Medtronic PERIGON study

Date: March 03, 2015

The attached Statistical Analysis Plan (SAP) for this study has been approved by the following staff and is now ready for use.

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Medtronic PERIGON Pivotal Trial

Statistical Analysis Plan

Version: 3.0
Date: March 03, 2015

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1 PURPOSE OF SAP

This Statistical Analysis Plan (SAP) is designed to document, before data are analyzed, the rationale for the trial design of the Medtronic PERIGON Pivotal Trial, and the planned analyses that will be included in trial reports. The design and analyses are consistent with the objectives of the Clinical Investigational Plan (CIP). This SAP does not limit the analysis in reports. Additional analysis of the trial data beyond this plan is expected.

2 RATIONALE FOR TRIAL DESIGN

The purpose of this trial is to evaluate the safety and efficacy of the Medtronic Model 400 bovine pericardial stented aortic bioprosthesis in a patient population undergoing surgical aortic valve replacement. This is a prospective, interventional, non-randomized, worldwide, multi-site clinical trial, with each center following a common protocol. All enrolled subjects will be assigned to aortic surgical valve replacement with the Model 400 Aortic Valve Bioprosthesis. The trial design is based on the recommendations of the FDA Heart Valve guidance document (2010) and EN ISO 5840:2009 standard for cardiac valve prostheses.

This statistical analysis plan is developed in line with the Clinical Investigational Plan Version 1D.

3 DESCRIPTION OF ANALYSIS

This trial has a safety objective (to evaluate the safety of the Model 400 valve with respect to valve-related adverse events and death) and an effectiveness objective (to confirm the effectiveness of the Model 400 valve with regard to NYHA classification and hemodynamic performance).

3.1 General Summaries

3.1.1 Description of Baseline Variables

Major baseline demographic and clinical variables will be summarized for the enrolled and implanted populations. All continuous variables will be summarized with means, standard deviations, medians, interquartile ranges, minimums, and maximums. Categorical variables will be summarized with frequencies and percentages.

3.1.2 Reports for which this Statistical Analysis Plan Applies

This SAP applies to the trial report for Pre-market Approval Application (PMA) to the Food and Drug Administration (FDA) and the final report.

This SAP applies to the trial report for CE mark submission and to the report for regulatory submissions in other geographies.
The analyses for CE mark approval and FDA approval may be used for regulatory submissions in other geographies.

This SAP applies to the main trial manuscript, though not everything specified here will be included in the manuscript.

3.1.3 Special Considerations

3.1.3.1 Report Timing and Cutoff Dates

Cutoff dates will be applied to all site case report forms. A Visit Cutoff Date and a Received Cutoff Date will be used. The visit cutoff date will be the first date on which at least 800 patient-years of data have been collected for the PMA report. The visit, assessment, and event dates will be used to determine which case report forms satisfy the visit cutoff date. The received cutoff date will be determined near the time of the database closure and will be chosen to ensure that all forms of critical importance have been received while still allowing adequate time for data cleaning between the received cutoff date and the date of database closure. The “logints” log-in timestamp field will be used to determine which case report forms satisfy the received cutoff date. CE mark report Visit Cutoff Date and a Received Cutoff Date will be used similarly when regulatory submission data requirement is met.

Any forms which do not have a visit date directly on the form will use the visit date from the corresponding form for that entry. Forms with multiple dates will apply cutoff dates to individual lines of data on the form.

3.1.3.2 Definition of Enrolled Subject

An enrolled subject is defined as a subject whose IRB/MEC-approved patient informed consent form has been signed and dated by all required parties.

3.1.3.3 Missing Data

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. 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.
3.1.3.4 P-Values

The statistical test for the safety objective will be performed at one-sided $\alpha=0.05$. All reported p-values greater than or equal to 0.0001 will be rounded to four decimal places. P-values less than 0.0001 will be displayed as “$<0.0001$.”

3.1.3.5 Kaplan-Meier Analyses

Kaplan-Meier analysis of event-free rates (or event rates) will be performed at 30 days, 6 months, 12 months and annually through five years. These times correspond to 30 days, 180 days, 365 days, 730 days, 1095 days, 1460 days, and 1825 days, respectively. At each time point with data, the product-limit estimate of the event-free rate (or event rate), the number of subjects at risk, the number of subjects with events, and the loglog transformed 95% confidence interval using the Peto 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 (including death).

3.1.3.6 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 Model 400 valve. 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.

