

**APPENDIX C**  
**STATISTICAL METHODS**

**CorCap<sup>®</sup> Cardiac Support Device (CSD) (P040049)**  
**Acorn Cardiovascular, Inc.**

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**REFERENCES**

## 1.0 GENERAL PRINCIPLES

Except as noted otherwise, all analyses are presented in concordance with the intent-to-treat principle, under which patients were assigned to their randomized groups regardless of the actual treatment received. The principal exception occurs in analyses of the 159-patient Focused Cohort, which was defined using a per-protocol rule which discarded patients randomized to, but not receiving, CorCap implant.

Analyses are stratified by size of clinical site (small, medium, large), and analyses of the full patient cohort are also stratified by concomitant surgery stratum (mitral valve repair [MVR] vs. No-MVR). Analyses based on regression or analysis of variance techniques include the baseline level of the outcome as a covariate.

For time-to-event analyses, time zero is defined as day of baseline surgery, or day of randomization if baseline surgery was not performed; however, all events occurring post-randomization and before the common closing date of July 4, 2004, are included.

All statistical hypothesis tests are two-sided, with p-values of 0.05 or less considered significant.

## 2.0 RANDOMIZATION METHODOLOGY

Randomization to CorCap or control was created using a randomized permuted-blocks method, with separate randomization lists created for each distinct combination of clinical site and MVR vs. no-MVR stratum, with block sizes of two or four for the initial block, and blocks of four thereafter.

The decision to allocate subjects to the MVR or no-MVR stratum was based on a clinical assessment of the need for mitral valve repair or replacement at baseline, and not on a randomized basis, creating the need for separate randomizations by stratum.

## 3.0 PRIMARY ENDPOINT

The study's primary endpoint is an ordinal composite based on three outcomes: vital status (mortality) as a safety outcome, and two efficacy results: occurrence of a major cardiac procedure indicative of worsening heart failure (a "qualifying" MCP as assessed by the study's Clinical Events Committee), and blinded core-lab assessment of change in New York Heart Association (NYHA) functional class from randomization to final follow-up visit.

Patients were classified as “worsened,” “same” or “improved” at final follow-up based on the three preceding elements:

Worsened – patient has died, has experienced a major cardiac procedure, or is classified as at least one category worse on blinded NYHA assessment, as compared to baseline.

Same – patient is alive, has not experienced a major cardiac procedure, and is judged on blinded assessment to be the same NYHA class as baseline.

Improved – patient is alive, has not experienced a major cardiac procedure, and is judged on blinded assessment to be at least one category improved over baseline NYHA classification.

This ordinal outcome was compared between treatment groups using a proportional-odds model with size of clinical site, concomitant surgery stratum and duration of follow-up (early vs. late enrollment, with July 4, 2002 as the cut date) as *a priori* stratifying factors, along with gender, baseline diastolic blood pressure and baseline peak VO<sub>2</sub> consumption as covariates; these three variables were found to differ between the randomized groups at baseline.

As the blinded core-lab assessment of NYHA was instituted after trial enrollment had begun, multiple imputation was used to model core-lab NYHA values for patients who were missing this score at baseline (see “**Multiple Imputation**,” below).

To provide a version of the primary endpoint without imputation, the composite endpoint was also analyzed by status at the end of the efficacy phase rather than change from baseline, in an *a priori* analysis specified in the protocol. For this analysis, a five-level ordinal composite was defined, under which patients who died were considered “class V” and those experiencing qualifying major cardiac procedures “class IV,” with core-lab NYHA classification at the final study visit providing the classification for patients without mortality or qualifying major cardiac procedures. Treatment groups were compared using the Cochran-Mantel-Haenszel method, with stratification by size of clinical site, MVR vs. no-MVR stratum, and baseline NYHA class as assessed by the site.

Time-to-event methods including Kaplan-Meier analysis were used to compare the individual events that are components of the primary endpoint (deaths and qualifying major cardiac procedures), and the NYHA classification component was analyzed using a proportional-odds model analogous to that performed for the composite endpoint, excluding patients who died or experienced a qualifying major cardiac procedure.

