciousness • hemiplegia, hemiparesis • numbness or sensory loss affecting 1 side of the body • dysphasia or aphasia • hemianopia • amaurosis fugax • other neurological signs or symptoms consistent with stroke **Stroke:** duration of a focal or global neurological deficit ⩾24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death **TIA:** duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct 2) No other readily identifiable non-stroke cause for the clinical presentation (eg, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the neurologist 3) Confirmation of the diagnosis by at least 1 of the following: • Neurologist or neurosurgical specialist • Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone
Stroke Definitions **Disabling stroke:** an mRS score of 2 or more at 90 days and an increase in at least 1 mRS category from an individual's pre-stroke baseline **Non-disabling stroke:** an mRS score of <2 at 90 days or one that does not result in an increase in at least 1 mRS category from an individual's pre-stroke baseline
Stroke Classifications **Ischemic:** an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue **Hemorrhagic:** an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage **Undetermined**: insufficient information to allow categorization as ischemic or hemorrhagic

Other Implantation/Catheterization Procedure-Related Adverse Events

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

Other Cardiac Adverse Events

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

Respiratory/Pulmonary Adverse Events

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

Other Neurologic Adverse Events

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

Gastrointestinal Adverse Events

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

Hematologic/Oncologic Adverse Events

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

Infection Adverse Events

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

Other Renal Adverse Events (Exclusive of AKI)

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

Allergic Reactions

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

Other

1200 Multi organ failure
1299 Other

4.0 Classification of Causal Relationships

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

Causal relationships between event and the TAV

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

	velocity ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** a left ventricular ejection fraction <50%. 2. Patient is considered low risk for SAVR, where low risk is defined as predicted risk of mortality for SAVR <3% at 30 days per multidisciplinary local heart team assessment 3. Bicuspid aortic valve anatomy (all sub-types) confirmed by MDCT
Key Exclusion Criteria	1. Significant ascending aortopathy requiring surgical repair 2. Ascending aorta diameter >4.5 cm 3. Age <60 years
Subject Evaluation	1. Clinical assessment at pre and post-procedure, discharge, 30 days, 1 year, and annually through 5 years and at years 7 and 10 2. Transthoracic echo at pre and post-procedure, 30 days, 1 year, and annually through 5 years and at years 7 and 10 3. Multi-Detector Computed Tomography at pre-procedure 4. Blood samples at pre-procedure; I.N.R. for subjects on Vitamin K antagonists (VKA) only at discharge, 30 days and annually through 5 years 5. 12-lead ECG at pre-procedure, discharge, and 30 days
Study Co-Chairs	Jeffrey Popma, MD, Interventional Cardiologist Beth Israel Deaconess Medical Center, Boston MA Michael Reardon, MD, Cardiothoracic Surgeon Houston Methodist Hospital, Houston TX
Study Co-Principal Investigators	John Forrest, MD, Interventional Cardiologist Yale University, New Haven CT Basel Ramlawi, MD, Cardiothoracic Surgeon Winchester Medical Center, Winchester VA
Professional Services	• Independent Echocardiography Core Laboratory • Independent Clinical Events Committee • Independent Data Safety Monitoring Committee • Independent Explant Pathology Core Laboratory
Duration	Total study duration is estimated to be 12 years (time from first subject implanted to ten-year follow-up on last subject implanted)

6. Product Description

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

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

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

6.1. Evolut PRO System

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

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

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

Table 1. The Evolut PRO system components

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

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

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

- Adverse events

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

- Clinical assessment
- TTE
- Adverse events

Other Evaluations

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

Visit Windows

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

8.13.4. Source Documents

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

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

Source documents must be retained by the investigational site and made available for monitoring or auditing by the sponsor's representative or representatives of the FDA and other applicable regulatory agencies or IRB/EC.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. Where printouts of electronic medical records are provided as source documents, or where copies of source documents are retained as source documents, they should be signed and dated by a member of the investigation site team indicating they are a true reproduction of the original source document.