The data from the subjects with attempted procedures, but who were not implanted with the Model 400 valve will be summarized separately, and reported as descriptive statistics. The subjects with attempted procedures will not be counted towards the total number of implants.

3.1.3.7 Interim Analysis

Interim analysis is planned when at least 200 patient-years of data are collected (see section 3.4 for details). However, there are no plans for early termination of the trial due to superiority or futility of the investigational therapy based on the interim results.

3.1.3.8 Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will conduct a medical review and classify/adjudicate, at a minimum, all deaths and endpoint related adverse events for seriousness and relatedness to the trial device/procedure according to definitions and processes outlined in the protocol and the CEC charter. All other events will be reviewed and classified by the Sponsor, by qualified internal Medtronic safety individual(s) to ensure they should not be adjudicated by the full CEC and that the events are appropriately classified by the investigator.

Additional details about the CEC are outlined in the CEC charter.
3.1.3.9 Data Safety Monitoring Board (DSMB)

A DSMB will be established to review accumulating data from the trial, and advise Medtronic on the continuing safety of current and future trial participants, and the continuing validity and scientific merit of the trial.

Additional details about the DSMB are outlined in the DSMB charter.

3.2 Safety Objective

The safety objective is to evaluate the safety of the Model 400 valve with regard to valve-related adverse events and death.

3.2.1 Endpoints

Safety of the valve will be evaluated by the time-related incidence of valve-related adverse events and death. The following valve-related adverse events will be evaluated in this trial: Thromboembolism, Thrombosis, Hemorrhage, Paravalvular leak (PVL), Endocarditis, Hemolysis, Structural valve deterioration, Non-structural dysfunction, Reintervention, Explant, and Death.

3.2.2 Hypothesis

The safety objective will be assessed by comparing linearized valve-related adverse event rates from subjects implanted with the Model 400 valve to acceptable linearized valve-related adverse event rates following valve replacement as defined by FDA in the Heart Valve Guidance 2010' and EN ISO 5840:2009'' as Objective Performance Criteria (OPC). The OPC for tissue valves (based on the linearized rate) are presented in Table 1.

Table 1: OPC for Tissue Prosthetic Heart Valves

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Linearized Rate (%) per Patient-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td>2.5</td>
</tr>
<tr>
<td>Valve Thrombosis</td>
<td>0.2</td>
</tr>
<tr>
<td>All Hemorrhage</td>
<td>1.4</td>
</tr>
<tr>
<td>Major Hemorrhage</td>
<td>0.9</td>
</tr>
<tr>
<td>All Paravalvular Leak</td>
<td>1.2</td>
</tr>
<tr>
<td>Major Paravalvular Leak</td>
<td>0.6</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1.2</td>
</tr>
</tbody>
</table>

The trial is designed to test the hypothesis that the true linearized adverse event rate for the Model 400 valve (R_Model400) is equal to or greater than twice the acceptable rate of commercially available tissue prosthetic valves (R_OPC). The null (H_0) and alternative (H_A) hypotheses are written as follows.

\[
H_0: R_{\text{Model400}} \geq 2 \times R_{\text{OPC}} \\
H_A: R_{\text{Model400}} < 2 \times R_{\text{OPC}}
\]

Where \( R_{\text{Model400}} \) is the linearized adverse event rate for the Model 400 valve and \( R_{\text{OPC}} \) is the acceptable rate of commercially available tissue prosthetic valves. To
reject the null hypothesis demonstrates statistically that the rate for the Model 400 valve is less than two times the acceptable rate.

### 3.2.3 Sample Size Methods and Assumptions

#### A. Sample Size Methods and Assumptions

Sample size estimation is based on the methods of Grunkemeier. The following are assumptions for the sample size estimate:

- One-sided alpha = 0.05
- Power = 1 - \( \beta \) = 80%
- \( 2XR_{\text{OPC}} \) = 2.4%
- \( R_{\text{Model400}} \) = 1.2%

In the above expressions, \( 2XR_{\text{OPC}} \) and \( R_{\text{Model400}} \) denote the Performance Goal (null hypothesis proportion) and true proportion, respectively.