#### 4.0 MULTIPLE IMPUTATION

In the PMA submission, multiple imputation for the missing baseline core-lab NYHA data was implemented using SAS software (Cary, N.C.) in the following fashion:

1. A group of 10 potentially explanatory variables collected at baseline (pre-randomization) were entered into a stepwise regression, ultimately producing a set of four predictors.
2. The four predictors – site NYHA, MLHF score, 6-minute walk distance and SF-36 physical functioning score at baseline – were employed in a multiple imputation model (SAS PROC MI) for core-lab NYHA at baseline, using Markov chain Monte Carlo simulation to produce 100 imputed datasets. The model assumed a normally-distributed response variable, and since the NYHA instrument is actually an ordinal response with four levels, the resulting imputed values were rounded off to the nearest whole number for the purpose of further analysis.<sup>1</sup>
3. The imputed datasets were collectively analyzed (SAS PROC MIANALYZE) to produce parameter estimates and p-values for the primary endpoint. The SAS method for combining effect sizes and standard errors across multiple datasets is consistent with the principles laid out in Little and Rubin<sup>2</sup> for preserving valid statistical inference.

Robustness of the results of the analysis of the primary endpoint was evaluated in several ways, including the “final-distribution” method without imputation noted above. Additionally, several more multiple imputation models were built to examine the impact of the specific predictors and the form of the original model shown above.

Three of these models again used SAS to multiply impute the missing data, but with an ordinal assumption on the core-lab NYHA response variable, using a logistic model. The differences among these three models were in the predictor variables used and in the fact that the third model imputed missing values in the treatment and control groups separately to avoid potential “cross-contamination.”

The fourth model was built in a blinded fashion by a third party who did not have access to identifying information, including which group was treatment and which was control, or knowledge of the nature of the trial or the identity of the sponsor company. The dataset provided for this version of the imputation was also denatured to eliminate informative names on predictor and response variables, to further assure a blinded evaluation of the data.

Full details on all of these imputation models, including their results, are available in the Expert Report by Donald B. Rubin, Ph.D. included with this submission as an attachment to the Expert Consultant Opinion Memorandum.

## 5.0 SECONDARY ENDPOINTS

Four secondary endpoints were designated *a priori* as “major secondary outcomes” by virtue of their clinical significance, including core-lab assessed left ventricular end diastolic volume (LVEDV), core-lab assessed left ventricular ejection fraction (LVEF), Minnesota Living with Heart Failure score (MLHF) and site-assessed NYHA class.

To estimate the overall treatment effect throughout the efficacy phase, these four outcomes were analyzed using longitudinal methods including main effects for randomization group and visit and their interaction term, and with the baseline value of the outcome as a covariate. Graphical representations of mean levels of the major secondary efficacy endpoints throughout follow-up are based on estimates obtained from the longitudinal analyses.

Additionally, to provide a means of collectively assessing the four major secondary endpoints in light of multiplicity issues, Hochberg’s method was applied to the four major secondary endpoints to generate a composite hypothesis test of secondary efficacy, with a two-sided p-value of 0.05 or less deemed a success on this criterion.

Other secondary endpoints (those not deemed “major” secondary variables) were analyzed using methods analogous to those detailed above, including longitudinal analyses, time-to-event methods and categorical analyses as appropriate to the structure of the endpoint and the timing of its collection during study follow-up.

## 6.0 SAFETY ENDPOINTS

Time-to-event methods (Kaplan-Meier cumulative event curves) and stratified Mantel-Haenszel chi-square tests were used to summarize deaths and serious adverse events (SAEs). Comparisons of SAEs were carried out for all four groups of patients: those who had MVR with and without the device, and those in the No-MVR group, with and without the device.

## 7.0 STRATUM-SPECIFIC ANALYSES

For various study endpoints, separate analyses of results in the MVR stratum and the no-MVR stratum were conducted using methods analogous to those used for the full patient cohort, to provide further insight into the effect of CorCap with and without concomitant MVR surgery at baseline.

#### REFERENCES

1. Schafer JL. 1997. *Analysis of Incomplete Multivariate Data*. London: Chapman & Hall.
2. Little R and Rubin D. 1987. *Statistical Analysis with Missing Data*. New York: J. Wiley & Sons.