POST APPROVAL STUDY EVALUATING THE LONG TERM SAFETY AND EFFECTIVENESS OF THE ENDURANT STENT GRAFT SYSTEM

(ENGAGE PAS)

Statistical Analysis Plan (SAP)

Investigational Plan Number: 10012289

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1 INTRODUCTION

This document outlines the detailed statistical analysis methods to be implemented for the Post-Approval Study (PAS) of Endurant™ Stent Graft and Delivery System (hereafter referred to as the Endurant Stent Graft System). This document is designed for internal use as a guideline for study Biostatistician and Statistical Programmer(s). The 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.

This version of this Statistical Analysis Plan (SAP) is created under the study protocol version B, which received the FDA approval on May 9, 2011 via PMA Supplement P100021/S002, and prior to enrollment of the first de novo subject.

2 STUDY OBJECTIVES

The study objective is to evaluate the long term safety and effectiveness of the Endurant Stent Graft System assessed at 5 years through freedom from Aneurysm-Related Mortality (ARM).

3 STUDY DESIGN

3.1 Study Enrollment

The post-approval performance of the Endurant Stent Graft System will be evaluated in a single-arm, non-controlled, non-randomized, and multi-center clinical study. Subjects must be diagnosed with an abdominal aortic aneurysm, considered candidates for endovascular repair, and fulfill the study eligibility criteria per protocol. Eligible subjects will be implanted with the Endurant Stent Graft System.

A total of 178 subjects will be prospectively enrolled. The Endurant Bifurcated Arm test group, consisting of 150 subjects from the FDA approved Endurant US PMA submission, will be rolled into the prospectively enrolled cohort, resulting in a total cohort of 328 subjects.

The post-approval study for Endurant Stent Graft System is expected to start enrolling in the United States in the summer of 2011. Initially, 20 sites will be enrolled in the study. As many as 25 investigational sites may participate. All sites will use the same investigational plan. The enrollment period is estimated to be 16 months. Investigators at any site may not enroll more than 20% (35 subjects) of the new subject enrollment population.

Data from 178 patients, who undergo AAA treatment with the Endurant Stent Graft System and complete 5 year follow-up, will be combined with the data from the 150 subject Endurant Test Group from the Endurant US IDE PMA submission for analysis and summary. Data from the study will be submitted to the FDA at 6 month intervals for the first two years, and annually thereafter. The duration of the clinical study from first enrollment through final follow-up and close-out is expected to be 6 years 5 months.

3.2 Analysis Strategy

The primary statistical analysis will be based on freedom from Aneurysm Related Mortality (ARM) at 5 years, and compared to a Performance Goal (PG), determined from literature.

This comparison will be performed based on a Kaplan-Meier (KM) analysis of the ARM. By-sex/gender and by-race (white vs. non-white) subset analyses will be performed on the 5-year ARM rate.

Data generated from the clinical study will be analyzed as specified in the following sections. Tabular and graphical data representations will be provided. In general, for categorical variables, frequency and percentage will be presented as descriptive statistics. For continuous variables, number of observations, mean, standard deviation, median, minimum, and maximum will be reported. Imaging results will be based on site reports. Prior to the close out report/final clinical study report, both monitored and unmonitored data will be included in the regulatory submission.

The results of females and nonwhites having undergone endovascular repair, and a literature review and study outcome description of both females and non-whites will be provided as part of the subset analyses with each regular post-approval study update. In addition, results of acute procedural and hospital experience-related endpoints will be evaluated.

3.3 Sample Size Consideration

The statistical analysis of the 5-year post approval safety endpoint assumes a 97.3% freedom from ARM at 5 years and a 10% annual attrition rate. These assumptions are based on:

- The current Vitality post-approval study results (P070027/R), which show a 96.9% freedom from ARM at 5 years as outlined in the 2010 study Annual Progress Report, and
- The absence of ARM and current 4% attrition rate observed in the bifurcated Endurant study arm during the first year of follow-up.

The planned sample size of 328 subjects, including 150 rollover subjects in the bifurcated arm of the IDE trial and 178 De Novo subjects, will yield approximate 220 evaluable subjects at the 5th year and this will provide a minimum of 90% statistical power for a 1-sided test at a 0.05 statistical significance level against the Performance Goal (PG). Therefore, according to these assumptions, enrolling additional 178 De Novo subjects will provide a sufficient sample size for the statistical hypothesis test on the 5-year post approval safety endpoint.

4 ANALYSIS SET

All analyses will be constructed using an Intent-to-Treat (ITT) population. This set is defined as all subjects who had an introduction of the Endurant Stent Graft System. The ITT analysis set will be used for all safety and effectiveness analyses.