If the endpoint event has a constant risk of \( R_{\text{OPC}} \) per patient-year, then the distribution of the number of endpoint events occurring during a fixed time of \( T \) patient-years is a random variable \( E \) with Poisson distribution of mean \( \lambda = R_{\text{OPC}} \times T \). Thus the probability of observing \( n \) or fewer events during \( T \) patient-years is:

\[
P_{\lambda}(E \leq n) = \sum_{k=0}^{n} \frac{e^{-\lambda} \lambda^k}{k!}
\]

To reject the null hypothesis of \( R_{\text{Model400}} \geq 2 \times R_{\text{OPC}} \), the number of events \( E \) occurring during \( T \) patient-years is less than or equal to the critical value of \( n_{cv} \). The critical value of \( n_{cv} \) is determined by the selected Type I (\( \alpha \)) and Type II (\( \beta \)) levels. That is:

\[
\begin{align*}
& P_{2\lambda}(E \leq n_{cv}) \leq \alpha \\
& P_{\lambda}(E \leq n_{cv}) \geq 1 - \beta
\end{align*}
\]

Thus the amount of data required to test the null hypothesis using the acceptable adverse event rate of 1.2% per patient-year is approximately 800 patient-years using the Poisson distribution, an alpha level of 5% and at least 80% power.

If all subjects are enrolled within a one year time frame, and followed for one year postoperatively, then a total of 556 implants are required, considering a 5% attrition rate (Grunkemeier 1994). Therefore, accounting for attrition and expected enrollment rates, up to 650 implants are expected.

#### B. Rationale for Choice of Hypothesis

As the OPC presented in Table 1, Valve Thrombosis, Major Hemorrhage and Major PVL rate are all less than 1.2% per patient-year, and to achieve the 80% power for these tests, a much larger sample size is required to evaluate these rare events. For example, to detect a Major Paravalvular Leak rate of 0.6% per patient-year, more than 1800 patient-years of data are required; and to detect a Valve Thrombosis rate of 0.2% per patient-year, more than 5000 patient-years of data are required. Such a large sample size requirement may leave the trial unexecutable. Thus, the smallest acceptable adverse event rate of 1.2% per patient-year (excluding Valve Thrombosis, Major Hemorrhage and Major PVL) is chosen for the sample size assumption.
3.2.4 Data Collection and Analysis Methods

A. Data Collection and Analysis

Adverse device effects and outcomes will be identified and reported by the Investigator at all visits. All deaths and endpoint related adverse events will be reviewed by the CEC.

Early postoperative events are defined as those occurring on or before 30 days post-operative. Late postoperative events are those occurring after 30 days post-operative.

Early rates of adverse events will be calculated as the number of early adverse events divided by the total number of subjects, expressed as a percentage.

The late events rates will be calculated using the linearized event rate methodology. That is, the rate will be the number of late events divided by the late post-operative patient-years. For those adverse events with OPC available, the linearized rates and their associated one-sided upper 95% confidence bounds will be compared to the Objective Performance Criteria (OPC) to show that they are within acceptable limits. Formally, the method introduced by Cox\textsuperscript{iv} which gives the relatively most accurate results\textsuperscript{v} will be used:

\[ X_{0.95, 2n_e + 1} / 2 Y_T \]

where \( n_e \) is the number of late events and \( Y_T \) is the late post-operative patient-years.

Kaplan-Meier survival analyses will also be performed to summarize valve-related adverse events and death. The Kaplan-Meier rate and the corresponding 95% confidence interval will be presented for each visit interval. In addition, number of subjects at risk, number of events, number of censored subjects and the Kaplan-Meier survival curve or event curve will also be displayed.

In addition, control articles based on current literature of previously approved heart valves will be selected. Adverse event data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, and allow additional evaluation of the Model 400 adverse event data.

B. Determination of Data for Analysis

All subjects who are enrolled in the trial and have a trial valve implanted will be included for analysis.

For subjects who are attempted but not implanted, their data will be summarized separately.

3.3 Effectiveness Objective

The effectiveness objective is to confirm the effectiveness of the Model 400 valve, with regard to NYHA Functional Classification and hemodynamic performance.
3.3.1 **Endpoints**

The effectiveness endpoints are:

- **NYHA Functional Classification** (at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years) is a classification system for defining cardiac disease and related functional limitations into four broad categorizations:

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td>
</tr>
<tr>
<td>Class II</td>
<td>Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td>
</tr>
<tr>
<td>Class III</td>
<td>Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

- **Hemodynamic Performance** (at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years) including:
  - effective orifice area (EOA)
  - effective orifice area index (EOAI)
  - peak pressure gradient
  - mean pressure gradient
  - valvular regurgitation
  - performance index
  - cardiac output
  - cardiac index

3.3.2 **Hypothesis**

No formal hypothesis will be evaluated for this objective. Control articles based on current literature of previously approved heart valves will be selected. Data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, and allow evaluation of the Model 400 data.

