Endurant Evo International Clinical Trial

Statistical Analysis Plan (SAP)

Version 1.0

04 May 2015

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1. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of Endurant Evo International Clinical Trial. This document is designed for internal use as a guideline for study Biostatistician and Statistical Programmer(s). Study protocol is the primary resource if clarification is needed for the contents of this document. Analysis results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report for this study.

As with any statistical analysis plan, the proposed methods and approaches to the data analysis should be viewed as flexible. Changes to the plan may arise if the emerging picture suggests that deviations from the original plan would provide a more reliable and valid analysis of the data. The purpose of this plan is to provide general, and in some instances, specific guidelines from which the analysis will proceed. Nonetheless, sound statistical reasoning must substantiate deviations from these guidelines.

2. Study Objective

The purpose of the Endurant Evo International Clinical Trial is to evaluate the safety and effectiveness of the Endurant Evo AAA Stent graft system for endovascular treatment of subjects with infrarenal abdominal aortic or aortoiliac aneurysms. The clinical evidence collected as part of this trial is expected to be used to support regulatory approval and subsequent commercialization of the Endurant Evo AAA Stent graft system in multiple international geographies.

Data collected during this trial may also be used in conjunction with data collected during a concurrently enrolling IDE trial to support PMA Approval of the Endurant Evo AAA Stent graft system in the United States.

The primary safety objective is to evaluate the safety of the Endurant Evo AAA stent graft system for the endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms. Safety will be assessed through the proportion of subjects who have a Major Adverse Events (MAE) reported within 30 days post-implantation.

The primary effectiveness objective is to evaluate successful delivery and deployment of the Endurant Evo AAA stent graft system with successful removal of the delivery system during the index procedure.

Secondary objectives include descriptive analyses of secondary endpoints as well as acute procedural and clinical utility measures.

3. Study Design

The Endurant Evo International Clinical Trial is a prospective, multi-center, pre-market, non-randomized, single-arm trial.

3.1. Treatment and Subject Enrollment

The study population will include those subjects who are appropriate candidates for endovascular repair of infrarenal abdominal aortic or aortoiliac aneurysms, and who meet the Inclusion/Exclusion criteria (defined in the Clinical Investigation Plan Section D).

For subjects that are treated with the bifurcated stent graft minimal 3 pieces will be implanted in the target segment; one bifurcated stent graft component and 2 limb stent graft components. For subjects that are treated with the AUI component approximately 2 pieces will be implanted in the

target segment; the AUI stent graft component and one limb stent component. Additional stent graft extensions might be needed to cover the complete target lesion length.

A sample of 40 subjects will be treated and evaluated at the 30-day primary safety endpoint. Data from these 40 subjects will be analyzed and used to support regulatory approval. All subjects treated will continue to be followed under this investigational protocol beyond the 30-day primary endpoint until 5 years post-implantation.

Subjects will have required follow-up evaluations at the following time points:

- 1 month following the index procedure
- 6 months following the index procedure
- 12 months following the index procedure
- Annually thereafter, until 5 years post index procedure

In addition to the 40 subjects to support regulatory approval, approximately 30 additional subjects may be treated to support geography-specific regulatory requirements. For these subjects, all inclusion/exclusion criteria, study methods, follow-up schedule and data-collected will be identical to the first 40 subjects.

Approximately 10 sites will participate in the clinical study. For the initial 40 subjects to be analyzed, no more than 20% (i.e. 8 subjects) will be treated from a single investigational site. Enrollment will be halted at sites that reach the 20% enrollment cap. Following enrollment of the first 40 subjects, up to approximately 30 additional subjects can be enrolled and a site where enrollment has been halted may resume enrolling. For the total cohort of 70 subjects again no more than 20% of subjects will be treated from a single investigational site which results in a maximum enrollment per site of 14 subjects.

The total enrollment period is not expected to exceed 12 months. All treated subjects will be followed until 5 years post-implantation. Thus total study duration from first subject treated to final subject exit could approach 6 years.

3.2. Sample Size Consideration

A sample of 40 subjects will be treated and analyzed to support regulatory approval. The sample size of 40 subjects is considered adequate to assess the primary safety endpoint, which is defined as the proportion of subjects experiencing a MAE within 30 days post-implantation.

