Endurant Evo
US Clinical Trial

Statistical Analysis Plan (SAP)

Version 1.0

15 April 2015

Prepared for:
Medtronic Aortic and Peripheral Vascular

Prepared by:
Yuqing Dai

TABLE OF CONTENTS

1. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of Endurant Evo US 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 Objectives

The purpose of the Endurant Evo US Clinical Trial is to demonstrate that the Endurant Evo Abdominal Aortic Aneurysms (AAA) Stent graft system is safe and effective for endovascular treatment of infrarenal abdominal aortic or aortoiliac aneurysms. The clinical evidence collected as part of this trial will be used in conjunction with data collected during the concurrently enrolling Endurant Evo International Clinical Trial to support Pre-Market Application (PMA) Approval of the Endurant Evo AAA Stent graft system.

The primary safety objective is to demonstrate the safety of the Endurant Evo AAA Stent graft system for the endovascular treatment of 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 demonstrate successful delivery and deployment of the Endurant Evo AAA Stent graft system with successful removal of the delivery system during the index procedure as well as the treatment success at 12 months.

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

3. Study Design

The Endurant Evo US 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 Aorto-Uni-Iliac (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.

Globally, a total of 140 subjects will be concurrently enrolled in the United States and outside the United States to support the primary endpoints. Up to 50% of subject data used to support PMA approval may come from subjects enrolled at sites outside of the US under a separate CE Mark study protocol; called the Endurant Evo International Clinical Trial protocol.

The Endurant Evo International Clinical Trial protocol and Endurant Evo US Clinical Trial protocol will be identical with respect to the inclusion/exclusion criteria, and follow up data collection.

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

Subjects will be followed until the last subject enrolled has completed the 1 year follow-up visit or until PMA approval is obtained in the US (whatever is later), however, Medtronic will work with FDA to determine if longer term follow after PMA approval is required.

The Endurant Evo Global Clinical program will be conducted at up to 30 sites worldwide with up to 20 sites participating under the Endurant Evo US Clinical trial protocol in the United States and with approximately 10 sites participating under the Endurant Evo International Clinical trial protocol outside the Unites States. In the United States, a minimum of 70 subjects will be enrolled at up to 20 investigational sites. Investigators at any single site may not enroll more than 20% of the total global enrollment (140 subjects) in the trial.

The total enrollment period is not expected to exceed 12 months. However, if a minimum of 50 high angulation indication subjects are not enrolled as part of the first 140 subject cohort, Medtronic will submit the PMA application to obtain approval for the 60°angulation indication with the 140 subject cohort data. In this event, Medtronic will continue enrollment for the high angulation indication and as result the total enrollment may be extended up to 2 years.

3.2. Analysis Strategy

The Endurant Evo US Clinical Trial will focus on balancing pre- and post-market clinical data to establish safety and effectiveness. Study success is defined as rejecting the null hypothesis for the primary safety endpoint test (≥20%), with a condition upon rejecting the null hypothesis for the post-market primary effectiveness test (≤80%). As such, the following analyses will be submitted:

- Pre-market: 30-day primary safety endpoint (hypothesis based, see 8.4)
- Pre-market: 6-month effectiveness analysis (descriptive)
- Post-market: 12-month primary effectiveness endpoint (hypothesis based, see 8.4)

The proposed clinical strategy described in this section will allow for appropriate evaluation of the safety and effectiveness of the Endurant Evo AAA stent graft system. Safety will be established through the hypothesis-based primary safety endpoint at 30 days. Reasonable assurance of effectiveness will be provided via the pre-market 6-month analysis and then confirmed at the 12-month post-market primary effectiveness endpoint.

3.3. Sample Size Consideration

The sample size for the Endurant Evo global program is calculated for both the primary safety endpoint and the primary effectiveness endpoint.

It is expected that the Endurant Evo AAA stent graft system will result in a MAE rate at 10% with respect to the primary safety endpoint and 90.5% treatment success for the primary effectiveness endpoint according to its predicates' performances shown in Table 1.

In order to pass both hypothesis tests with an overall study power of 80%, a sample size of 119 evaluable subjects will be required to pass each hypothesis with 90% statistical power (target significance level is 0.025.) To account for attrition of 15% (85% imaging compliance) at 12 months, 140 subjects will be enrolled globally to ensure at least 119 evaluable subjects. Note that a minimum of 50 subjects will be enrolled with the high neck angulation indication and a minimum of 70 subjects will be enrolled with percutaneous access. If a minimum of 50 high angle indication subjects are not enrolled as part of the first 140 subject cohort, Medtronic will continue enrollment for the high angulation indication but submit the PMA application to obtain approval for the 60° angulation indication with the 140 subject cohort data.

Table 1: Clinical Data from Talent AAA eLPS and Endurant Studies[1]

Predicates	MAE within 30 Days	Successful Aneurysm Treatment at 12 Months
Talent AAA eLPS Arm	11% (18/166)	86% (107/125)
Endurant IDE Bifurcated Arm	4% (6/150)	95% (115/121)
Endurant IDE AUI Arm	11% (5/44)	97% (35/36)

4. Analysis Sets

4.1. Primary analysis set

The primary analysis set will consist of the Intent-to-Treat (ITT) population. This analysis set is defined as all subjects who were enrolled. The subject will be considered to be enrolled when arterial access has been established with an attempt to introduce the Endurant Evo AAA stent graft.

4.2. Secondary analysis set

A secondary analysis set will be the Per-Protocol population. This analysis set is comprised of all ITT subjects who met inclusion and exclusion criteria, received the test device, and completed 12- month follow-up (including death but excluding withdrawal or lost to follow-up subjects within the 12- month follow-up period).

