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

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Statistical Analysis Plan

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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Transcatheter Aortic Valve Replacement (TAVR) with Medtronic TAVR System in Patients with Severe Bicuspid Aortic Valve Stenosis and at Low Predicted Risk of Mortality with Surgical Aortic Valve Replacement (SAVR)
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Jian Huang, Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AR	Aortic regurgitation
AS	Aortic stenosis
AVR	Aortic valve replacement
BAV	Balloon aortic valvuloplasty
BSA	Body surface area
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
CT	Computed tomography
CVA	Cerebrovascular accident
ECG	Electrocardiogram/Electrocardiography
eCRF	Electronic Case Report Form
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MI	Myocardial infarction
MR	Mitral Regurgitation
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PPI	Permanent Pacemaker
PVL	Paravalvular Leak
QoL	Quality of Life
STS	Society of Thoracic Surgeons
TAVI	Transcatheter aortic valve implantation
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TTE	Transthoracic echocardiography
UADE	Unanticipated Adverse Device Effect

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).

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

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

A study report will be prepared for submission to FDA at the time when all 150 consecutive subjects with an attempted implant have had the chance to complete their 30-day follow-up visit, have died, or have exited from the study, for the purpose of seeking market approval. Another study report may be prepared at the time when all the 150 attempted implant subjects have completed their 1 year follow-up visit. After all subjects have completed all protocol-specified follow-up, a final clinical report including updated long-term safety and efficacy data will be prepared and submitted.

The results from the primary endpoints of the Low Risk bicuspid study cohort may be presented relative to the procedural safety and efficacy results from the TAVR arm of the Low Risk Trial randomized cohort.

4. Study Objectives

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

5. Investigation Plan

This is a multi-center, prospective, single-arm clinical study designed to evaluate 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.

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.

The population includes males and females with severe aortic stenosis with a clinical indication for surgical aortic valve replacement with a bioprosthesis who are at low predicted risk of mortality at 30 days for surgical aortic valve replacement and have bicuspid aortic valve anatomy.

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

All follow-up periods are defined as the number of days after the date of the index procedure (first attempted procedure). The index procedure = Day 0.

Baseline	Within 12 weeks prior to submitting to the screening committee (except for MDCT and coronary arteriography as noted in CIP 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

6. Determination of Sample Size

6.1. Historical Data

Historical data for the primary endpoints were derived from previous clinical studies of the Medtronic TAVR system (Evolut R and Evolut PRO systems) in subjects with tricuspid aortic valve anatomy. The criteria for the selected studies included the following considerations:

- Studies were conducted for regulatory purposes
- Safety endpoint events were adjudicated by CEC
- Echocardiographic endpoints were evaluated by a core laboratory

Information on the studies that were used is provided in Table 1.

Table 1. Information on the studies that contributed to the historical data

Study Title	Enrollment Period	Age (Mean± SD)	STS PROM Score (Mean± SD)	Number of Evolut R Subjects	Number of Evolut R Systems Implanted	All-cause Mortality or Disabling Stroke Rate at 30 Days	Device Success[1]
SURTAVI and SURTAVI CAS	APR 2015 – JUL 2017	78.8 ± 6.4	4.0 ± 1.4	391	391	1.02% (4/394)	95.32% (367/385)
Evolut R IDE (US &OUS)	OCT 2013 – JUL 2015	83.2 ± 7.0	7.3 ± 3.5	301	297	4.3% (13/301)	93.5% (272/291)
Evolut 34R IDE	JUN 2016 – OCT 2016	81.8 ± 8.2	5.5 ± 2.8	60	60	1.7% (1/60)	96.6% (57/59)
Evolut R PRO	JUN 2016 – NOV 2016	83.3 ± 7.2	6.4 ± 3.9	60	60	3.3% (2/60)	95.0% (57/60)
Weighted Average						2.4%	94.7%

[1] Defined as: Absence of procedural mortality, AND correct positioning of a single prosthetic heart valve into the proper anatomical location, AND absence of moderate or severe total prosthetic valve regurgitation (at 18 hours to 7 days).

6.2. Sample Size

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.

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. Table 2 provides the level of precision with

the 95% confidence intervals around possible endpoint rates in bicuspid subjects at sample sizes of 150 subjects (assuming that when occurred, the endpoint rates in bicuspid subjects are similar to those in the historical data from tricuspid subjects). The rates provided are based on the weighted average from historical data presented in Table 1.

Table 2. Confidence intervals for sample sizes of 150 subjects.

Endpoint	Possible Rate in Bicuspid Subjects (n)[1]	Sample Size	95% Exact Binomial Confidence Interval
All-cause mortality or disabling stroke at 30 days	2.7% (4)	150	0.7%, 6.7%
Device success	94.7% (142)	150	89.8%, 97.7%

[1]Rate values from the weighted average of the historical data are rounded up to correspond to the nearest whole number for subjects with an endpoint for sample sizes of 150; n denotes number of subjects with an endpoint.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subjects disposition will be summarized, including the number of subjects enrolled, attempted implant, implanted, died, explanted, withdrawn, lost-to follow up, and completed each visit during the study.

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 (eg., screening, enrollment, index procedure).

7.1.3. Analysis Sets

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.

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 below.

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. 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.

All data collected from enrolled, attempted implant, and implanted subjects will be utilized in the analyses as appropriate. Analyses of the primary and additional endpoints will be descriptive, and no statistical hypothesis tests will be performed.

7.2. General Methodology

Descriptive statistics will be used to report study data. For continuous variables (eg. age), the mean, median, standard deviation, minimum, maximum and interquartile ranges (IQR) will be presented. For categorical variables, the number and percentage of subjects in the category of interest will be presented.