Considering the reported MAE rate from the ENGAGE Post-Approval Study (PAS), which evaluated the long-term safety and effectiveness of the Endurant Stent graft system in 328 subjects[1], it is estimated that 2 of 40 (5%) subjects treated with Endurant Evo AAA stent graft system will experience a MAE. The precision of this assumed 5% point estimate can be assessed by calculating the difference from the 1-sided 95% upper confidence limit. This difference, or margin of error, is calculated to be < 10% for the Endurant Evo International Clinical Trial and is therefore considered adequate to assess the primary safety endpoint[2, 3].

3.3. Analysis Strategy

The Endurant Evo International Clinical Trial is not hypothesis driven; all endpoints will be analyzed descriptively.

4. Analysis Sets

4.1. Primary analysis set

All analysis will be performed on the intent-to-treat (ITT) analysis set, which includes all subjects who underwent the arterial access with an attempt to introduce the Endurant Evo AAA stent graft.

4.2. Subset

Subset analysis will be performed by-sex for the primary endpoints descriptively and reviewed for clinical significant difference.

5. Endpoints

Primary Safety Endpoint

The primary safety endpoint is defined as the proportion of subjects experiencing a MAE within 30 days post-implantation. MAEs include the occurrence of any of the following events:

- All-cause mortality
- Bowel ischemia
- Myocardial infarction
- Paraplegia
- Procedural blood loss ≥1000 cc
- Renal failure
- Respiratory failure
- Stroke

Primary Effectiveness Endpoint

Technical success at the index procedure (as assessed intra-operatively) is defined as successful delivery and deployment of the Endurant Evo AAA Stent graft system in the planned location and with no unintentional coverage of both internal iliac arteries or any visceral aortic branches and with successful removal of the delivery system.

Secondary Endpoints

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- All cause-mortality within 30, 183, and 365 days
- Aneurysm-related mortality within 30, 183, and 365 days
- Secondary procedures to correct Type I and III endoleaks within 30, 183 and 365 days
- Secondary endovascular procedures within 30, 183 and 365 days
- Serious adverse events within 30, 183 and 365 days
- Aneurysm rupture within 30, 183 and 365 days
- Conversion to open surgery within 30, 183 and 365 days
- Major adverse events within 183 and 365 days
- Stent graft migration at 12-month follow-up visit (as compared to 1-month imaging)
- Aneurysm expansion > 5 mm at 12-month follow-up visit (as compared to 1-month imaging)
- All endoleaks based on imaging findings at 1- month, 6-month and 12-month visits
- Stent graft occlusion based on imaging findings through 6 months and 12 months
- Device deficiencies based on imaging findings through 6 months and 12- months

Secondary endpoints will be assessed at annual follow-up visits until 5 years post-implantation.

Additional Observations

The following acute procedural observations and clinical utility measures will be reported:

- Mean duration (min) of procedure (time between initial skin access to final skin closure)
- Proportion of subjects who underwent general/local/epidural/spinal anesthesia
- Proportion of subjects who underwent unilateral/bilateral percutaneous access
- Proportion of subjects requiring blood transfusions, excluding cell saver
- Mean volume (cc) of estimated blood loss
- Mean duration (min) of radiation exposure
- Radiation exposure (mGy)
- Mean length of time (hours) in intensive care unit
- Mean length of time (days) of hospital stay (from the index procedure to hospital discharge)

Health-related quality of life outcomes will be assessed at baseline, 1-month, 6-month and 12-month follow-up visits using the EQ5D questionnaire.

6. Definitions

Detailed definitions for secondary endpoints are provided in Clinical Investigational Plan Appendix L.2.

7. Interim Analysis

No interim analysis is planned prior to the regulatory submission.

8. Statistical Methods of Analyses

8.1. General consideration

All endpoints will be analyzed descriptively. In general, qualitative parameters will be described by their distribution frequencies; quantitative parameters will be described by their mean, standard deviation, minimum, maximum, median, and number of subjects with assessable data.

