Medtronic Statistical Analysis Plan	
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Clinical Investigation Plan Identifier	MDT2-15-14
Study Product Name	Avalus aortic bioprosthesis 17mm
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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	PERIGON Japan Study
Clinical Investigation Plan Identifier	MDT2-15-14
Clinical Investigation Plan Version	1.0 (CIP PERIGON Japan PMR (EN&JP) Ver1.0 21Nov2019)
Sponsor/Local Sponsor	Medtronic Japan, Co., Ltd. 1-2-70 Konan, Minato-ku, Tokyo 108 - 0075 Japan

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Elizabeth Gearhart, Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
EOAI	Effective Orifice Area Index
NYHA	New York Heart Association
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Device Effects

3. Introduction

PERIGON Japan is a multi-center, interventional, non-randomized trial with long-term (3-5 years) follow up of subjects enrolled in the PERIGON Japan study and implanted with the Avalus valve. The purpose of this study is to evaluate the safety and effectiveness of the Medtronic 17mm Avalus aortic valve bioprosthesis in a patient population that has undergone SAVR. Regulatory approval was granted before the 5-year subject follow-up period was over. The rest of the follow-up period will be conducted under Ethical Guidelines for Medical and Health Research Involving Human Subjects. This Statistical Analysis Plan (SAP) is designed to document, before data are analyzed, the rationale for the design of the study and the planned analyses that will be included in study reports, based on PERIGON Japan CIP version 1.0 (CIP PERIGON Japan PMR (EN&JP) Ver1.0 21Nov2019). Specifically, this SAP will document the planned analyses for the 4 year annual report and 5 year final report.

4. Study Objectives

The purpose of this study is to evaluate the safety and effectiveness of the Medtronic 17mm Avalus aortic valve bioprosthesis in a patient population that has undergone SAVR in the preceding MDT-2215 trial. Regulatory approval was granted before the 5-year subject follow-up period was over. The follow-up period after regulatory approval is granted will be conducted under Ethical Guidelines for Medical and Health Research Involving Human Subjects.

5. Investigation Plan

A multi-center, interventional, non-randomized trial with long-term follow up of subjects enrolled in MDT-2215 trial and implanted with a 17mm Avalus valve. The total expected duration of the trial is approximately 5 years.

5.1 Inclusion Criteria

- Subject enrolled in the MDT-2215 study and being followed up continuously.

5.2 Exclusion Criteria

- Subjects will be excluded if study investigator considers it is difficult for the subject to participate in the study because of medical reasons.

6. Determination of Sample Size

A total of 11 subjects were implanted with the Avalus valve in the MDT-2215 study, at the time of protocol approval, 10 subjects remained in active follow-up. Subjects who meet all inclusion criteria and no exclusion criteria at the time of this study commencement will be invited to participate. All implanted subjects from the MDT-2215 study are included in all analysis up to time of study exit.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

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

7.1.2 Clinical Investigation Plan (CIP) Deviations

A protocol deviation is defined as an event within a study that did not occur according to the CIP or Clinical Trial Agreement. Protocol deviations will be reported regardless of whether they are pre-approved by Medtronic. 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.

7.1.3 Analysis Sets

The primary analysis will be evaluated for the implanted population. The implanted population consists of all enrolled subjects who are actually implanted with the Medtronic 17mm Avalus aortic valve bioprosthesis. To be considered implanted, the subject's device disposition form must show at least one device with a final disposition of "Implanted." Time zero begins at the date of the procedure.

7.2 General Methodology

The study objective and endpoints are descriptive, and no statistical hypothesis testing will be performed. Continuous variables will be summarized as means, medians, standard deviations, first and

third quartiles, minimums, and maximums. Categorical variables will be summarized as frequencies and percentages.

7.3 Center Pooling

The analysis will include data from all contributing sites, no site pooling analyses are planned.

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

Unless specified otherwise in each objective, no statistical techniques will be used to impute missing data. 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 potential impact of missing data can be assessed.

In the case of partial dates, the general rule is as follows:

- 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 and no later than the study exit date. If additional information about the partial dates might be known, for example, the event occurs after 15th of the month, then data may be analyzed as if it occurred on the 16th of the month.

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 the implanted set. Continuous variables will be summarized as means, medians, standard deviations, first and third quartiles, minimums, and maximums. Categorical variables will be summarized as frequencies and percentages.

7.7 Treatment Characteristics

Surgical procedure characteristics will be summarized for the implanted set. Continuous variables will be summarized as means, medians, standard deviations, first and third quartiles, minimums, and maximums. Categorical variables will be summarized as frequencies and percentages.

7.8 Interim Analyses

No interim analysis is planned.

7.9 Evaluation of Objectives

7.9.1 Primary Endpoint

The primary endpoints are as follows:

1. Efficacy - Functional and Anatomical:
   a. Changes in New York Heart Association (NYHA) Class at 1 year compared to baseline and effective orifice area index (EOAI) at 1 year post implant.

The primary endpoints were achieved with the preceding MDT-2215 trial. The primary endpoints are not applicable to PERIGON Japan research, which is a long term follow-up study.

7.9.2 Secondary Endpoints

The Secondary Endpoints are as follows:

1. Assessment of NYHA classification will be evaluated annually through 5 years.

   NYHA functional classification will be summarized using frequency tables. NYHA functional class will be evaluated based on the percentage of subjects in each specific NYHA class at each postoperative time-point and the percentage of subjects at each postoperative time-point who have improved, worsened, or not changed in NYHA class compared to preoperative baseline.

2. Effective orifice area index will be evaluated annually through 5 years.
3. Hemodynamic performance annually up to 5 years including:
   a. effective orifice area
   b. peak pressure gradient
   c. mean pressure gradient
   d. valvular regurgitation
   e. performance index
   f. cardiac output
   g. cardiac index

   Valvular regurgitation will be summarized with a frequency table for each visit interval and the other Hemodynamic Performance endpoints will be summarized as with continuous data. For each subject with paired data, the change from baseline may also be calculated at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years.

7.9.3 Safety Endpoints

The following valve-related adverse events as defined by ISO5840:2009 will be evaluated in this study:

1. Thromboembolism
2. Thrombosis
3. Hemorrhage (all and major)
4. Paravalvular leak (all and major)
5. Endocarditis
6. Hemolysis
7. Structural valve deterioration
8. Non-structural dysfunction
9. Reintervention

10. Explant
11. Death

    Safety of the valve will be evaluated by the incidence of valve-related adverse events, reintervention, explant, and death. The endpoints will be summarized and the number of events as well as number and proportion of subjects experiencing an event will be reported. The endpoint is descriptive and no statistical hypothesis test will be performed.

7.10 Safety Evaluation

The analysis of the study safety data will be based on CEC-adjudicated events. AE summaries will be based on MedDRA coding. To provide a comprehensive safety evaluation, the safety data will be presented at aggregate and individual event levels as tables and listings. Any Unanticipated Adverse Device Effects (UADEs) will be reported as proportions of subjects experiencing the event.

7.11 Changes to Planned Analysis

Analysis corresponds to the planned analysis in the PERIGON Japan Clinical Investigation Plan Version 1.0 (CIP PERIGON Japan PMR (EN&JP) Ver1.0 21Nov2019).

8. Validation Requirements

Statistical programming for the analysis datasets, primary endpoint and secondary endpoints require Level 1 (independent) validation. Other objectives and sub-group analyses require level 2 (peer review) validation.