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Statistical Analysis Plan

Clinical Investigation Plan Title	Medtronic CoreValve™ Evolut™ PRO System China Clinical Study (Evolut PRO China Clinical Study)
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Initial release	[redacted]
2.0	• Moved text from Section 7.3 to Section to Section 5 and updated Section 7.3. • Removal of Figure 1 Flow chart of study entry process and associated text. This flow chart is in the CIP and is not necessary to include in SAP. • Clarified disposition of subjects in Section 7.1.1. • Modified the K-M method in Section 7.2.2. • Added Per-Protocol set in Section 7.1.3. • Removed NMPA submission language. • Updated the analysis set for Device success. • Added sensitivity analysis to Sections 7.9.1 and 7.9.2.	[redacted]

3.0	• Updated wording in following sections to post-marketing and to align with CIP 5.0
	  ○ Section 3.
	  ○ Section 5.
	• Updated following sections regarding the use of echocardiographic data
	  ○ Added section 7.5 Use of Echocardiographic Data
	  ○ Wording in section 5.1
	• Updated for clarity in section 7.1.3, 7.2.1, 7.2.2, 7.4, 7.10, 8.
	• Replaced duplicate wording in section 7.7 and 7.8 with reference to section 7.2.1
	• Minor formatting updates throughout
		[redacted]

2. List of Abbreviations and Definitions of Terms

Term/Acronym	Definition
AE	Adverse event
AS	Aortic stenosis
AVR	Aortic valve replacement
BAV	Balloon aortic valvuloplasty
CEC	Clinical Events Committee

Term/Acronym	Definition
CIP	Clinical Investigation Plan
CVA	Cerebrovascular accident
EOA	Effective orifice area
EOAI	Effective orifice area index
ERC	Eligibility Review Committee
HIT/HITTS	Heparin-Induced Thrombocytopenia / Heparin-Induced Thrombocytopenia and Thrombosis
ICD	Implantable Cardioverter Defibrillator
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
NMPA	National Medical Product Administration
NYHA	New York Heart Association
PROM	Predicted risk of mortality
RBBB	Right bundle branch block
SAVR	Surgical aortic valve replacement
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
TTE	Transthoracic echocardiography /echocardiogram
VARC	II Valve Academic Research Consortium II
WBC	White blood cell

3. Introduction

This Statistical Analysis Plan has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports. This statistical analysis plan is developed based on the Clinical Investigational Plan (CIP) Revision 5.0. As of CIP 5.0, the study transitioned to the post-market phase.

The purpose 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 will include males and females with severe symptomatic aortic stenosis who are considered at high risk for SAVR. This is a prospective, observational, single arm, interventional, multi-center, post-market study.

Data will be analyzed and Clinical Study Reports (CSRs) will be prepared for the primary endpoint (at 30 days) and annually through 5 years. The final analysis will be performed when all implanted subjects have completed their 5-year follow-up.

4. Study Objectives

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).

4.1 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).

4.2 Secondary Endpoints

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

- Safety
  1) The VARC II 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:
     - 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)

4.3 Additional Outcome Measures

1) Event rates of the following TAVI-related complications:
   - change to surgery
   - need for cardiopulmonary mechanical assistance
   - coronary occlusion or obstruction
   - annular rupture or dissection
   - ventricular perforation
   - mitral valve damage
   - prosthetic valve displacement, migration, or embolism
   - 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 year
    - Mean aortic gradient
    - Effective orifice area
    - 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

5. Investigation Plan

This is a prospective, single arm, multi-center, interventional, post-market study. 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.

The study will be conducted at approximately 6 centers with a maximum of 8 centers in China with approximately 65 subjects with a maximum of up to 70 subjects with an attempted implant using the Evolut PRO system. There is no minimum number of subjects required for each clinical institution. No site will implant more than 20 subjects, excluding the roll-in subjects, without prior authorization from Medtronic. By completion of the enrollment phase, 58 attempted implanted subjects from 4 activated sites were enrolled.

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, or through resolution of potential related adverse events (whichever comes later) to assess safety and then terminated from the study.

Estimating 65 subjects with a maximum of up to 70 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 will be considered “roll-in” subjects. The maximum number of roll-in subjects among all sites will be 20 subjects. 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.

5.1 Measures to Minimize Bias

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

- An Eligibility Review Committee (ERC) will confirm subject eligibility and anatomical suitability.
- 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.