4.1 Subset Analyses

By-sex/gender and by-race (white vs. non-white) subset analyses will be performed on the 5-year ARM rate. In addition, this study will also attempt to better understand the overall outcomes in females and non-whites undergoing endovascular repair (EVAR) with the Endurant bifurcated device. The study report will summarize the current research results of females and nonwhites having undergone EVAR, and a literature review and study outcome description of both females and non-whites will be provided with each regular post-approval study update.

5 ENDPOINTS

5.1 Primary Study Endpoint

The primary endpoint is freedom from aneurysm-related mortality (ARM), measured at 5 years (1826 days), and compared to the Performance Goal (PG), determined from the literature as described in Section 7.2. ARM is defined as

ARM is defined as death from rupture of the abdominal aortic aneurysm or from any procedure intended to treat the AAA. If a death occurred within 30 days of any procedure intended to treat the AAA, then it is presumed to be aneurysm related unless there is evidence to the contrary. Deaths occurring after 30 days of any procedure intended to treat the AAA that are procedure-related should be aneurysm related.

The null hypothesis that will be tested is:

H_0: ARMF5 ≤ 92 %,

where ARMF5 is the 5-year freedom from ARM rate in the population of patients treated with the Endurant Bifurcated Abdominal Stent Graft System and 92.0% is the PG.

The alternative hypothesis is:

H_1: ARMF5 > 92 %,

where ARMF5 is as above.

This comparison will be performed based on a Kaplan-Meier (KM) analysis of the ARM. All deaths will be adjudicated by a CEC to determine device, procedure and/or AAA relatedness.

5.2 Additional Measures

The following metrics will be evaluated:

1. Technical Success
    a. Technical success of the Endurant Stent Graft System (assessed intra-operatively) is defined as:

Successful delivery and deployment of the stent graft is defined as deployment

of the Endurant Stent Graft System in the planned location and with no unintentional coverage of both internal iliac arteries or any visceral aortic branches and with the removal of the delivery system

2. Major adverse event (MAE) rates within 30 days of the initial or secondary procedures, including:
    a. All-Cause Mortality
    b. Bowel Ischemia
    c. Myocardial Infarction
    d. Paraplegia
    e. Procedural Blood Loss ≥ 1000 cc
    f. Renal Failure
    g. Respiratory Failure
    h. Stroke

At 12 months and subsequent 4 yearly follow-ups, the following will be reported:

3. All cause mortality
4. Aneurysm-related mortality
5. Aneurysm rupture
6. Aneurysm expansion
7. Conversions to open repair
8. Stent graft migration (>10mm compared to the first post-implant CT)
9. Stent graft patency
10. Endoleaks
11. Secondary endovascular procedures
12. Stent-graft integrity
13. Adverse Events, as follows:
    a. Clinical sequelae directly associated with a Technical Observation.
    b. Those adverse events that meet the definition of a Major Adverse Event (MAE).
    c. Those adverse events directly associated with the death of the subject
14. Health Related Quality of Life Scores through 12 months

No inferential analyses of above measures are planned.

5.3 Acute Procedural and Hospital Experience

The following acute procedural and hospital experience-related outcomes will be summarized using descriptive statistics.

1. Mean duration (min) of procedure.
2. Proportion of subjects who underwent general anesthesia.
3. Mean volume (cc) of estimated blood loss.
4. Proportion of subjects requiring blood transfusions.
5. Mean length of time (hours) in intensive care unit.
6. Mean length of time (days) of overall hospital stay (from index procedure to discharge).

No inferential analyses of above outcomes are planned.

6 DEFINITIONS

6.1 Age

Age will be calculated using date of birth and date of the index implantation ((date of procedure – date of birth + 1)/365.25), where date of birth is from the Screening Form, and date of index procedure is from the Endovascular Procedure Form.

6.2 Study Day

Study day will be calculated from the date of index procedure, i.e. Day 0. Study day of an event will be calculated as date of the event – date of procedure. Day 1 is the day immediately after the index implantation. Study day of an event which occurs prior to Day 0 will be presented as a negative number, if any.

6.3 Time Window for Analyses

Throughout this study, all attempts will be made to collect complete and compliant data. Thus, the majority of data are expected to be within the protocol-specified timeframes for follow-up visits. However, in practice, it may not be possible to achieve this completely. For example, an unscheduled visit may take place and then the patient may miss the next follow-up or withdraw.

For these exceptions, and to take into account all available data, the following rules and time windows will be applied in the statistical analyses (Table 1).