The survival from all-cause mortality over one year time or longer will be described by the Kaplan-Meier survival curve and the associated Kaplan-Meier estimate will be calculated along with its standard error using the Greenwood method.

For events such as AEs, deaths and secondary procedures, that can occur or are observed at any time during the study, no time window will be applied. For such events, an event that occurs “within 1 month or 30 days” is an event that takes place between Days 0 to 30, inclusive. Similarly, an event that occurs “within 12 months or 365 days” is an event occurring between Day 0 to Day 365, inclusive. Date of event onset will be used to determine when the event occurred. Day 0 is referring to the day of index procedure.

For image-based assessments, such as stent-graft endoleak, patency, and other observations, the following time windows will be applied for by-visit data summaries:

Table 1: Time Windows for Statistical Analyses

Study Visit	Target Day	Time Window
Implant	Day 0	Day 0
1 Month	Day 30	1 – 90 days
6 Months	Day 183	91 – 304 days
12 Months	Day 365	305 – 548 days
2 Year	Day 731	549 – 913 days
3 Year	Day 1096	914 – 1278 days
4 Year	Day 1461	1279 – 1644 days
5 Year	Day 1826	1645 – 2009 days

If different type of mages are used but have different finding in the same time window, the imaging technique and sensitivity matrix (Appendix 12.1) will be applied. Finding from higher visibility image will be used for analysis. If there are two or more assessments from the same type of image in the same time window, then the assessment closest to the target day will be used in the analysis of event rate at a given time point.

Statistical analyses for this study will be performed using the Statistical Analysis System (SAS) for Windows (Version 9.1 or higher) or other widely-accepted statistical or graphical software.

8.2. Baseline Characteristics and Poolability of Data

Summaries of subject disposition, demographics, baseline characteristics, and subject accountability will be provided.

Data from all geographies will be pooled for analysis. The poolability is assumed given that study data are collected and managed by a central database under one data management plan, including the use of Data Monitoring Committee (DMC), Clinical Event Committee (CEC), Independent Physician Reviewer (IPR) and core imaging laboratory.

8.3. Handling of Missing Data

During statistical analysis, imputation of missing data will not be performed except for data related to the onset date of an adverse event or a death. In cases where the onset date of an event or a death is incomplete and unresolvable via data query, the 15th day of the known month or July 1st of the known year will be used.

8.4. Analysis of the Primary Endpoints

For the primary endpoint, a one-sided 95% confidence interval based on binomial distribution will be constructed in addition to event count and frequency.

The analysis for the regulatory submission will take place when 40 subjects have been implanted with the study device for at least 30 days except that a subject expires early. Endpoints as defined in Section 5 will be analyzed for these 40 ITT subjects.

MAE Rate Calculation:

All MAEs will be adjudicated by the Clinical Event Committee (CEC) per protocol expect for the procedural blood loss ≥1000 cc, which will be site reported at the index procedure. MAE rate will be calculated as follows (Table 2):

Table 2: MAE Rate Calculation:

MAE rate = m/(m + k)	Within 30 Days	Within 183 Days	Within 365 Days
m = No. of Subjects Who Had MAE(s)	No. of subjects who had at least one MAE with onset day from Day 0 to Day 30, inclusive.	No. of subjects who had at least one MAE with onset day from Day 31 to Day 183, inclusive.	No. of subjects who had at least one MAE with onset day from Day 184 to Day 365, inclusive.
k = No. of Subjects Who Had No MAE	No. of subjects who have been in study for at least 1 day and without an MAE.	No. of subjects who have been in study for at least 91 days and without an MAE.	No. of subjects who have been in study for at least 305 days and without an MAE.

If a subject is early terminated from the study, the last day that the subject has been seen will be the duration in study, which can be the day of last follow-up, last imaging taken, an AE reported, or withdrawal from the study. If a subject is still in the study, the duration in study will be the time from index procedure to the cut off day that the database is locked or data snapshot is taken.