- All sites will follow a standardized protocol for acquisition of echocardiographic endpoint data.
- An independent Echo Core Lab will evaluate all echocardiograms through the 30-days follow up assessment. Echocardiographic study endpoint results through 30 days will be based on core lab assessments.
- Study sites should follow their institutional procedures for maintenance of echocardiography and laboratory equipment used for assessing the study variables.

5.2 Inclusion and Exclusion Criteria

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 $\geqslant$ 8% AND $\leqslant$ 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

Exclusion criteria

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

1. Any condition considered a contraindication for placement of a bioprosthetic valve (e.g., subject is indicated for mechanical prosthetic valve)
2. Age is less than 65 years
3. 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
4. Blood dyscrasias as defined: leukopenia (WBC <1000 mm^3), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states
5. Untreated clinically significant coronary artery disease requiring revascularization
6. Severe left ventricular dysfunction with left ventricular ejection fraction (LVEF) <20% by echocardiography, contrast ventriculography, or radionuclide ventriculography
7. End stage renal disease requiring chronic dialysis or creatinine clearance <20 cc/min.
8. Ongoing sepsis, including active endocarditis
9. Any percutaneous coronary or peripheral interventional procedure with a bare metal or drug eluting stent performed within 30 days prior to study procedure

10. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 10 weeks of enrollment
11. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
12. Recent (within 6 months of Heart Team assessment) cerebrovascular accident (CVA) or transient ischemic attack (TIA)
13. Gastrointestinal (GI) bleeding that would preclude anticoagulation
14. Subject refuses a blood transfusion
15. 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)
16. Estimated life expectancy of less than 12 months due to associated non-cardiac co-morbid conditions
17. 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
18. Currently participating in an investigational drug or another device study (excluding registries)
19. Evidence of an acute myocardial infarction ⩽30 days before the study procedure
20. Need for emergency surgery for any reason
21. Liver failure (Child-Pugh class C)
22. Patients requiring TAV implantation via carotid aortic access
23. Currently undergoing radiation therapy

Anatomical exclusion criteria:

24. Pre-existing prosthetic heart valve in any position
25. Mixed aortic valve disease (aortic stenosis with severe aortic regurgitation with predominant aortic regurgitation > 3+)
26. Severe mitral regurgitation
27. Severe tricuspid regurgitation
28. Moderate or severe mitral stenosis
29. Hypertrophic obstructive cardiomyopathy
30. Echocardiographic or Multi-Detector Computed Tomography (MDCT) evidence of intracardiac mass, thrombus, or vegetation
31. Non-calcified aortic valve
32. Unicuspid valve verified by echocardiography
33. Bicuspid aortic valve with no raphe or 2 raphes (Sievers classification type 0 or type 2)
34. Sinus of Valsalva diameter unsuitable for placement of the self-expanding bioprosthesis

35. Aortic annulus diameter of < 18 or > 26 mm.
36. Significant ascending aortopathy requiring surgical repair
37. Ascending aorta diameter > 4.5 cm
38. 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)

5.3 Schedules and Visit Window

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
Aes, SAEs and Device-related events[3]	X	X	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 enrollment (i.e., written informed consent obtained)
[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

6. Determination 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 and was confirmed during the NMPA consultation meetings and protocol synopsis submitted with no further objections/feedback (October 2018 through March 2019).

The total sample size of the primary study population is 50 attempted implants, exclusive of the roll-in population. There is no minimum number of subjects required for each clinical institution. No site will implant more than 20 subjects, excluding the roll-in subjects, without prior authorization from Medtronic.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The distribution of enrolled subjects table will be used to summarize the disposition of enrolled subjects. Number of subjects consented, number of subjects enrolled, number of subjects with an attempted implant, and number of subjects implanted will be reported.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Protocol violations (study deviations) will be reported to Medtronic throughout the study by each site and identified through monitoring activities.

Deviations will be summarized by type for each interval. The percent of subjects with the deviations will be calculated based on the number of subjects eligible for the specified visit (e.g., screening, enrollment, index procedure).

