Optimize PRO Study

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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Optimize PRO TAVR Post Market Study
Clinical Investigation Plan Version	6.0, 04 May 2021
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Sponsor/Local Sponsor	Global Sponsor (funding source): Medtronic, Inc. Coronary and Structural Heart Clinical [redacted] Local Sponsors: Medtronic of Canada ULC [redacted] (EU Legal Representative) Medtronic Bakken Research Center BV [redacted] Medtronic Australia Pty. Ltd [redacted] Medtronic New Zealand Limited [redacted]

Confidentiality Statement

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Shuzhen Li, Principal Statistician
2.0	• Changed SAP template to current version B. • Section 2: added EMEA abbreviation. • Section 6.3.2.1: updated to follow same language as CIP V5. • Section 7: updated sample size by adding enrollment in EMEA. • Section 8.1.3: replaced 'as treated (AT)' with 'attempted implant'. • Section 8.6: added additional interim analysis. • Section 8.7.4: added rate of permanent pacemaker implantation at 30 days for non-EMEA vs. EMEA centers. • Section 8.8: added language for a death listing per ISO 14155:2020 D.7g required for SAP template version B. • Section 8.7.1: added PP set 1 analysis set. • Section 8.7.3: added PP set 1 analysis set. • Section 8.7.5: added PP set 1 analysis set. • Section 8.7.6: added PP set 1 analysis set.	[redacted]
3.0	• Updated CIP to version 6, 04 May 2021. • Updated sponsor information on page 1. • Section 2: added ANZ abbreviation. • Section 6.3.2: 600 subjects updated to 650. • Section 7: added 50 subjects at up to 7 sites in ANZ and sample size for roll-in	[redacted]

Version	Summary of Changes	Author(s)/Title

	population was updated to up to 204 subjects.
	• Section 8.6:
	  ○ Updated first interim analysis to take place when at least 100 subjects are enrolled in the attempted implant set and followed through 30 days post procedure.
	  ○ Added that additional interim analyses may occur as deemed necessary. Removed language stating another interim analysis will occur after 400 subjects are enrolled in the attempted implant set.
	• Section 8.7.4: Modified language to state that pacemaker implantation rates at 30 days will be compared by region (US/CAN, EMEA, and ANZ and added one sentence to clarify overall rate of permanent pacemaker implantation will be provided.
	• Section 8.8: added language to provided 2 additional listing (AE/Device Deficiencies) to meet ISO 14155:2020 requirements.	

4.0	• Changed SAP template to current version C. • Updated version 4.0 in document header and cover page. • Section 3: added a sentence referring to the FX addendum. • Added Section 9: Analysis for FX Addendum.	[redacted]
5.0	• Section 3. Purpose SAP: FX Addendum CIP version updated. • Section 7. Determination of Sample Size: add full name of EMEA and ANZ. • Section 8.1.3 Analysis Sets: Add the 'Medtronic TAV device' in the definition of 'Implanted Set' and updated the definition of PP Set 2. • Add Section 8.7. Echocardiographic Assessments After Reintervention. • Section 9.5. Statistical Methods: added sentences referring to echocardiographic assessments after reintervention.	[redacted]

Version	Summary of Changes	Author(s)/Title
	• Section 10. Changes to Planned Analysis: Add the FX Addendum CIP version date. • Minor formatting and typographical updates.	

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ANZ	Australia, New Zealand
AR	Aortic Regurgitation
AT	As Treated
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
CSH	Medtronic Coronary and Structural Heart
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EHRA	European Heart Rhythm Association
EMEA	Europe, Middle East, and Africa
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HAVB	high degree atrioventricular block
IMP	Implanted
LBBB	left bundle branch block
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
PP	Per Protocol
PPI	Permanent Pacemaker Implantation
RBBB	Right Bundle Branch Block
SAP	Statistical Analysis Plan
STS	Society of Thoracic Surgeons
TEE	Transesophageal Echocardiography
TAVR	Transcatheter Aortic Valve Replacement
UADE	Unanticipated Adverse Device Effect

3. Purpose of SAP

This Statistical Analysis Plan (SAP) 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 (SAP) has been developed based on the Optimize PRO TAVR Post Market Study Clinical Investigational Plan (CIP) (6.0, 04 May 2021) and has been

updated based on the Optimize PRO Clinical Investigation Plan - FX Addendum (3.0, 15 December 2022).