Table1. Time Windows for analyses

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

If there are 2 or more assessments in the same time window, then the assessment closest to the target day will be used in the analysis.

For an adverse event or death, date of onset will be defined as the time when the event occurred. In cases where the date of onset is incomplete, the 15th day of the known month or July 1st of the known year will be used. Furthermore, adverse events or death may be

observed at any time during the study, so no time windows will be applied. An event that occurs "within 1 month" is an event that takes place between Days 0 to Day 30 inclusive. The same applies to events such as adverse events or death within 1 year, i.e., from Day 0 to Day 365, inclusive.

6.4 Duration of Follow-up

If a subject is not expired, then duration of follow-up will be calculated from the last date of follow-up visit or the last known assessment recorded on the Study CRF, whichever is later. If a subject is expired, then the duration of follow-up will be calculated using the date of death. If a subject withdraws from the study, the duration of follow-up will be calculated using the date of withdrawal. Data except death, if any, reported after the date of withdrawal will be excluded from reporting.

6.5 Change in Aneurysm Diameter

Changes in aneurysm diameter will be calculated from the change in site reported measurements of the maximum aneurysm diameters from the 1-month to the follow-up measurement.

A "stable" aneurysm is defined as having a change in maximum aneurysm diameter of 5.0 mm or less in either direction. An aneurysm that becomes smaller in size by more than 5.0 mm is defined as "decreased" in diameter, and that has grown by more than 5.0 mm is defined as "increased" in diameter.

6.6 Count of Stent Graft Patency, Migration, and Loss of Integrity

Stent graft patency, migration, and loss of integrity will be counted only once in the time period when it occurred, but not again in any subsequent time periods. If there are multiple images within the same time window of a time point, only the result on the image that is closest to the target day will be included in the analysis for the time point. Event seen on subsequent images will be counted at the next time point.

6.7 Count of Endoleak

Endoleak may occur and resolve without intervention. If there are multiple images within the same time window of a time point, only the result on the image that is closest to the target day will be included in the analysis for the time point.

6.8 Quality of Life Assessment

EQ-5D, a preference based measure of health status, will be used. Scoring of the EQ-5D will follow the user guide by EuroQoL (Cheung 2009). EQ-5D Index will be calculated using US general population preference weights.

7 STATISTICAL METHODS OF ANALYSIS

7.1 General Considerations

All analyses will be performed using the ITT analysis set.

Data collected from the clinical study will be analyzed as specified in the following sections. In general, for categorical variables, frequency and percentage will be presented as descriptive statistics. For continuous variables, number of observations, mean, standard deviation (SD), median, minimum, and maximum will be presented for data summary. Subject data listings will be provided to support summary tables if needed.

Data from all study sites will be grouped together for analysis. Subjects from IDE cohort may be summarized separately from the de novo subjects as needed. Detailed table templates are provided along with this statistical analysis plan.

All table and statistical analysis programming will be performed using SAS® for Windows (Version 9.1 or higher), or other widely-accepted statistical or graphic software.

7.2 Subject Disposition

The number of subjects who received the Endurant Stent Graft System as well as duration of follow-up will be summarized by follow-up time. The follow-up rate will be presented separately for clinical follow-up and site reported images CT/MRA and KUB. Subjects eligible for a follow-up visit are those who had or are due for a follow-up. Subject who has reached the upper end of time window is considered due for the follow-up.

7.3 Subject Demographics and Baseline Characteristics

All demographics and baseline characteristics will be summarized by study cohort as well as all subjects.

Demographic data include: age (years), sex, and race (white/non-white).

Baseline aneurysm characteristics include: maximum aneurysm diameter (mm), proximal neck diameter (mm), right iliac diameter (mm), left iliac diameter (mm), proximal neck length (mm), infrarenal and suprarenal neck angles (°).

Medical history findings (yes/no) include: cardiac, pulmonary, renal cerebrovascular/neurological, vascular and other conditions. Baseline SVS score will be calculated based on Chaikof, *et al.* (2002).

When data are not available or partially available, the summary will be based on available data. No imputation of missing data will be made. Nevertheless, missing data in the baseline variables are expected to be very limited.

7.4 Analyses of Primary Study Endpoint

The statistical hypothesis will be tested by calculating a 1-sided 95% confidence limit for the 5-year KM estimate and comparing it to the Performance Goal (PG). The confidence limit will be based on the Greenwood standard error and using a normal approximation. If the

lower confidence limit is greater than the Performance Goal (PG), then the null hypothesis (see Section 7.1) will be rejected in favor of the alternative hypothesis and a higher than 92% freedom from ARM rate at 5 year will be concluded.