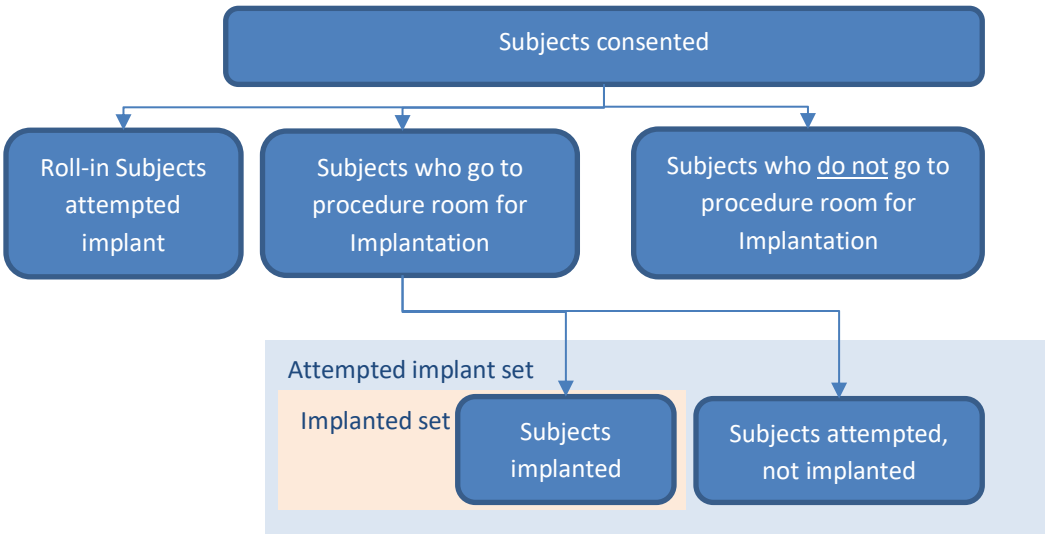
7.1.3 Analysis Sets

The two main analysis sets for this study are defined as follows:

- 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.
- 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.

Index procedure (TAVR) is defined as the first procedure that the Medtronic EnVeo™ PRO Delivery Catheter System is introduced.

Figure 2. Analysis sets for the study endpoints



Roll-in population: The first two attempted subjects at each site will be considered "roll-in" subjects. The maximum number of roll-in subjects among all sites will be 20 subjects. The roll-in population will be followed per the same protocol as the primary study population (n= 50 subjects with attempted implant, exclusive of "roll-in" patients); however, results from the roll-in population will be analyzed separately from the primary study population.

Additionally, a per-protocol set was defined as follows:

- Per-Protocol set: Includes all subjects who are implanted, with evaluable primary endpoint, and no major protocol deviation. Possible major protocol deviations may include but not limited to, in a priority queue, missing primary safety endpoint or primary efficacy endpoint, using non-study device, violating inclusion/exclusion criteria, out of time window assessment (e.g., 30-day echocardiogram performed earlier than the start of the visit window). Protocol deviations will be listed and reviewed in the blind data review meeting (if applicable) before the final hard lock.

  Exclusion from the per-protocol set will be finalized and documented prior to the primary endpoint hard lock. Any Per-Protocol set analysis will be provided separately as needed.

Statistical analysis will be performed when the primary study population (n= 50 subjects with attempted implant, exclusive of "roll-in" patients) are followed for 30 days.

The primary analysis for the primary safety objective, secondary safety objectives, device success, and the additional outcome measures of safety outcomes, NYHA and quality of life will use the attempted implant set. Primary efficacy endpoint, valve performance, and other outcome measures related to valve dysfunction, and hemodynamic performance metrics will use the implanted set.

7.2 General Methodology

7.2.1 General Summaries

All continuous variables will be summarized with means, medians, standard deviations, first and third quartiles, minimums, and maximums. For categorical variables the counts and percentages of subjects will be presented.

7.2.2 Kaplan-Meier Analyses

Survival analysis using the Kaplan-Meier (KM) method will be applied on time-to-event outcomes, for example safety related endpoints. The Kaplan-Meier estimate and the loglog transformed two-sided 95% confidence interval using the Greenwood standard errors will be reported at 1 month (30 days), 6 months (183 days), 1 year (365 days), 2 years (730 days), 3 years (1095 days), 4 years (1460 days), and 5 years (1825 days).

For subjects without an event, the date of censoring will be the latest date of all follow-up visits, assessments, and events (including death in those objectives where death is not the endpoint).

7.3 Center Pooling

No poolability analyses are planned.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

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., incorrect 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. Sensitivity analysis will be conducted for primary endpoints.

