Medtronic

Medtronic CoreValve™ Evolut R™ FORWARD Study

Statistical Analysis Plan (SAP)

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Approvals

The undersigned have reviewed this document and agree with its contents.

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1. Introduction / Purpose of SAP

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of the Medtronic Coronary and Structural Heart (CSH) CoreValve™ Evolut R™ FORWARD clinical study. The purpose of this plan is to provide a framework which answers the study objectives in a statistically rigorous fashion, without bias or analytical deficiencies.

Specifically, the Plan has the following purpose: to prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of statistical analysis in the medical device industry.

This Statistical Analysis Plan applies to the study final report. This SAP also applies to the main study manuscript, though not everything specified here will be included in the manuscript.

2. Study Design

The study objective is to document the clinical and device performance outcomes of the Evolut R system used in routine hospital practice in a large patient cohort for the treatment of symptomatic native aortic valve stenosis or a stenosed, insufficient, or combined surgical bioprosthetic valve failure necessitating valve replacement.

This is a prospective, single arm, multi-center, observational, post market study. In Australia and Canada it is a prospective, single arm, multi-center pre-market study. Approximately 1000 subjects implanted with the Evolut R system will be included. Subjects will be followed at 30 days, 1, 2 and 3 years after the procedure. Based on clinical assessments during the course of the study, follow up may be extended to up to 5 years post procedure.

Enrollment parameters are included in the study to avoid introduction of bias to the trial results due to disproportionate enrollment. Enrollment shall not exceed 7.5% (75 patients) of the total implanted patients at any individual site. In addition, enrollment shall not exceed 40% (400 patients) of the total implanted patients at any individual country.

Enrollment will be competitive across sites. The per-site and per-country enrollment cap may be increased upon Sponsor approval. There is no set minimum number of patients to be enrolled per site; however there is an expected minimum enrollment of 15 subjects per site.

At the time when the study-wide enrollment cap of 1000 implanted subjects has been reached, further enrollment into the study will cease regardless of whether individual sites have reached their per-site cap.

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

- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and safety 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 Echo Core Lab will evaluate all echocardiograms. Echocardiographic study endpoint results 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.
- Study monitors will verify patients' data and ensure compliance with the Clinical Investigational Plan and other study requirements.

Subject selection criteria are based on the Instructions for Use of the Evolut R System.

Inclusion Criteria
- Symptomatic native aortic valve stenosis or a stenosed, insufficient, or combined surgical bioprosthetic valve failure necessitating valve replacement

- Acceptable candidate for elective treatment with the Evolut R System and in conformity with the local regulatory and medico economic context
- Age ≥80 years OR considered to be at high or greater risk for surgical aortic valve replacement (AVR) where high risk is defined as:
  - Society of Thoracic Surgeons (STS) predicted risk of mortality ≥8%

  OR
  - Documented heart team agreement of risk for AVR due to frailty or comorbidities
- Geographically stable and willing to return to the implanting site for all follow-up visits
- Of legal age to provide informed consent (patient Informed Consent or Data Release Form) in the country where they enroll in the trial
- The patient has been informed of the nature of the study, is able and willing to provide consent without assistance from a legal representative and has consented to participate, and has authorized the collection and release of his/her medical information by signing a Patient Informed Consent or Data Release Form.

Exclusion Criteria

- Known hypersensitivity or contraindication to aspirin, heparin (HIT/HITTS) and bivalirudin, ticlopidine, clopidogrel, Nitinol (Titanium or Nickel), or sensitivity to contrast media, which cannot be adequately premedicated
- Preexisting mechanical heart valve in aortic position
- Ongoing sepsis, including active endocarditis
- Anatomically not suitable for the Evolut R system
- Estimated life expectancy of less than 1 year
- Participating in another trial that may influence the outcome of this trial
- Need for emergency surgery for any reason

3.   Description of Analyses

3.1. General Summaries

All continuous variables will be summarized with means, medians, standard deviations, minimums, and maximums. Categorical variables will be summarized with frequencies and percentages.

3.2. Baseline Characteristics

Baseline demographic and clinical variables will be summarized for the attempted implant analysis set (safety set) as defined in section 3.4.

3.3. Handling of Dropouts and Missing Data

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

Unless otherwise specified in each objective, no statistical techniques will be used to impute missing data for continuous or categorical outcomes. If a subject's data are missing for any reason, that subject will not be included in that portion of the analysis. 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 pre-procedure events and assessments must occur between the enrollment date and the procedure date and post-procedure events and assessments must occur no earlier than the procedure date.

3.4. Analysis Sets

Subjects who are taken to the procedure room for implantation will comprise the study population evaluated for the study objectives and associated endpoints.

The analysis sets are further defined as follows:

- o **Safety Set (Attempted Implant):** The safety set includes all subjects who are brought into the procedure room for implantation.
- o **Device Success/ Hemodynamic Performance Set (Implanted):** The device success/ hemodynamic performance set includes all subjects who are implanted with the Evolut R TAV, defined as the Evolut R TAV is placed in the aortic annulus and completely released from the EnVeo R catheter delivery system.