4. Introduction of Study Design

4.1. Background and Rationale

Transcatheter aortic valve replacement (TAVR) has been shown to be a safe and effective treatment for patients with severe aortic stenosis who are at extreme, high, intermediate surgical risk [1-3]. Since CoreValve™ became commercially approved in the United States by the Food and Drug Administration (FDA) in 2014, the procedure and valve iterations have become increasingly efficient with reducing complications. The Evolut™ PRO and Evolut™ PRO+ valve's outer pericardial wrap was designed to enhance annular sealing to promote a decrease in paravalvular leak [4]. There is also a growing shift towards optimizing the TAVR care pathway by protocolizing the pre-, peri-, and post-procedure assessments. This optimization can further increase the efficiency of the procedure and subsequently decrease the length of hospital stay and reduce health care costs [5,6].

This procedural efficiency has not translated to a reduction in permanent pacemaker implantation (PPI) rates. Rates have decreased with newer generation TAVR valves; however, variability continues [7]. There is a lack of consensus regarding the management of post-TAVR conduction abnormalities leading towards heterogenous PPI rates across institutions and potentially unnecessary pacemakers for abnormalities that could have resolved intrinsically over time [8,9]. Previous studies indicate most of high degree atrioventricular block (HAVB) and left bundle branch block (LBBB) occur prior to hospital discharge, and early monitoring is key to identifying and managing persistent TAVR-induced conduction abnormalities [10,11].

The objective of this study is to collect outcome data on valve performance and a prespecified TAVR care pathway. Additionally, this study will protocolize the management of the post-TAVR conduction disturbance and evaluate whether a consistent deployment technique will reduce the variability of new onset conduction disturbances.

4.2. Purpose

The purpose of this study is to collect clinical evidence on valve performance and procedural outcomes associated with an "optimized" TAVR care pathway and using the Evolut™ PRO and Evolut™ PRO+ devices.

5. Study Objectives and Endpoints

5.1. Objectives

5.1.1. Study Objective

The study objective is to collect post-market clinical evidence on valve performance and procedural outcomes associated with an "optimized" TAVR care pathway and post-TAVR conduction disturbance pathway while using the Evolut™ PRO and Evolut™ PRO+ devices.

5.1.2. Primary Objective

The primary objective is to collect short-term clinical evidence on the safety of the Evolut™ PRO and Evolut™ PRO+ devices.

5.1.3. Secondary Objective

The secondary objective is to collect clinical evidence on valve performance and procedural outcomes.

5.1.4. Exploratory Objective

The exploratory objective is to collect longer-term clinical evidence on the safety of the Evolut™ PRO and Evolut™ PRO+ devices, as well as collect evidence on reasons for hospital readmissions post-TAVR.

5.2. Endpoints

The following endpoints will be used to evaluate the primary objective.

5.2.1. Primary Endpoint

The primary endpoint is the rate of all-cause mortality or all-stroke at 30 days.

5.2.2. Secondary Endpoints

The following are the secondary endpoints:

- Median days from index procedure to discharge
- Percentage of subjects with ≥ moderate aortic regurgitation (AR) at discharge
- Rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days

5.2.3. Additional Exploratory Endpoints

The following are additional exploratory endpoints:

- 30-day and 1-year hospital re-admission rates

- 1-year composite of all-cause mortality or all-stroke

6. Investigation Plan

6.1. Study Design

Optimize PRO is a post-market, multi-center, prospective, non-randomized study. 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 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.
- Core labs will evaluate all echocardiograms and ECGs. Echocardiographic trial endpoint and ECG results will be based on Core Lab assessments.
- Subjects will be screened to confirm eligibility for enrollment with pre-defined inclusion and exclusion criteria.