In the case of partial dates, if only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15th of that month. If only the year is known, the event or assessment will be analyzed as if it occurred on June 30th of that year. These resolutions of partial dates are subject to all the reasonable restrictions, for example, pre-procedure events and assessments must occur between the enrollment date and the procedure date, post-procedure events and assessments must occur no earlier than the procedure date, and AE awareness date must be on or later than AE onset date.

7.5 Use of Echocardiographic Data

7.5.1 Echo Core Lab

An independent Echo Core Lab will evaluate all echocardiograms through the 30-day follow up assessment. Echocardiographic-related primary and secondary endpoints will be based on the core lab assessments. As the study has transitioned to post-market, further echocardiographic-related data and results will be site-reported.

7.5.2 Echocardiographic Data After Reinterventions

Unless otherwise specified, echocardiographic data collected after reinterventions will be excluded from all analyses, as the reported data is not associated with the implanted index valve's performance.

At the time of the primary endpoint analysis, no reinterventions occurred in any subjects prior to the 30 day visit and the primary endpoint analysis included all available echos.

7.6 Adjustments for Multiple Comparisons

There are no planned multiple comparisons expected and thus no multiplicity adjustments are planned for this study.

7.7 Demographic and Other Baseline Characteristics

Descriptive statistics, as defined in 7.2.1, will be used to report demographic and clinical characteristics at baseline. Major baseline demographic and clinical variables will be summarized for the attempted implant analysis set as defined in 7.1.3.

7.8 Treatment Characteristics

Descriptive statistics, as defined in 7.2.1, will be used to report procedure characteristics for the attempted implant analysis set as defined in 7.1.3. Information to be summarized includes, but is not limited to, variables such as valve sizes, anesthesia type, and access route.

7.9 Interim Analyses

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.

7.10 Evaluation of Objectives

7.10.1 Primary Safety Objective

All-cause mortality at 30 days.

Hypothesis/Decision criteria:

No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive, and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:

The endpoint is the KM event rate of all-cause mortality at 30 days post procedure.

Data Collection and Analysis Method:

Data will be collected on event case report form (CRF). Death will be adjudicated by the CEC. CEC adjudicated all-cause mortality will be used in the analysis.

Analysis Dataset:

This objective will be analyzed for all subjects in the attempted implant set.

Sensitivity Analysis:

Sensitivity analysis will be performed using the following criteria. Proportions and 95% confidence intervals under each scenario will be reported:

- Complete analysis: excludes all subjects that dropped out or withdrew before 30 days
- Worst-case analysis: assumes all subjects that dropped out or withdrew before 30 days are dead
- Best-case analysis: assumes all subjects that dropped out or withdrew before 30 days are alive
- Tipping point analysis: if the number of missing subjects is n (n>1), a stepwise analysis between the best-case and worst-case scenarios will be conducted by the following steps:

  Step 1: assumes one subject is dead, n-1 subjects alive, and calculate the proportion.

  Step 2: assumes two subjects are dead, n-2 subjects alive, and calculate the proportion.

  The calculation will be iterative until the last step: assumes n-1 subjects are dead, one subject alive, and calculate the proportion.

7.10.2 Primary Efficacy Objective

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

Hypothesis/Decision criteria:

No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive, and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:

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

Data Collection and Analysis Method:

Data will be collected in the ECHO CORE LAB CRF at 30-days post procedure. Frequency and percent of moderate or severe aortic regurgitation will be analyzed. To calculate the percent of moderate or severe aortic regurgitation, the numerator will be the number of patients with total Aortic Prosthetic Regurgitation on the ECHO CORE LAB CRF equals to moderate, moderate to severe, and severe at 30-day post procedure, and the denominator will be the number of patients whose 30-day total aortic regurgitation are not missing.

Analysis Dataset:

This objective will be analyzed for all subjects in the implanted set.

Sensitivity Analysis:

For primary efficacy endpoint, the primary outcome will be calculated by excluding subjects whose 30 days echo data were not evaluable. A sensitivity analysis will be performed using the following criteria. Proportion and 95% confidence interval under each scenario will be reported:

- Worst-case analysis: assumes all unable-to-be-assessed cases are failures
- Best-case analysis: assumes all unable-to-be-assessed cases are successes
- Tipping point analysis: if the number of missing subjects is n (n>1), a stepwise analysis between the best-case and worst-case scenarios will be conducted by the following steps:

  Step 1: assumes one subject is dead, n-1 subjects alive, and calculate the proportion.