For time to event variables, Kaplan-Meier analyses of event rates at 30 days, 1 year and annually through end of study will be presented. For these analyses, the time points will correspond to 30 days, 365 days, 730 days, 1095 days, 1460 days, 1825 days, 2190 days, 2555 days, 2920 days, 3285 days and 3650 days post implantation respectively. At each time point with data, the product limit estimate of the event, the number of subjects at risk, the number of subjects with events, and the 95% confidence interval will be presented. For subjects without an event, the date of censoring will be the latest date of all follow-up visits, assessments, and events (including death).

7.3. Site Poolability

Although data for this study will be collected from multiple site, no site pooling 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.

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. Unless otherwise specified, no statistical techniques will be used to impute missing data. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

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 the restrictions that events must occur no earlier than the procedure date.

7.5. Adjustments for Multiple Comparisons

No multiple comparisons/multiplicity adjustments will be made.

7.6. Demographic and Other Baseline Characteristics

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, maximums, and interquartile ranges. Categorical variables will be summarized with frequencies and percentages.

7.7. Treatment Characteristics

Procedure data will be summarized for the attempted implant analysis set. Continuous variables will be summarized with means, medians, standard deviations, minimums, maximums, and interquartile ranges. Categorical variables will be summarized with frequencies and percentages.

7.8. Interim Analyses

No interim analyses will be conducted for this observational study.

7.9. Evaluation of Objectives

7.9.1. Primary Safety Endpoint

All-cause Mortality or Disabling Stroke Rate 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 or disabling stroke at 30 days post procedure.

Data Collection and Analysis Method:

Data will be collected on event case report form. Death and stroke events will be adjudicated by the CEC. CEC adjudicated all-cause mortality or disabling stroke will be used in the analysis.

Analysis Dataset:

This objective will be analyzed for all attempted implant set.

7.9.2. Primary Efficacy Endpoint

Device Success Rate.

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, defined as composite endpoint:

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

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 18 hours to 7 days:

- Absence of moderate or severe prosthetic valve regurgitation. Total Aortic Prosthetic Regurgitation on the ECHO CORE LAB form equals to none, trace, mild, or mild to moderate.

All of 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 (eg, the field "Post-implant Severity of Total Aortic Regurgitation" ="Unable to Assess" or "Not Recorded") and without a "NO" response to any of the components. In addition to the device success rate, the 95% C.I. will also be provided.

Analysis Dataset:

This objective will be analyzed for the implanted analysis set.

7.9.3. Additional Outcome Measures

1. All-cause mortality at one year, and annually through 10 years

   Event rate estimates will be provided at 1 year and annually thereafter up to 10 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

2. All stroke (disabling and non-disabling) at one year, and annually through 10 years

   Event rate estimates will be provided at 1 year and annually thereafter up to 10 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

3. New permanent pacemaker implantation at 30 days

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

4. Myocardial Infraction at 30 days

   Event rate estimates will be provided at 30 days 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, one year, and annually through 10 years

   Event rate estimates will be provided at 30 days, 1 year and annually thereafter up to 10 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

6. Prosthetic valve endocarditis at 30 days, one year, and annually through 10 years

   Event rate estimates will be provided at 30 days, 1 year and annually thereafter up to 10 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

7. Prosthetic valve thrombosis at 30 days, one year, and annually through 10 years

   Event rate estimates will be provided at 30 days, 1 year and annually thereafter up to 10 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

8. Valve-related dysfunction requiring repeat procedure at 30 days, one year, and annually through 10 years

   Event rate estimates will be provided at 30 days, 1 year and annually thereafter up to 10 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

9. Repeat hospitalization for ascending aorta disease at 30 days, one year, and annually through 10 years

   Event rate estimates will be provided at 30 days, 1 year and annually thereafter up to 10 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

10. Repeat hospitalization for aortic valve disease at 30 days, one year, and annually through 10 years

    Event rate estimates will be provided at 30 days, 1 year and annually thereafter up to 10 years for the attempted implant set. The outcome is descriptive including Kaplan-Meier rates and no statistical hypothesis test is specified.

11. Hemodynamic performance metrics by Doppler echocardiography
    a. Mean aortic gradient at baseline, 30 days, one year, annually through 5 years and at years 7 and 10
    b. Effective orifice area at baseline, 30 days, one year, annually through 5 years and at years 7 and 10
    c. Degree of total, peri, and transvalvular prosthetic regurgitation at baseline, 30 days, one year, annually through 5 years and at years 7 and 10

    The echocardiographic measurements will be reported at each of the specified time points for the implanted set with Echo 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.

    Prosthetic regurgitation severity will be reported as proportions at each specified time point.

12. New York Heart Association (NYHA) functional classification at baseline, 30 days, one year and annually through 5 years and at years 7 and 10

    NYHA classifications will be summarized with frequencies and percentages at baseline, 30 days, 1 year, and annually through 5 years and at years 7 and 10. 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. Health-related quality of life as assessed by
    a. Kansas City Cardiomyopathy (KCCQ) instrument at baseline, 30 days, one year, annually through 5 years
    b. EQ-5D survey at baseline, 30 days and one year

    The KCCQ, EQ-5D will be summarized with means, medians, standard deviations, minimums, maximums, and interquartile ranges, at each specified time point for the attempted implant set. No statistical hypothesis test is specified.

7.10. 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. Level 1 or 2 validation (peer review) will be used for additional analyses, data summaries, and listings.

9. References

NA

10. Statistical Appendices

There are no statistical appendices for this study.