6.2. Duration

The enrollment period is estimated to be approximately 36 months and subjects will be followed for up to one-year post index procedure; 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 approximately 4 years.

6.3. Selection of Subjects

6.3.1. Study Population

The study population includes patients with symptomatic native aortic valve stenosis that necessitates valve replacement who meet the criteria for on-label use of the Evolut PRO and Evolut PRO+ system in accordance with Instructions for Use and local regulations.

6.3.2. Subject Enrollment

This study will involve up to 650 subjects (not including roll-in subjects) based on the number of subjects with an attempted TAVR procedure among all active sites. To ensure a widespread distribution of data and to minimize bias in the study results, no site will implant more than 50 subjects without prior authorization from Medtronic. Subjects who exit from the study after implantation will not be replaced.

6.3.2.1. Roll-In Subjects

For all participating centers, the first three subjects implanted will be considered "roll-in" subjects and will not be included in the 650-subject study cohort attempted implant set. The purpose of the roll-in subjects is to provide Investigators the time for training and familiarization with the protocolized implant technique. The Training and Education team will review and provide recommendations for transition of sites from roll-in phase to attempted implant analysis phase. Medtronic will notify each site with official correspondence on approval to move into the attempted implant analysis phase.

Roll-in subjects will complete in-clinical follow-up evaluations as noted in CIP section 10.1.5 Follow-Up Evaluations however the results for the roll-in population will be analyzed separately from the study primary analysis cohorts.

6.3.3. Inclusion Criteria

Prospective subjects must meet all the following inclusion criteria to be eligible for participation:

1. Acceptable candidate for treatment with the Evolut™ PRO or Evolut™ PRO+ system in accordance with the Instructions for Use and local regulations;
2. Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater;
3. Subject and the treating physician agree that the subject will return for all required post procedure follow-up visits;
4. Anatomically suitable for transfemoral TAVR with the Medtronic TAVR system;
5. Subject meets the legal minimum age to provide Informed Consent based on local regulatory requirements.

6.3.4. Exclusion Criteria

Subjects are not eligible for study participation if they meet ANY of the following exclusion criteria:

1. Contraindicated for treatment with the Evolut™ PRO or Evolut™ PRO+ system in accordance with the Instructions for Use;
2. Anatomically not suitable for the Evolut™ PRO or Evolut™ PRO+ system;
3. Reduced ventricular function with left ventricular ejection fraction (LVEF) <35% as measured by resting echocardiogram;
4. Previous aortic valve replacement;
5. Frailty assessments identify:

- Subject is <80 years of age and three or more of the following apply; OR subject is ≥80 years of age and two or more of the following apply
  - Wheelchair bound
  - Resides in an institutional care facility (e.g. nursing home, skilled care center)
  - Body Mass Index <20kg/m^2
  - Grip strength <16kg
  - Katz Index score ≤4
  - Albumin <3.5 g/dL

6. Bicuspid valve verified;
7. Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) >70°;
8. Implanted with pacemaker or ICD;
9. Prohibitive left ventricular outflow tract calcification;
10. Estimated life expectancy of less than 12 months due to associated non-cardiac co-morbid conditions;
11. 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;
12. Currently participating in an investigational drug or another device trial (excluding registries);
13. Need for emergency surgery for any reason;
14. Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable*.

*Notes: Vulnerable subjects include individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. EXAMPLE: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention [12].

7. Determination of Sample Size

The sample size for the study cohort - Attempted Implant population is approximately 400 subjects at up to 46 sites in the US and Canada, at least 200 subjects at up to 15 sites in Europe, Middle East, and Africa (EMEA), and approximately 50 subjects at up to 7 sites in Australia and New Zealand (ANZ). The sample size for the roll-in population is up to 204 subjects.