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

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

8.13.5. Subject Confidentiality

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

- Causal relationship of the event to the TAVR implant procedure
- Treatment required
- Outcome or status of the event
- Date of resolution
- For all deaths, investigators should assess and document the following information on the Adverse Event eCRF
    - Date of death
    - Primary death category
    - Causal relationship of the event to the TAV or surgical valve
    - Causal relationship of the event to the DCS and/or LS
    - Causal relationship of the event to the implant procedure

In addition, for all endpoint-related adverse events and deaths, sites should submit relevant, de-identified source documents to Medtronic for the Clinical Events Committee (CEC) members to use in their adjudication of the event. The CEC may request source documentation on additional events at their discretion and according to the CEC Charter.

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

10.2.2. Anticipated Adverse Events

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

10.2.3. Adverse Event Reporting Requirements for Clinical Sites

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

Table 7. Required timeframes for adverse event reporting to Medtronic

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

12. Statistical Design and Methods

12.1. Sample Size and Results Reporting

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

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

12.2. Enrolled Subjects and Analysis Sets

Enrolled Subjects

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

Analysis Sets

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

Attempted implant set: The attempted implant set consists of all enrolled subjects with an attempted implant procedure, defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed. Subjects will be analyzed according to their first attempted procedure (TAVR). Day 0 is date of first attempted procedure.

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

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

The study will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with 21 CFR Parts 11, 50, 54, 56 and 812, and ISO 14155:2011.

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

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

13.2. Institutional Review Board

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

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

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

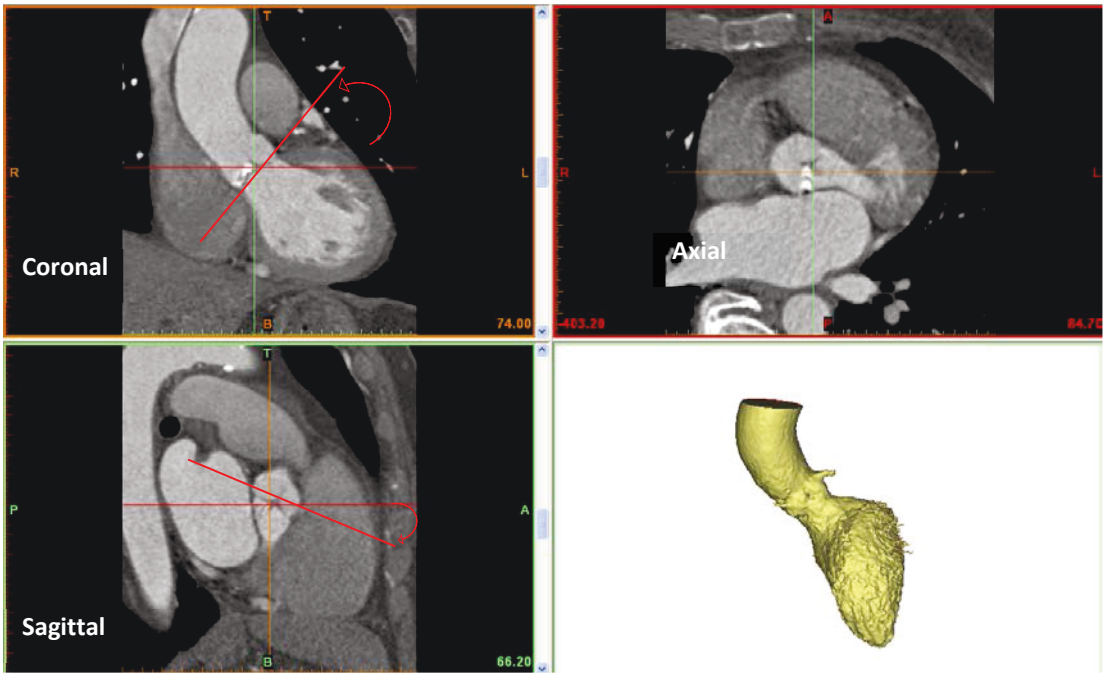

Figure 12. Example images in original orientation (axial, coronal, and sagittal). Red curved arrow and line indicate adjustment of coronal and sagittal planes to align with aortic basal annulus**.**