3.5. Kaplan-Meier Analyses

In the Kaplan-Meier analysis, the product-limit estimate of the event rate, the number of subjects at risk, the number of subjects with events, the Peto standard error of the estimate, and the loglog transformed 95% confidence interval using the Peto standard error at 1 month (30 days), 1 year (365 days), 2 years (730 days) and 3 years (1095 days) 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 in those objectives where death is not the endpoint).

3.6. Primary Objective

The primary objective of this study is to demonstrate that the all-cause mortality rate at 30 days post procedure is less than the pre-specified performance goal of 10.0%.

3.6.1. Primary Hypothesis

H_0: $\pi \geq 10.0\%$

H_a: $\pi < 10.0\%$

Where π denotes the binary rate of all-cause mortality rate at 30 days post procedure. This one-sided test will be carried out at the 0.05 significance level using the Fisher exact test.

3.6.2. Primary Endpoint Definition

The primary endpoint is the binary rate of all-cause mortality at 30 days post procedure. The numerator will be the number of subjects who died on or before 30 days post procedure, and the denominator will be the number of subjects in the safety set (defined in section Analysis Sets3.4) who died on or before 30 days post procedure, or whose latest date of all follow-up visits, assessments, and events is at least 30 days post procedure.

In addition, the KM event rates for all-cause mortality at 30 days, 1 year, 2 years and 3 years, as well as the KM plot will be provided.

3.6.3. Rational for Choice of Hypothesis

The performance goal for all-cause mortality at 30 days was established through the following data sources:

- Data from the CoreValve IDE clinical study
- Review of the published literature on the Medtronic CoreValve System current through April 2013

Criteria for selection of the articles included the following:

- Study was published in peer reviewed journal
- Study was multi-center
- Results were representative of high or above risk population
- Results for all-cause mortality were reported by device type
- Study was not a first in man, feasibility, or confined to early Medtronic CoreValve experience

Of the literature reviewed, 4 articles were selected. Information on the historical data is presented in Table 1.

Table 1 Information on Control Data Sources for Primary Safety Endpoint

Author	Study Name	Number of CoreValve Patients	Age (years) Mean ± SD	Logistic Euroscore (%) Mean ± SD	STS Score (%) Mean ± SD	All-Cause Mortality at 30 days (%)
US CoreValve IDE study: Extreme Risk Cohort[1]		639	83 ± 8	23 ± 17	10 ± 6	9.1
US CoreValve IDE study: High Risk Cohort[1]		390	83 ± 7	18 ± 13	7 ± 3	3.3
Bosmans	Belgian Registry	141	82 ± 6	25 ± 15	Not reported	11
Gilard	FRANCE 2 Registry	1043	82 ± 7	21 ± 14	14 ± 11	9.4
Chieffo	PRAGMATIC	453	81 ± 7	21 ± 13	8 ± 6	7.5
Moat	UK TAVI Registry	452	81 ± 7	18 (11-28)	Not reported	5.8
Random effects meta-analytic rate						7.3
						(95% CI 5.4 - 10.0)

1. Data include all access routes.

The random effect meta-analysis showed that the all-cause mortality rate at 30 days post procedure for CoreValve was 7.3% with a 95% C.I. of 5.4% to 10.0%. We expect Evolut R TAV will have a similar rate as CoreValve, which is 7.3% at 30 days. And the all-cause mortality rate for Evolut R will not be higher than the upper bond of the 95% C.I. for CoreValve. Therefore the performance goal was set to 10.0%.

3.6.4. Sample Size Consideration

Assumptions for the sample size estimation are as followings:

  One-sided alpha = 0.05
  π_0 = 10.0%
  π = 7.3%
  Power = 90%

In the above expressions, π_0 and π denote the Performance Goal (null hypothesis proportion) and the expected true proportion, respectively, for all-cause mortality rate at 30 days. Using an exact binomial test, Power Analysis and Sample Size (PASS) software calculates that a total of 934 evaluable subjects is required to attain 90% power in a one-sided test at the 0.05 level of significance. The final sample size is increased to1000 evaluable subjects to account for 7% attrition rate.

3.6.5. Data Collection and Analysis Methods

Death data will be collected on a separate site death case report form. All-cause death events will be adjudicated by the CEC. And the data on the CEC death adjudication form will be used in the analysis.

The all-cause mortality rate at 30 days post procedure will be compared with the performance goal of 10%, with a one-sided Fisher exact test at the 0.05 significance level. The analysis for this objective will be based on the safety set.

3.6.6. Missing Data

Every effort will be undertaken to minimize missing data. A minimal amount of missing data is anticipated for the primary endpoint. However, if outcome data are missing, the primary analysis will be based on the complete case. To assess the potential impact of these missing data, a sensitivity analysis will be conducted which will include a complete case, a best case (assume missing subjects

are alive), a worst-case (assume missing subjects have died), and a tipping point analysis. In addition, the Kaplan-Meier rate at 30 days and its standard error, as a secondary analysis, will be used in the calculation of the test statistic.