This is not a hypothesis-driven study, therefore the sample size of 650 subjects was not determined by statistical sample size methods. With >25% of TAVR patients experiencing new conduction disturbances[10], 650 patients will provide a sufficient sample (~160 patients) to evaluate the conduction disturbance management pathway.

8. Statistical Methods

8.1. Study Subjects

8.1.1. Disposition of Subjects

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

8.1.2. Clinical Investigation Plan (CIP) Deviations

Protocol deviations will be reported regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. CIP deviations will be summarized by follow up visit.

8.1.3. Analysis Sets

Within the enrolled population (subjects who signed consent form) the following analysis sets are distinguished:

- **The attempted implant set:** The attempted implant set consists of all enrolled subjects with an attempted TAVR implant procedure, defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia or conscious sedation administered, vascular line placed, TEE placed, or any monitoring line placed. Subjects will be analyzed according to their first attempted procedure. Enrolled subjects that do not receive an attempted TAVR implant are to be exited from the study. Time zero begins on the date of first attempted implant procedure.
- **The implanted (IMP) set:** The implanted set consists of all the attempted implant subjects who are actually implanted with the Medtronic TAV device. Subjects with an

attempted implant that do not actually receive a TAV are to be exited from the study following discharge from the index hospitalization. Time zero begins on the date of first attempted implant procedure.

- **Per-protocol (PP) set 1 for TAVR care pathway:** This per-protocol set 1 consists of all implanted subjects with percutaneous and transfemoral access only and no concomitant procedures including percutaneous coronary intervention (PCI). This per-protocol set 1 will be used for the secondary endpoint median days from index procedure to discharge. Time zero begins on the date of first attempted implant procedure.
- **Per-protocol (PP) set 2 for conduction disturbance pathway:** This per-protocol set 2 consists of all attempted implant subjects whose peri- and post-TAVR index procedure follows the conduction disturbance pathway management and cusp overlap technique. The cusp overlap technique followed can be defined as the 4 essential COT steps followed, which means the MUO case evaluation step 1, step 2 and/or 3, step 5 and step 15 are each followed. This per-protocol set 2 will be used for the secondary endpoint rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days.
- **Roll-in:** Roll-in subjects will not be analyzed with the study cohort attempted implant, implanted, or per protocol sets and will be analyzed separately using descriptive statistics.

8.1.4. Index Procedure

Index procedure is defined as the first procedure that the Medtronic EnVeo™ PRO Delivery Catheter System or Evolut™ PRO+ Delivery Catheter System is introduced.

8.2. General Methodology

Descriptive statistics will be used to report study data.

For continuous variables (e.g., age), the mean, median, standard deviation, minimum, maximum, and first and third quartiles 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 or event-free rates at 1 and 12 months will be presented. For these analyses, the time points will correspond to 30 days and 365 days post-implantation, respectively. At each time point with data, the product limit estimate of the event or event-free rates will be presented. In addition, 95% confidence interval using the Greenwood standard error 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 (for non-death events).

8.3. Missing Data

Every effort will be undertaken to minimize missing data. However, some missing data is inevitable, and the trial is designed with the expectation that there may be up to 6% of primary data missing at 12 months. 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.

8.4. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the attempted implant analysis set. Continuous variables will be summarized with means, medians, standard deviations, minimums, maximums, and first and third quartiles. Categorical variables will be summarized with frequencies and percentages.

8.5. 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 first and third quartiles. Categorical variables will be summarized with frequencies and percentages.

8.6. Interim Analyses

The first interim analysis will be conducted after 100 subjects are enrolled in the study cohort – attempted implant set and followed through 30 days post procedure.

As this is not a hypothesis driven study, additional interim analyses may occur as deemed necessary.

8.7. Echocardiographic Assessments After Reintervention

All post-reintervention echocardiographic data will be excluded from hemodynamic analyses unless specified otherwise. Echocardiographic assessments after the first reintervention date will be excluded from any analyses using echo data. Reinterventions will be based on CEC adjudication.