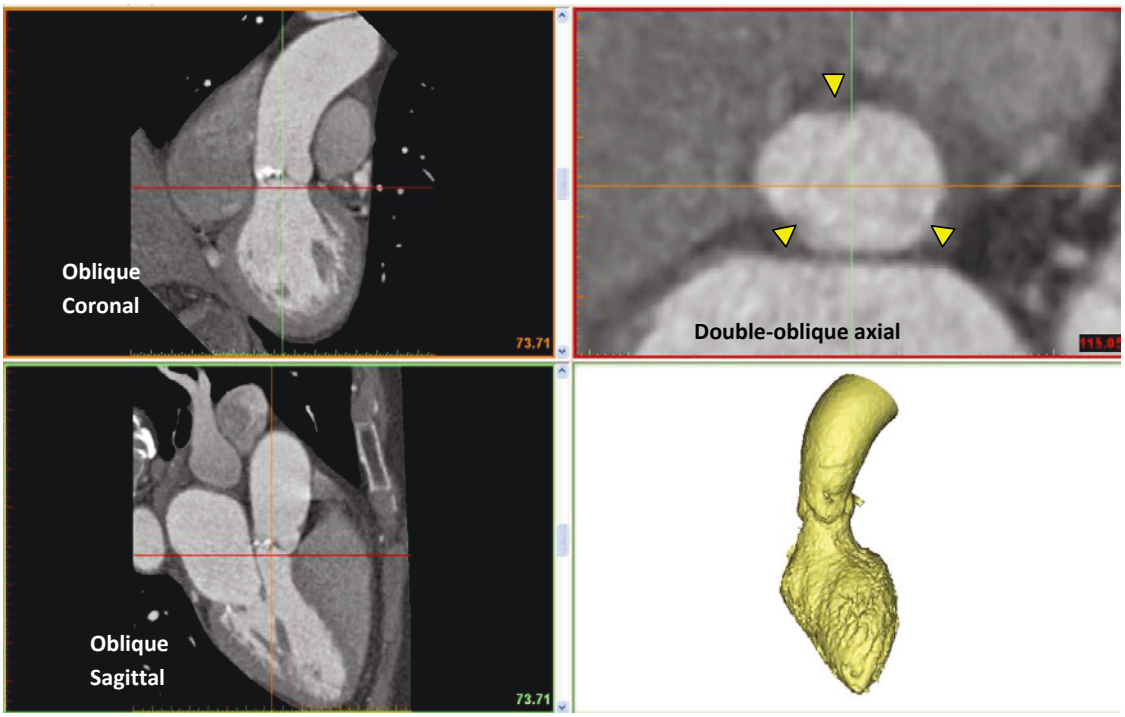

Figure 13. Example images of reformatted oblique coronal (upper left), oblique sagittal (lower left), double oblique axial (upper right), and 3D reconstruction (lower right). Yellow arrowheads indicate most caudal attachment of three leaflets of the aortic valve).