Subjects who die from aneurysm-related death as determined by the CEC will be considered as having the event. The time from the initial implant to the time of death is the time to event. Other subjects will be considered censored at the date of last follow-up visit / contact or the date of death due to other reasons.

7.5 Analyses of Additional Measures

For additional measures, which are all proportions, a 2-sided 95% confidence interval will be constructed based on the binominal distribution, i.e., using the exact method. Because these confidence intervals are strictly descriptive, i.e., no statistical hypothesis to be tested, no multiplicity adjustment of the confidence level will be performed. These analyses will be performed on all subjects at the study close out.

7.6 Analyses of Acute Procedural and Hospital Experience Outcomes

All analyses on acute procedural and hospital experience outcomes are considered as additional to that for the primary and secondary endpoints. For duration of procedure, volume of estimated blood loss, length of time in intensive care unit (ICU) and length of time in hospital (from index procedure to discharge) will be summarized using mean, standard deviation, median, min and max. For proportion of subjects undergoing general anesthesia and proportion of subjects requiring blood transfusion, the number and percentage of subjects in each category will be presented. All ITT subjects with available data will be included in the analysis.

Note that length of time in the intensive care unit will be set to 0 if a subject did not report time in the intensive care unit.

7.7 Analyses of Quality of Life Assessments

Individual dimension, overall self-rating, EQ-5D index, as well as change from baseline in EQ-5Q index will be summarized descriptively.

7.8 Subset Analyses

By-sex/gender and by-race (white vs. non-white) subset analyses will be performed on the 5-year ARM rate. A 2-sided 95% confidence interval based on a KM estimate of the rate will be calculated using the Greenwood standard error and normal approximation. In addition, this study will also attempt to better understand the overall outcomes in females and non-whites undergoing endovascular repair (EVAR) with the Endurant bifurcated device. The study report will summarize the current research results of females and nonwhites having undergone EVAR, and a literature review and study outcome description of both females and non-whites will be provided with each regular post-approval study update. Publications to be examined will include single-center experiences and multicenter trials. Specifically, descriptive statistics will be used to summarize literature derived outcomes in patients with the EVAR therapy, literature-derived Endurant specific outcomes, and the post-approval study outcomes. These summaries will be conducted to the level of detail available in both the literature and the post-approval study trial subsets, including device safety and effectiveness measures such as aneurysm-related mortality, endoleaks, aortic ruptures, etc

8 HANDLING OF DROPOUTS OR MISSING DATA

Intent-to-treat analysis allows for the evaluation of all subjects who enrolled the study, even though some may not complete the study (e.g., subjects who are, for any reason, lost to follow-up, drop-outs, or terminated by investigator). The intent-to-treat principle means that analysis will be based on observed results of all subjects for the treatment as they are enrolled to receive. Imputation of missing data will not be performed in the intent-to-treat analysis, unless otherwise specified. For example, to determine the rate of MAEs within 365 days, only following subjects with observations will be counted for the rate:

The numerator consists of:

- The number of subjects that experienced an MAE during Day 0 and Day 365, inclusive.

The denominator consists of:

- The number of subjects evaluated during the analysis window (i.e., last day in study>=305), plus
- Any subjects not evaluated during the analysis window, but that had an MAE during Day 0 and Day 304, inclusive.

Note that subjects that were followed less than 305 days and no MAE reported during the follow-up period will be excluded from the analysis of this rate because no complete observations were made to these subjects due to withdrawal or lost to follow-up.

For the analysis of primary endpoint, freedom from ARM rate at 5 years, the KM analysis will be applied. Subjects who lost to follow-up or withdraw consent will be considered censored at the date of withdrawal. Therefore, no subjects in the intent-to-treat analysis set will be excluded from the analysis. Vital status of other subjects at 5 years will be determined. For the purposes of analyzing ARM, subjects who die of unrelated causes will be considered censored at time of death.

9 HANDLING OF DATA FROM UNSCHEDULED FOLLOW-UP VISITS

In addition to scheduled visits at 1 month, 6 months, 12 months, and annually thereafter, subjects may return for unscheduled visits. If 2 or more visits fall within the same time window given in Section 6.3, the visit that is closer to the target date of the scheduled visit will be used for analysis.

10 REFERENCES

Chaikof E., *et al.* (2002). Identifying and grading factors that modify the outcome of endovascular aortic aneurysm repair. J Vasc Surg, **35**, 1061-6.

Cheung K., *et al.* (2009) User Guide – Basic information on how to use EQ-5D, www.euroqol.org.

11 APPROVAL

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

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