8.8. Evaluation of Endpoints

8.8.1. Primary Endpoint

The primary endpoint is the rate of all-cause mortality or all-stroke 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:

All-cause mortality or all-stroke event rate estimate will be provided at 30 days post procedure.

Data Collection and Analysis Dataset:

Data will be collected on a CEC CRF. This objective will be analyzed for both the attempted implant set, per-protocol (PP) set 1 for TAVR care pathway cohort, and per-protocol (PP) set 2 for Conduction Disturbance pathway.

Analysis Method:

A Kaplan-Meier analysis will be performed.

8.8.2. Secondary Endpoint #1

Median days from index procedure to discharge.

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:

Days from index procedure to discharge will be summarized.

Data Collection and Analysis Dataset:

Data will be collected on a Procedure (PROC) and/or Discharge (DISC) CRF. This objective will be analyzed for the attempted implant set, per-protocol (PP) set 1 for TAVR care pathway cohort, and per-protocol (PP) set 2 for Conduction Disturbance pathway.

Analysis Method:

Descriptive statistics will be provided. The mean, median, standard deviation, minimum, maximum, and first and third quartiles will be presented.

8.8.3. Secondary Endpoint #2

Percentage of subjects with ≥ moderate aortic regurgitation (AR) at discharge.

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:

Aortic valve function will be based on core lab echocardiographic recordings. The parameter to be estimated is the grade of aortic valve regurgitation using echo, in subjects at discharge.

Data Collection and Analysis Dataset:

Data will be collected on Core lab ECHOCARDIOGRAM CRF. This objective will be analyzed for both the implanted (IMP) set, per-protocol (PP) set 1 for TAVR care pathway cohort, and per-protocol (PP) set 2 for Conduction Disturbance pathway. In addition, AR data will be summarized at each follow up visit.

Analysis Method:

AR will be presented with frequencies and percentages at screening, discharge and 1-year post procedure.

8.8.4. Secondary Endpoint #3

Rate of pacemaker implant for new onset or worsening conduction disturbance 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:

Pacemaker implant for new onset or worsening conduction disturbance event rate estimate will be provided at 30 days post-procedure.

Data Collection and Analysis Dataset:

Data will be collected on a Permanent Pacemaker Implant CRF. This endpoint will be analyzed for both the attempted implant set and per-protocol (PP) set 2 for Conduction Disturbance pathway.

Analysis Method:

A Kaplan-Meier analysis will be performed. The overall rate of permanent pacemaker implantation at 30 days will be provided. The rates of permanent pacemaker implantation at 30 days by region (US/CAN, EMEA, and ANZ) centers will be provided and compared.

8.8.5. Additional Exploratory Endpoint #1

30-day and 1-year hospital re-admission rates.

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:

Rehospitalization event rate estimate will be provided at 30 days and 12 months post-procedure.

Data Collection and Analysis Dataset:

Data will be collected on a Rehospitalization (REHOSP) CRF. This endpoint will be analyzed for both the attempted implant set, per-protocol (PP) set 1 for TAVR care pathway cohort, and per-protocol (PP) set 2 for Conduction Disturbance pathway.

Analysis Method:

A Kaplan-Meier analysis will be performed.

8.8.6. Additional Exploratory Endpoint #2

1-year composite of all-cause mortality or all-stroke rates.

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:

Composite of all-cause mortality or all-stroke event rate estimate will be provided at 12 months post-procedure.

Data Collection and Analysis Dataset:

Data will be collected on an CEC CRF. This objective will be analyzed for both the attempted implant set, per-protocol (PP) set 1 for TAVR care pathway cohort, and per-protocol (PP) set 2 for Conduction Disturbance pathway.

Analysis Method:

A Kaplan-Meier analysis will be performed.

8.9. Safety Evaluation

Primary and secondary safety endpoints will be summarized as noted in Section 8.7 of this SAP. Adverse events will be provided in a listing and summarized.