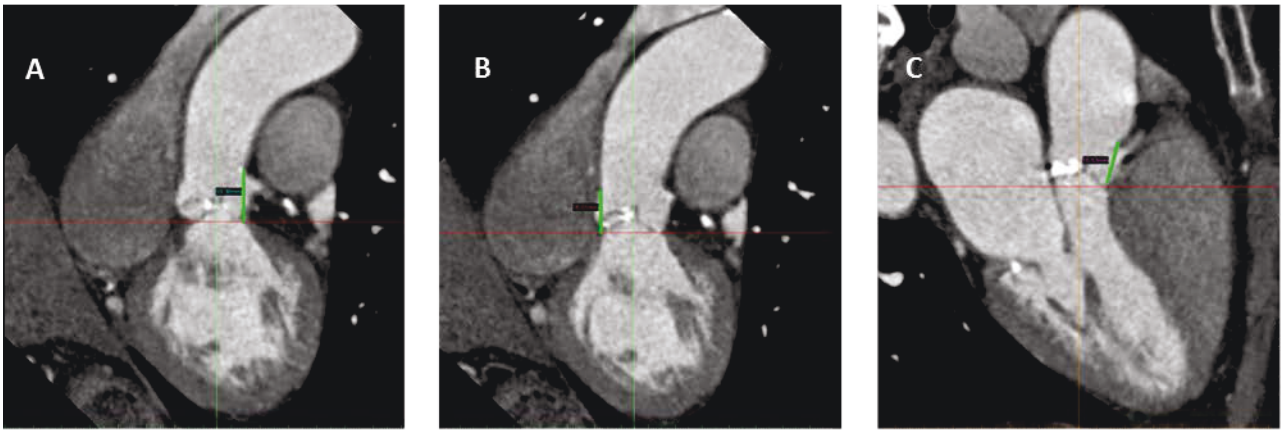

Figure 16. Examples of sinus of Valsalva heights **(A)** left coronary **(B)** non coronary **(C)** right coronary

4.0 Evolut PRO and Evolut R TAV Sizing Matrix

Table 14. Dimensional sizing criteria for Evolut PRO TAV

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

Table 15. Dimensional sizing criteria for Evolut R TAV

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

1.0 STS Factors (continued)

Factor	Definition
Chronic lung disease	Presence of lung disease and severity level as follows: None Mild: FEV1 60% to 75% of predicted, and/or on chronic inhaled or oral bronchodilator therapy. Moderate: FEV1 50% to 59% of predicted, and/or on chronic steroid therapy aimed at lung disease. Severe: FEV1 <60 or Room Air pCO2 >50. CLD present, severity not documented Unknown A history of chronic inhalation reactive disease (asbestosis, mesothelioma, black lung disease or pneumoconiosis) may qualify as chronic lung disease. Radiation induced pneumonitis or radiation fibrosis also qualifies as chronic lung disease. (if above criteria is met) A history of atelectasis is a transient condition and does not qualify. Chronic lung disease can include patients with chronic obstructive pulmonary disease, chronic bronchitis, or emphysema. It can also include a patient who is currently being chronically treated with inhaled or oral pharmacological therapy (eg, beta-adrenergic agonist, anti-inflammatory agent, leukotriene receptor antagonist, or steroid). Patients with asthma or seasonal allergies are not considered to have chronic lung disease.
Peripheral vascular disease	History of peripheral arterial disease (includes upper and lower extremity, renal, mesenteric, and abdominal aortic systems). This can include: • claudication , either with exertion or at rest • amputation for arterial vascular insufficiency • vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (excluding dialysis fistulas and vein stripping) • documented aortic aneurysm with or without repair • positive noninvasive test (eg, ankle brachial index ≤0.9, ultrasound, magnetic resonance or computed tomography imaging of >50% diameter stenosis in any peripheral artery, ie, renal, subclavian, femoral, iliac), or angiographic imaging **Excludes disease in the carotid cerebrovascular arteries, or thoracic aorta. PVD does not include deep vein thrombosis*

APPENDIX V: DEFINITIONS: SAFETY ENDPOINTS AND EFFICACY EVENTS

Definitions of adverse events to be evaluated as clinical safety endpoints, other related complications, and efficacy events are provided in Sections 1.0, 2.0, and 3.0, respectively [54]. The CEC and site investigators will code safety endpoint events according to these definitions, using the associated code list provided on Section 4.0, Event Code List.

1.0 Safety Endpoint Definitions

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

2.0 Other Related Complications

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

Causal relationships between event and the TAVR delivery system

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