3.3.3 **Sample Size Methods and Assumptions**

Sample size calculations were not performed for the effectiveness objective. Sample size for this trial was based on the safety objective.

3.3.4 **Data Collection and Analysis Methods**

NYHA functional classification and hemodynamic data will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables.
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.

All echocardiograms will be analyzed by an echo core lab which will determine the values for the Hemodynamic Performance endpoints. 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. These data will be summarized by valve size.

Control articles based on current literature of previously approved heart valves will be selected. Effectiveness data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, to allow for evaluation of the Model 400 valve effectiveness data.

3.4 Interim Analysis

An interim analysis of the trial data is planned to evaluate the early safety profile of the Model 400 valve. The interim analysis may be included as supplementary information in a submission for CE Mark, and may be used for regulatory submissions in other geographies.

3.4.1 Safety Objective

The safety objective is to evaluate the safety of the Model 400 valve with regard to valve-related adverse events and death.

3.4.1.1 Endpoints

Safety of the valve will be evaluated by the time-related incidence of valve-related adverse events and death. The following valve-related adverse events will be evaluated in this analysis: Thromboembolism, Thrombosis, Hemorrhage, Paravalvular leak, Endocarditis, Hemolysis, Structural valve deterioration, Non-structural dysfunction, Reintervention, Explant, and Death.

3.4.1.2 Hypothesis

The safety objective will be assessed by comparing a composite linearized adverse event rate from subjects implanted with the Model 400 valve to twice the composite linearized adverse event rate of valve-related Thromboembolism, Endocarditis, Major PVL and Thrombosis. The composite rate was developed using individual valve-related event rates from the Objective Performance Criteria (OPC) as defined by FDA Heart Valve Guidance 2010 and EN ISO 5840:2009 From Table 1, twice the composite linearized adverse event rate of Thromboembolism, Endocarditis, Major PVL and Thrombosis is 2 X (2.5 + 0.2 + 0.6 + 1.2) = 9%.
The interim analysis hypothesis is to test that the true composite linearized adverse event rate of Thromboembolism, Endocarditis, Major PVL and Thrombosis for the Model 400 valve ($P_{\text{Model400}}$) is equal to or greater than twice the composite linearized adverse event rate of commercially available tissue prosthesis valves.

The null ($H_0$) and alternative ($H_A$) hypotheses are written as follows:

$$H_0: P_{\text{Model400}} \geq 9\%$$
$$H_A: P_{\text{Model400}} < 9\%$$

Where $P_{\text{Model400}}$ is the composite linearized adverse event rate for the Model 400 valve.

3.4.1.3 Sample Size Methods and Assumption

A. Sample Size Methods and Assumptions

A fixed sample size group sequential design with O'Brien-Fleming boundaries for one interim analysis will be utilized. A fixed sample size design of 400 patient-years with one interim analysis at 200 patient-years achieves at least 90% power. The assumptions for sample size / power calculation:

- $P_{\text{Baseline}}$ (the baseline rate: observed in the literature) = 3.5%
- $P_{\text{Model400}}$ (the assumed rate for Model 400) = 3.5%
- Type I error ($\alpha$) = 0.05
- One interim analysis at 200 patient-years

The objective will be evaluated with a fixed sample size group sequential design with one interim analysis at 200 patient-years and one possible second analysis at 400 patient-years.

B. Rationale for Choice of Hypothesis

The composite rate and hypothesis were chosen because it provides an overall evaluation of safety of the device by incorporating significant device-related events that are clinically relevant to evaluating a new bioprosthetic heart valve.

3.4.1.4 Data Collection and Analysis Method

There will be up to two analyses of this objective. The first analysis will occur when 200 patient-years of data are collected and the second analysis will occur when 400 patient-years of data are collected. Spending function with boundaries similar to that for O'Brien-Fleming will be used to control the Type I and Type II error probabilities. The table below illustrates the O'Brien-Fleming boundaries and the associated z-statistic and p-value for each analysis under an assumption that 200 patient-years of data are observed at the interim analysis. However, if the observed patient-years of data are different at the time of the interim analysis, the boundaries and p-values will be recalculated to reflect the appropriate percentage of the total sample size observed at the time of the interim analysis.