  Step 2: assumes two subjects are dead, n-2 subjects alive, and calculate the proportion.

  The calculation will be iterative until the last step: assumes n-1 subjects are dead, one subject alive, and calculate the proportion.

7.10.3 Secondary Safety Objectives

1. **The VARC II Combined Safety Endpoint at 30 days**

   Hypothesis/Decision criteria:

   No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive, and no statistical hypothesis test will be performed.

   Endpoint Definition/Parameters to Be Estimated:

   The VARC II 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)

Data Collection and Analysis Method:

Data will be collected on event case report form. The safety endpoints will be adjudicated by the CEC. CEC adjudicated results will be used in the analysis. The corresponding Clinical Events Committee (CEC) codes are provided in the Clinical Events Committee (CEC Charter).

A Kaplan-Meier analysis will be performed for the VARC II Composite Safety Endpoint at 30 days post procedure.

Analysis Dataset:

This objective will be analyzed for all subjects in the attempted implant set.

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

Hypothesis/Decision criteria:

No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive, and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:

Individual components of the VARC II composite safety endpoint at 30 days 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)

Data Collection and Analysis Method:

Data will be collected on event case report form. The safety endpoints will be adjudicated by the CEC. CEC adjudicated results will be used in the analysis. The corresponding Clinical Events Committee (CEC) codes are provided in the Clinical Events Committee (CEC Charter).

A Kaplan-Meier (KM) analysis will be performed for each individual component of the VARC II Composite Safety Endpoint at 30 days post procedure.

Analysis Dataset:

This objective will be analyzed for all subjects in the attempted implant set.

3. **New permanent pacemaker at 30 days**

Hypothesis/Decision criteria:

No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive, and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:

The endpoint is the KM event rate of new permanent pacemaker at 30 days post procedure.

Data Collection and Analysis Method:

Data will be collected on event case report form. Site reported New permanent pacemaker will be used in the analysis. Subjects with a pacemaker or ICD at baseline will be excluded.

Analysis Dataset:

This objective will be analyzed for all subjects in the attempted implant set.

7.10.4 Secondary Efficacy Objectives

1. **Device success at 24 hours to seven days**

Hypothesis/Decision criteria:

No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive, and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:

Device success at 24 hours to seven days, defined as:

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

Data Collection and Analysis Method:

The components of device success will be determined as follows:

- No death event occurs within 30 days post-procedure, or on or before the discharge date (if the discharge date is longer than 30 days post-procedure);
- In the procedure CRF, the answer to “Correct positioning of the prosthetic heart valve into proper anatomical location” and “only 1 TAV implanted” should be both “YES”;
- The criteria for ECHO will be based on the ECHO Core Lab Data for the time interval of 24 hours to 7 days:
  - Mean aortic gradient < 20 mmHg or peak velocity < 3 m/sec;
  - Absence of moderate or severe prosthetic valve regurgitation. Total Aortic Prosthetic Regurgitation on the ECHO CORE LAB form is less than moderate.
  - Absence of patient-prosthesis-mismatch:
    - For subjects with BMI < 30 kg/m2, index effective orifice area (EOAi) > 0.85 cm2 /m2

- For subjects with BMI ⩾ 30 kg/m2, index effective orifice area (EOAi) > 0.70 cm2 /m2

BMI = weight(kg)/(height (m)) ^{2}, where weight and height are recorded on the ECHO CORE LAB form.

All the above components must be satisfied to count as a device success. If any of the above components fails, the endpoint will be counted as a failure.

For the overall device success rate, the numerator will be the number of subjects whose procedures result in device success as described above, and the denominator will be the number of subjects whose device success results are not missing. Note that this analysis excludes those subjects with a missing response to any of the above three components (e.g., the field "Post-implant Severity of Total Aortic Regurgitation" ="Unable to Assess" or "Not Recorded", missing mean aortic gradient, or missing peak velocity, etc.) and without a "NO" response to any of the components. The binary rate of device success and the exact two-sided 95% confidence interval will be estimated.

Analysis Dataset:

This objective will be analyzed for all subjects in the attempted implant set.

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

Hypothesis/Decision criteria:

No specific hypotheses or pass/fail criteria have been set. The analysis will be descriptive, and no statistical hypothesis test will be performed.

Endpoint Definition/Parameters to Be Estimated:

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

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

Data Collection and Analysis Method:

Each individual parameter will be collected in the ECHO CORE Lab CRF at 30-days post procedure.