Imaging based Event Rate Calculation:

Imaging assessment will be performed by site as well as the core lab. Assessments from the core lab will be analyzed separately from those by site. Imaging based event rate will be calculated using statistical analysis windows as follows (Table 3):

Table 3: Imaging based Event Rate Calculation:

Event rate = m/n	At1 Month	At 6 Months	At 12 Months
m = No. of Subjects Who Had Event(s)	No. of subjects who had an event with scan day within the 1-month window.	No. of subjects who had an event with scan day within the 6-month window.	No. of subjects who had an event with scan day within the 12-month window.
n = No. of Subjects Who Had Readable Images	No. of subjects who had a readable image within the 1-month window.	No. of subjects who had a readable image within the 6-month window.	No. of subjects who had a readable image within the 12-month window.
Event rate = m/n	Through1 Month	Through 6 Months	Through 12 Months
m = No. of Subjects Who Had Event(s)	No. of subjects who had an event with scan day within the 1-month window.	No. of subjects who had an event with scan day within 1- or 6-month windows.	No. of subjects who had an event with scan day within 1-, 6- or 12-month windows.
n = No. of Subjects Who Had Readable Images	No. of subjects who had a readable image within the 1-month window.	No. of subjects who had an event (counted in m) or had a readable image	No. of subjects who had an event (counted in m) or had a readable image

		within the 6-month window.	within the 12-month window.

8.5. Analysis of the Secondary Endpoints

Descriptive statistical analyses will be performed on secondary endpoints. No inferential statistical analysis is planned for secondary endpoints.

Event rates such as mortality, secondary procedures, serious adverse events, conversion to open surgery, and aneurysm ruptures will be calculated in the same way as the MAE rate, specified in Table 2.

The survival from all-cause and aneurysm-related mortality over one year time or longer will be presented with the Kaplan-Meier survival curve and the associated Kaplan-Meier estimate will be calculated along with its standard error using the Greenwood method.

Imaging based event rate such as stent graft migration, aneurysm expansion, endoleaks, stent graft occlusions, and device deficiencies will be calculated in the way as specified in Table 3.

9. Additional Data Summaries / Supplemental Analyses

Descriptive data summaries will be provided for acute procedural observations and clinical utility measures.

10. Data Screening and Acceptance

Data management will be done according to Medtronic SOPs and the Data Management Plan for this clinical study. These documents will be made available upon request.

All collected data will be reviewed for completeness, correctness and consistency. In case of issues, queries will be sent to the investigator or designee to complete, correct or comment the data.

11. List of Planned Tables, Listings, and Figures

List of planned tables, listing, and figures for the analyses can be found in a separate table shell document.

12. Appendices

12.1. Imaging Technique and Sensitivity

Anatomy/Stent Graft Issue Detected	CT with contrast	CT without contrast	MRA	MRI	Abdominal X-ray	Duplex CDUS (Ultrasound)	Angiogram, Aortagram and Arteriogram
AAA Diameter and Length	1	2	1	2	4	3	3
Stent graft migration	1	2	1	2	3	4	2-3
Stent graft fracture	2	3	2	3	1	4	2-3
Stent graft kinking	2	3	2	3	1	4	2-3
Stent graft twisting	2	3	2	3	1	4	2-3
Stent graft patency	1	4	1	4	4	2	2-3
Endoleaks	1	4	1	4	4	2	2-3
Occlusion	1	4	1	4	4	2	2-3
Stenosis	1	4	1	4	4	2-3	2-3
Stent Graft Fabric Defect	1	4	1	4	4	4	2-3
1= Highly visible	2 = visible	3 = Not very visible (potential artifacts)				4 = Invisible	

12.2. Table, listing, and figure templates/shells

A separate document includes planned table, listing and figure templates/shells.

13. References

1. PMA P100021/R, (24-Month Interim Post Approval Study Status Report ENGAGE Post Approval Study Endurant Stent Graft System, 11Dec2012.

2. United States Government Accountability Office (2010) Report to Congressional Requesters: FDA's Consideration of Evidence from Certain Clinical Trials. GAO-10-798, p 17.

3. Wangge G, Klungel OH, Roes KCB, de Boer A, Hoes AW, et al. (2010) Room for Improvement in Conducting and Reporting Non-Inferiority Randomized Controlled Trials on Drugs: A Systematic Review. PLoS ONE 5(10): e13550. doi:10.1371/journal.pone.0013550.