Table 2: O'Brien-Fleming boundary at the interim and 400 patient-year analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Z-statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interim</td>
<td>-2.3585, 0.0000</td>
<td>0.0092, 0.5000</td>
</tr>
<tr>
<td>400 patient-years</td>
<td>-1.6677</td>
<td>0.0477</td>
</tr>
</tbody>
</table>
*S-Plus 8.2/S+ SeqTrial used with the O’Brien-Fleming Type I error spending function.

The above sample rate boundaries are also shown in Figure 1:

**Figure 1: Event Rate boundaries using O’Brien-Fleming Method**

Since there may be up to two analyses, there are two thresholds for which the observed test statistic will be evaluated. Call this set of thresholds $Z_t = (Z_1, Z_2)$. Each of these thresholds will be a standard normal $Z$ statistic evaluated at the nominal alpha level for the analysis. For example, in the table above, the nominal alpha level for the interim analysis is 0.0092 with an associated $Z$ statistic of -2.3585. Thus, if the $Z$ statistic is smaller than -2.3585, the null hypothesis may be rejected at the interim analysis. Similarly, if the null hypothesis cannot be rejected at the interim analysis, the null hypothesis may be rejected at the 400 patient-years analysis provided the $Z$ statistic is smaller than -1.6677. To reject the null hypothesis demonstrates statistically that the Model 400 valve composite adverse event rate is less than 9%. This method preserves the Type I error rate at 5% since the conservative O’Brien-Fleming rules are utilized in setting the rejection thresholds $Z_t$.

- At the interim analysis (200 patient-years), if the data support the alternative hypothesis that the Model 400 valve composite rate is <9%, the results will be summarized and submitted as applicable as described in section 3.4. The 400 patient-year analysis will not be performed under this scenario.
- If the criteria are not met at the 200 patient-year interim analysis, the trial will continue to gather data to at least 400 patient-years and then summarize the data and submit as applicable as described in section 3.4.

Each component of the composite adverse event rate will also be summarized and described. Kaplan-Meier survival analyses will also be performed to summarize the adverse event data.
In both scenarios, the trial conduct will not be altered, and the trial will not stop, but continue until at least 800 patient-years of data are collected.

3.4.2 Effectiveness Objective
The effectiveness objective is to confirm the effectiveness of the Model 400 valve with regard to the NYHA Functional Classification and hemodynamic performance.

3.4.2.1 Endpoints
The effectiveness endpoints are:
- NYHA Functional Classification (at discharge or within 30 days, 3-6 months, 1 year and annually thereafter through 5 years)
- Hemodynamic Performance (at discharge or within 30 days, 3-6 months, 1 year and annually thereafter through 5 years) including
  - effective orifice area (EOA)
  - effective orifice area index (EOAI)
  - peak pressure gradient
  - mean pressure gradient
  - valvular regurgitation
  - performance index
  - cardiac output
  - cardiac index

3.4.2.2 Hypothesis
No formal hypothesis will be evaluated for this objective. Control articles based on current literature of previously approved heart valves will be selected. Data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, and allow evaluation of the Model 400 data.

3.4.2.3 Sample Size Methods and Assumptions
Sample size calculations were not performed for the effectiveness objective. Sample size for this interim analysis was based on the safety objective.

3.4.2.4 Data Collection and Analysis Methods
NYHA functional classification and echocardiographic hemodynamic data will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables.

For NYHA, a frequency table will be presented for each visit interval to show how many subjects fall into each of the four categories of NYHA functional classification. For each subject with paired data, the number of classes changed from baseline will be calculated at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years and summarized into categories as Improved, No Change and Worsened.

All echocardiograms will be analyzed by an echo core lab which will determine the values for the Hemodynamic Performance endpoints. 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. These data will be summarized by valve size.

Control articles based on current literature of previously approved heart valves will be selected. Effectiveness data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, to allow for evaluation of the Model 400 valve effectiveness data.

3.5 Additional Analyses

Additional analyses will be performed on the implanted population for safety and effectiveness data.

3.5.1 Safety Endpoints

The safety endpoints include the valve-related adverse events of Thromboembolism, PVL, reoperation, explant and all-cause mortality. Events that occurred in less than five subjects will not be evaluated by the additional analyses.

3.5.1.1 Sites Analysis

Sites that successfully implanted less than 5 subjects will be considered “small sites” and will be pooled together as one site.