The below 3 listings will be provided for the attempted implant set:

- A listing of deaths and reasons for deaths.
- A listing of adverse events with AE start and end dates, severity, outcomes, and procedure/device relatedness.
- A listing of device deficiencies.

9. Analysis for FX Addendum

9.1. Introduction

The Optimize PRO Clinical Investigation Plan (Parent protocol or Parent CIP) is the governing document for Optimize PRO Clinical Investigation Plan - FX Addendum. The purpose of the FX Addendum is to provide details and requirements for analysis unique to participation in the FX Addendum portion of the study.

9.2. Objective

The purpose of this analysis to collect post-market clinical evidence in the United States, on valve performance and procedural outcomes associated with the Evolut FX Device.

9.3. Endpoints

9.3.1. Primary Endpoints

The primary endpoint is the rate of all-cause mortality or all stroke at 30 days.

9.3.2. Secondary Endpoints

The following are the secondary endpoints:

- Median days from index procedure to discharge
- Percentage of subjects with ≥ moderate aortic regurgitation (AR) at discharge
- Rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days
- Percentage of subjects with an NCC depth of implant between 1.0 and 5.0 mm
- Percentage of subjects with an absolute canting value |NCC-LCC| of ≤ 2.0 mm

9.3.3. Additional Exploratory Endpoints

The following are additional exploratory endpoints:

- 30-day and 1-year hospital re-admission rates
- 1-year composite of all-cause mortality or all-stroke
- Percent of patients with a major vascular complication
- Percent of patients that require a recapture or resheath of the TAV
- Percent of patients in which the target depth of implant was achieved
- Orientation of valve relative to native anatomy

9.4. Sample Size

The sample size for the attempted implant population is approximately 150 subjects at approximately 10 sites in the US.

9.5. Statistical Methods

Refer to Section 8 for details on the statistical analysis for the Optimize PRO study. The roll-in analysis set will not be applicable for the FX Addendum. The analysis will be descriptive, and no statistical hypothesis tests will be performed.

The attempted implant set, implanted set, PP set 1 for TAVR care pathway, and PP set 2 for conduction disturbance pathway will be defined the same for subjects enrolled in the FX Addendum.

The primary analysis cohort for the primary endpoint and secondary safety and effectiveness endpoints will be the attempted implant set. Secondary and additional exploratory endpoints will be analyzed for both the attempted implant set, per protocol (PP) set 1 for TAVR care pathway cohort, and per protocol (PP) set 2 for Conduction Disturbance pathway. However, Percentage of subjects with an NCC depth of implant between 1.0 and 5.0 mm, Percentage of subjects with an absolute canting value |NCC-LCC| of ≤ 2.0 mm, Percentage of subjects in which the target depth of implant was achieved, and Echocardiography data will be analyzed based on the implanted set.

All post-reintervention echocardiographic data will be excluded from hemodynamic analyses unless specified otherwise. Echocardiographic assessments after the first reintervention date will be excluded from any analyses using echo data. Reinterventions will be based on CEC adjudication.

10. Changes to Planned Analysis

The planned analyses in this SAP are aligned with the planned analyses noted in the CIP (6.0, 04 May 2021). Additionally, all analyses defined for the FX Addendum are consistent with the version of the Addendum for which this plan was developed (3.0, 15 December 2022).

11. Validation Requirements

Level 1 validation (independent validation) will be used for the analysis datasets and the primary and secondary endpoints. Level 2 validation (peer review) will be used for additional analyses, data summaries, and listings.

12. References

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10. Auffret V, Puri R, Urena M et al. Conduction Disturbances After Transcatheter Aortic Valve Replacement: Current Status and Future Perspectives. Circulation 2017;136:1049-1069.

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12. International Standard ISO 14155:2011(E). Clinical investigation of medical devices for human subjects - Good Clinical Practice.

13. Statistical Appendices

There are no statistical appendices for this study.