[1] Results are from the Talent AAA (Talent AAA Control data referenced in Endurant Clinical Study Report, Appendix 2 of M090018_M005 Clinical Module), Endurant (P100021) PMA 90-day update submission submitted via P100021/A002, and Endurant PMA supplement via P100021/S021. The results on successful aneurysm treatment are reported at 12 months and included all occlusions through the time period

4.3. Subsets

Subset analyses by-sex, by-race (based on subjects enrolled in the US only, since collection of race and ethnicity data may not be allowed outside the US as per local law and regulation), and by-region/study site will be performed on the primary safety and effectiveness endpoints using descriptive statistics and reviewed for clinical significant difference.

In addition to the full cohort analyses, separate descriptive analyses on the AUI sub-group and percutaneous access subgroup will be provided in the PMA submission. Percutaneous or surgical cut-down is the access method used for delivering the main section or AUI device.

Subset analysis of the subjects treated with percutaneous access vs. surgical cut-down will be compared on various access site complications and conversions to a different access site or type of access.

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

The primary effectiveness endpoint is defined as the proportion of subjects with both technical success at the time of index procedure and treatment success at 12 months post-implantation. Successful aneurysm treatment is achieved based on the following criteria:

- 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

AND

- Treatment success consisting of freedom from:
    - AAA diameter increase, defined as > 5 mm increase in maximum diameter as measured on CT scan (or MRA/MRI) at 12-month follow-up as compared to 1-month imaging
    - Types I and III endoleaks at 12-month follow-up including those requiring intervention through 12 months
    - Aneurysm rupture within 365 days
    - Conversion to surgery within 365 days
    - Stent graft migration resulting in a serious adverse event or requiring secondary intervention through 12 months

- Stent graft occlusion through 12 months

Secondary Endpoints

The following secondary endpoints will be evaluated:

- 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 183 and 365 days
- Secondary procedures within 183 and 365 days
- Serious adverse events within 30, 183, and 365 days
- Conversion to open surgery within 183 and 365 days
- Aneurysm ruptures within 183 and 365 days
- Major adverse events within 183 and 365 days
- Stent graft migration at 6- and 12-month follow-up visits (as compared to 1-month imaging)
- Aneurysm expansion >5 mm at 6- and 12-month follow-up visits (as compared to 1-month imaging)
- All endoleaks based on imaging findings at 1-, 6-, and 12-month follow-up visits
- Stent graft occlusions based on imaging findings through 1-, 6- and 12 months
- Device deficiencies based on imaging findings through 6 and 12 months.

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 the primary and secondary endpoints are provided in Clinical Investigational Plan Appendix L.2.

7. Interim Analysis

No interim analysis is planned prior to the PMA submission.

8. Statistical Methods of Analyses

8.1. General consideration

All observations 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.

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 2: 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
In case long term follow up data will be collected, the following time windows will apply.		
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

Descriptive data summaries of subject disposition, demographics, baseline characteristics, and subject accountability will be provided.

The poolability of subjects enrolled in the Endurant Evo US Clinical trial and subjects enrolled in the Endurant Evo International Clinical Trial is assumed given that both study protocols will be similar with respect to, inclusion/exclusion criteria, clinical treatment, definitions of clinical events, one data monitoring plan, Data Monitoring Committee (DMC), Clinical Event Committee (CEC), Independent Physician Reviewer (IPR) and core imaging laboratory.

At the data analysis stage, the data poolability will be reviewed for the primary endpoints. Results from Endurant Evo US Clinical Trial and Endurant Evo International Clinical Trial subjects will be presented separately for clinical review as well as tested using a Chi-square test.

A poolability analysis among geographies/investigational sites will be assessed descriptively for the primary endpoints by geographic regions. Small investigational sites (less than 5 subjects) will be grouped with other nearby sites for the by-region analysis.

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.

Sensitivity analysis using tipping point method may be performed, as needed, to assess the impact of missing data.

8.4. Analysis of the Primary Endpoints

Statistical Hypothesis:

The primary safety endpoint will be tested against a predetermined safety Performance Goal (PG) using the following statistical hypotheses:

$H0: p \geq 20\%$ vs. $H1: p < 20\%$

where p is the proportion of subjects experiencing a MAE within 30 days of the index procedure in the target population of subjects treated with the Endurant Evo AAA Stent graft system and 20% is the safety PG.

The primary effectiveness endpoint will be tested against a predetermined effectiveness PG using following statistical hypotheses:

$H0: q \leq 80\%$ vs. $H1: q > 80\%$

where q is the proportion of subjects who have a successful aneurysm treatment in the target population of subjects treated with the Endurant Evo AAA Stent graft system and 80% is the effectiveness PG.

If the null hypothesis (H0) is rejected at the one-sided 0.025 statistical significance level, it is considered that the PG for the associated endpoint has been reached.

Both safety and effectiveness endpoints are dichotomous study outcomes; hence, an exact method based on the binomial distribution will be used for the hypothesis testing.

MAE Rate Calculation:

All MAEs will be adjudicated by the Clinical Event Committee (CEC) per protocol. MAE rate will be calculated as follows (Table 3):

Table 3: 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. For the primary effectiveness endpoint analysis, its imaging components are based on the code lab assessments only. Imaging based event rate will be calculated using statistical analysis windows as follows (Table 4):

Table 4: 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 within the 6-month window.	No. of subjects who had an event (counted in m) or had a readable image 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 3.

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 4.

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 Appendix.

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 attachment includes a list of planned tables, listings and figures.