The evaluation of the effect of sites over time to valve-related adverse events and death will be performed as follows:

Cox Proportional Hazards model will be used to evaluate the site effect on valve-related adverse events. If the resulting p-value for site is > 0.15, the data will be considered to be poolable across trial sites. Otherwise if the resulting p-value for site is ≤ 0.15, further exploratory analysis will attempt to identify covariates that may explain possible heterogeneity among the sites. All other possible clinically meaningful baseline risk factors then will also be included in the above model as independent variables. A backwards elimination process will be utilized to pare the model down. In this process, the single-term baseline variable with the highest p-value will be removed from the model (except site) until all factors have a p-value less than 0.15.

The possible clinically meaningful baseline risk factors include: age at implant, gender, preoperative NYHA classification, previous aortic valve replacement, valve size, and concomitant CABG.

If this multivariate model does result in p-value of site > 0.15 after adjustment for these baseline factors, then outcome results will again be considered poolable across trial sites. If the resulting p-value for site is still ≤ 0.15 after adjustment for these factors, results will be presented by investigational center and the clinical significance of these differences will be assessed.
Any observation with missing values for the response or explanatory variables will be excluded from the analysis.

### 3.5.1.2 Valve Size Analysis

The evaluation of the effect of valve size over time to the valve-related adverse events and death will be performed as follows:

Cox Proportional Hazards model will be used to evaluate the valve size effect on valve-related adverse events and death.

Due to possible small sample sizes in the smallest and largest valve sizes, the 17 mm may be combined with the 19 mm and the 27 mm may be combined with the 29 mm size to create larger groups of valve sizes. Thus, four indicator variables for valve size (representing 17 mm to 19 mm, 21 mm, 23 mm, 25 mm, and 27 mm to 29 mm) may be created and included in the model.

Valve size will be considered to be significantly associated with time to valve-related adverse events and death if the p-value <0.05.

### 3.5.1.3 Gender Analysis

Assessment of the possible gender differences will be examined in the freedom from (or event rate) valve-related adverse events and death after implantation of the Model 400 valve.

The possible gender differences in the freedom from death and valve-related adverse events will be evaluated using the log-rank test.

Differences in gender will be considered to be significant if the p-value <0.05.

### 3.5.1.4 Risk Factor Analysis

Risk factors associated with time to death (all causes), reoperation and explant will be evaluated using Cox Proportional Hazards model.

Variables evaluated as possible risk factors for death (all causes), valve-related reoperation and explant include age at implant, gender, preoperative NYHA classification, previous aortic valve replacement, valve size, and concomitant CABG. Other important concomitant procedures may also be included in this analysis.

A backwards elimination process will be utilized to pare the model down. In this process, the single-term baseline variable with the highest p-value will be removed from the model until all factors have a p-value less than 0.15.
3.5.2 Effectiveness Endpoints

The effectiveness endpoints include mean gradient, effective orifice area, valvular regurgitation and NYHA classification.

3.5.2.1 Valve Size Analysis

Mean gradient, effective orifice area and valvular regurgitation at one year postoperative will be summarized by valve size.

3.5.2.2 Gender Analysis

Mean gradient, effective orifice area and valvular regurgitation at one year postoperative will be summarized by gender.

For subjects with data available at both the baseline and one-year evaluations, the change in NYHA classification will be summarized by gender and time interval. NYHA improvement (at least one class) was classified as “improvement” or “no improvement”. The chi-square test will be used to evaluate the possible relationship between improvement in NYHA classification from the preoperative to the one-year postoperative evaluation and gender.

4 REVISION PROCESS

This SAP will be revised as necessary. The trial statistician will be responsible for any revisions and obtaining appropriate approvals of this SAP. Revisions will be approved as defined in the clinical department standard operating procedures (SOPs).

5 DISTRIBUTION

The trial statistician will be responsible for execution of this SAP and distribution of revisions to the appropriate clinical staff.

6 REVISION HISTORY

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Author</th>
<th>Summary of Changes</th>
</tr>
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<tbody>
<tr>
<td>1.0</td>
<td>3/25/14</td>
<td>Cathy Zeng</td>
<td>Initial Release</td>
</tr>
<tr>
<td>2.0</td>
<td>4/18/14</td>
<td>Cathy Zeng</td>
<td>Revision to clarify the intent of the interim analysis as supplementary information</td>
</tr>
<tr>
<td>3.0</td>
<td>3/3/15</td>
<td>Cathy Zeng</td>
<td>To align SAP with CIP version 1D</td>
</tr>
</tbody>
</table>

7 REFERENCES

i FDA Heart Valve Guidance 2010.

ii ISO 5840:2009: Cardiovascular implants – Cardiac valve prostheses.


FDA Heart Valve Guidance 2010.