For mean gradient and effective orifice area, the descriptive statistics (mean, median, standard deviation, minimum, maximum and interquartile ranges) will be presented.

Degree of aortic regurgitation will be reported as proportions at 30 days post procedure.

Analysis Dataset:

This objective will be analyzed for all subjects in the implanted set.

7.10.5 Other Outcome Measures

1. **Event rates of the following TAVI-related complications:**

- change to surgery
- need for cardiopulmonary mechanical assistance
- coronary occlusion or obstruction
- annular rupture or dissection
- ventricular perforation
- mitral valve damage
- prosthetic valve displacement, migration, or embolism
- acute kidney injury (up to 7 days post procedure)

Data Collection and Analysis Method:

Event rate estimates for each of the above TAVI-related complications will be provided at 30 Days, 6 months, 1 year and annually through 5 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

2. **All-cause mortality at 6 months, one year, and annually through 5 years**

   Event rate estimates will be provided at 6 months, 1 year and annually through 5 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

3. **All stroke (disabling and non-disabling) at 6 months, one year, and annually through 5 years**

   Event rate estimates will be provided at 6 months, 1 year and annually through 5 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

4. **Myocardial infarction at 30 days, 6 months, one year, and annually through 5 years**

   Event rate estimates will be provided at 30 days, 6 months, 1 year and annually through 5 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

5. **Life-threatening bleeding at 30 days, 6 months, one year, and annually through 5 years**

   Event rate estimates will be provided at 30 days, 6 months, 1 year and annually through 5 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

6. **New AV-Conduction disturbances (LBBB and RBBB) at 30 days**

   Event rate estimates will be provided at 30 days for the attempted implant set. The outcome is descriptive including proportion rates and no statistical hypothesis test is specified.

7. **Prosthetic valve endocarditis at 30 days, 6 months, one year, and annually through 5 years**

   Event rate estimates will be provided at 30 days, 6 months, 1 year and annually through 5 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

8. **Prosthetic valve thrombosis at 30 days, 6 months, one year, and annually through 5 years**

   Event rate estimates will be provided at 30 days, 6 months, 1 year and annually through 5 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

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**

   Event rate estimates will be provided at 1 year and annually through 5 years for the implanted set. The outcome is descriptive including proportion rates and no statistical hypothesis test is specified.

10. **Valve-related dysfunction requiring repeat procedure at 30 days, 6 months, one year, and annually through 5 years**

    Event rate estimates will be provided at 30 days, 6 months, 1 year and annually through 5 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

11. **Valve hemodynamic performance metrics by Doppler echocardiography at one year and annually through 5 year**

    a. Mean aortic gradient

    b. Effective orifice area

    c. Degree of aortic regurgitation (transvalvular, paravalvular, total)

    The echocardiographic measurements will be reported at 1 year and annually through 5 years for the implanted set with site-reported echocardiographic data. No statistical hypothesis test is specified.

    For mean gradient and effective orifice area, the descriptive statistics (mean, median, standard deviation, minimum, maximum and interquartile ranges) will be presented.

    Degree of aortic regurgitation will be reported as proportions.

12. **New York Heart Association (NYHA) functional classification at 30 day, 6 months, one year and annually through 5 years**

    NYHA classifications will be summarized with frequencies and percentages at 6 months, one year and annually through 5 years. All attempted implant subjects with available NYHA collections (I/II/III/IV) will be included in the analysis. No statistical hypothesis test is specified.

13. **Post-operative EQ-5D quality of life at 30 days and one year**

    EQ-5D will be summarized with means, medians, standard deviations, minimums, maximums, and interquartile ranges, at 30 days and 1 year for the attempted implant set. No statistical hypothesis test is specified.

7.11 Safety Evaluation

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.

7.12 Health Outcomes Analyses

No health outcomes analyses are planned for this study.

7.13 Changes to Planned Analysis

The planned analyses in this SAP are aligned with the planned analyses noted in the CIP.

8. Validation Requirements

Level 1 validation (independent validation) will be used for the analysis datasets and the primary endpoints. For the primary endpoint analysis during the pre-market phase, Level 1 or 2 validation (peer review) will be used for additional analyses, data summaries, and listings within China CRO team, while the Medtronic statistician and/or programmer will do an independent level 1 or 2 validation.

9. References

NA

10. Statistical Appendices

There are no statistical appendices for this study.