**TEMPLATE FOR STATISTICAL SECTIONS OF CLINICAL STUDY PROTOCOL**

Statistics are important in multiple sections: objectives, endpoints, sample size, and analysis. These sections should never conflict and should always be 'obviously consistent'. By 'obviously consistent' I mean there should be a one-to-one match throughout these sections. Each objective should match with the endpoint that will be used to evaluate that objective. The primary objective and endpoint should be used for the sample size calculation and each objective should have an analysis plan appropriate to assess the objective with formal statistics.

## OBJECTIVES

The objectives of this study are formulated to support substantial equivalence of ABC (study device) and DEF (control device) for effectiveness and safety.

### Primary Objective

The primary objective of this study is to establish the substantial equivalence of ABC (study device) and DEF (control device) for effectiveness.

### Secondary Objective

The primary objective of this study is to establish the substantial equivalence of ABC (study device) and DEF (control device) for safety.

### Other Objectives

Other objectives of this study include comparisons of ABC (study device) and DEF (control device) on Z, Y and X.

## STUDY DESIGN

This study is designed as a multicenter, randomized, blocked, blinded, longitudinal clinical trial. The study design was selected to facilitate collection of unbiased data that will appropriately and efficiently be used to evaluate the study objectives. All patients will be followed for 1 year post device implantation; with assessments at 1, 3, 6, 9 and 12 months.

Subjects will be randomized to one of the two groups (ABC – study device or DEF – control device) at a ratio of 1:1 via the method of sealed randomization envelopes. This randomization method will result in sealed envelopes containing the computer-generated, random assignment. Randomization will occur in blocks so that blocks of equal numbers of subjects will be used to avoid potential runs of assignments. The randomization code will be generated specifically for each study center.

## ENDPOINTS

### Primary Endpoint

The primary endpoint in this study is 'vvv', which will be used to assess substantial equivalence for efficacy.

### Secondary Endpoint

The primary endpoint in this study is 'vvv', which will be used to assess substantial equivalence for safety.

### Other Endpoints

The other endpoints examined in this study are Z, Y, X and W.

## JUSTIFICATION OF SAMPLE SIZE

9999 patients will be enrolled in this study. The sample size required for this study was determined using estimates from the previous study published in Circulation (Smith et al, 2000). With an overall success rate of 'SS', maximum allowable difference between groups of 'B', a statistical power of 90% and an alpha level of 5%, 9999 patients are required for this study.

## DATA ANALYSIS

### General Analyses

In general, continuous variables will be summarized with standard descriptive statistics including means, standard deviations, medians, and ranges. Categorical variables will be summarized with frequencies and percentages. Ninety-five percent confidence intervals will be provided for descriptive statistics, as warranted.

When inferential analyses are conducted for continuous variables, they will primarily be based on parametric general linear models such as multiple regression and analysis of variance. Markedly non-normally distributed data will be transformed prior to inferential comparisons. For variables that cannot be successfully transformed, nonparametric methods will be used.

Categorical variables will be analyzed with logistic regression or categorical response models. If expected frequencies are too small for asymptotic assumptions, exact testing techniques will be used.

Adverse events will be assessed at each follow-up visit and when serious adverse events or device-related adverse events occur. The event rates will be summarized as percentages for each time point, along with 95% confidence intervals.

Subject characteristics are assumed to be comparable at the start of the study, as randomization is designed to ensure balance between the groups on the baseline characteristics, so no formal statistical group comparisons will be conducted on the subject characteristics.

An overall alpha-level of 0.05 will be used as a cut-point for statistical significance and all statistical tests will be two-sided. All data will be analyzed using SAS (SAS Institute, Inc., Version 8.2, 2001).

### Primary Analysis

Primary success rates will be summarized with proportions and 95% confidence intervals. Groups will be compared using Blackwelder's test for equivalence.

### Secondary Analyses

Secondary success rates will be summarized with proportions and 95% confidence intervals. Groups will be compared using Blackwelder's test for equivalence.

### Other Analyses

The effect of the devices on the primary endpoint will be assessed in the primary analysis. However, it is recognized that other factors may be affecting the primary success rate. To this end, multivariable logistic regression will be used to identify independent predictors of success.