3.7. Secondary Objectives

3.7.1. Secondary Objective #1 (Efficacy) - Device Success

This objective is to characterize the device success rate per the VARC-2 definition.

3.7.1.1.   Hypothesis and/or Parameters to Be Estimated

The objective is descriptive and no statistical hypothesis test will be performed. The binary rate of device success and the two-sided 95% confidence interval will be estimated.

3.7.1.2.   Sample Size Consideration

There was no sample size calculation for this objective.

3.7.1.3.   Endpoint Definition

Device success, defined in accordance with the VARC-2 composite endpoint of device success:
* 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 < 3 m/sec), and absence of moderate or severe prosthetic valve regurgitation.

3.7.1.4.   Data Collection and Analysis Methods

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 implant CRF, the answer to "Was a single Evolut R deployed in the proper anatomical location?" should be "YES";
* The criteria for ECHO will be based on the ECHO Core Lab Data for the time interval "Discharge":
    * Absence of patient-prosthesis-mismatch
        * For subjects with BMI < 30 kg/m^2, index effective orifice area (EOAi) > 0.85 cm^2/m^2
        * For subjects with BMI ≥ 30 kg/m^2, index effective orifice area (EOAi) > 0.70 cm^2/m^2
        * BMI = weight(kg)/(height (m))^2, where weight and height are recorded on the ECHO CORE LAB form
    * 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 not equal to moderate or severe.

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 (either success or failure). Note that this analysis excludes those subjects with a missing response to any of the above five components (eg, 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. In addition to the device success rate, the 95% C.I. will also be provided. This objective will be analyzed for the implanted analysis set defined in section 3.4.

3.7.2. Secondary Objective #2 (Efficacy) - Hemodynamic Performance

This objective is to characterize the hemodynamic performance at 24 hours to 7 days (discharge) and 1 year post procedure.

3.7.2.1.   Hypothesis and/or Parameters to Be Estimated

The objective is descriptive and no statistical hypothesis test will be performed.

3.7.2.2.   Sample Size Consideration

There was no sample size calculation for this objective.

3.7.2.3.   Endpoint Definition

The following hemodynamic metrics as measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory will be summarized:
- Mean prosthetic valve gradient
- Effective orifice area
- Degree of prosthetic valve regurgitation (transvalvular, paravalvular, and total).

3.7.2.4.   Data Collection and Analysis Methods

Echo core lab data will be used. This objective will be analyzed for the implanted analysis set.

3.7.3. Secondary Objective #3 and #4 (Safety) - Event Rate of the VARC-2 Combined Safety Endpoint and Individual Safety Components at 30 Days

These two objectives are to characterize the safety event rates at 30 days based on the VARC-2 Combined Safety Endpoint and individual safety components.

3.7.3.1.   Hypothesis and/or Parameters to Be Estimated

The objectives are descriptive and no statistical hypothesis test will be performed.

3.7.3.2.   Sample Size Consideration

There was no sample size calculation for these objectives.

3.7.3.3.   Endpoint Definition

The VARC-2 Combined 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)

3.7.3.4.   Data Collection and Analysis Methods

The CEC codes for the VARC-2 Combined Safety Endpoint:
- All-cause mortality (CEC Death Form)
- All stroke (disabling and non-disabling) (CEC: 102 to 107)
- Life-threatening bleeding (CEC: 110)
- Acute kidney injury: stage 2 or 3 (including renal replacement therapy) (CEC: 114 to 115)

- Coronary artery obstruction requiring intervention (CEC: 152)
- Major vascular complication (CEC: 120 to 127)
- Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)
  - Catheter intervention to repair or replace Evolut R
  - Surgery intervention on Evolut R

As described in section 3.5, a Kaplan-Meier analysis will be performed for the VARC-2 Combined Safety Endpoint at 30 days post-procedure and for each individual component. These objectives will be analyzed for the safety analysis set defined in section 3.4.

3.7.4. Secondary Objective #5 (Safety) - Event Rate of New Permanent Pacemaker Implant at 30 Days

This objective is to characterize the event rate of new permanent pacemaker implant at 30 days.

3.7.4.1.   Hypothesis and/or Parameters to Be Estimated

This objective is descriptive and no statistical hypothesis test will be performed.

3.7.4.2.   Sample Size Consideration

There was no sample size calculation for this objective.

3.7.4.3.   Endpoint Definition

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

3.7.4.4.   Data Collection and Analysis Methods

Data will be collected on a site reported permanent pacemaker implant form. As described in section 3.5, a Kaplan-Meier analysis will be performed for the event rate of new permanent pacemaker implant at 30 days post-procedure. This objective will be analyzed for the safety analysis set defined in section 3.4.

3.8. Interim Analysis

No formal interim analysis is planned, and there are no plans for early termination of the study.

4.   Revision Process

The study statistician will be responsible for execution of this statistical analysis plan, including any revisions and obtaining of appropriate approvals and distributions to the appropriate clinical staff.

5.   Revision History

Version	Date	Author	Summary of Changes
1.0	08DEC2015	Hongyan Qiao	Initial Release