

**CORCAP<sup>®</sup> CARDIAC SUPPORT DEVICE**  
**EXPERT CONSULTANT OPINION MEMORANDUM**  
**November 13, 2006**

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\* Biographical statements are appended at the end of this report.

## INTRODUCTION

Congestive heart failure (CHF) affects approximately 5 million people in the United States and is the leading cause of hospitalization for people 65 years of age and older.<sup>1</sup> The disease is diagnosed in approximately 500,000 people yearly, and the annual rate of CHF-related hospitalizations has nearly doubled over the past 10 years. The prognosis for CHF patients is considered poor, with a 5-year mortality of approximately 50%. In the U.S., more than 300,000 patient deaths are attributed to CHF annually, and the estimated direct and indirect cost of heart failure for 2006 is estimated to be \$29.6 billion.<sup>2</sup>

The standard of care for treatment of CHF is pharmacotherapy. However, despite optimal drug treatment, systolic dysfunction commonly progresses, resulting in worsening of symptoms. Despite the known limitations of standard CHF therapy in mitigating the progression of both the disease and its symptoms, treatment options beyond the current standard of care for patients with advanced heart failure are very limited.

Because CHF arises when the heart is damaged or weakened, surgical treatments focus on repair or replacement of the underlying pathology affecting the heart (e.g. valve repair) or, when the heart muscle is extensively damaged, heart transplantation. Aside from valvular disease and coronary artery disease, structural abnormalities in the heart are known to play a role in CHF, and clinical evidence supports a strong causal relationship between cardiac chamber dilation and heart failure. Because dilation, and not contractile dysfunction, appears to be responsible for the severity of the disease, the mitigation or prevention of the deleterious dilation process is an important therapeutic endpoint for patients with this life-threatening illness. For this reason, it is understood that a therapy that specifically targets remodeling offers an important step in the treatment of heart failure. Acorn Cardiovascular Inc. (Acorn) has developed and studied the CorCap Cardiac Support Device (CSD) specifically for the purpose of mitigating ventricular dilation and remodeling.

As experts in the fields of CHF and biostatistics, we were requested to provide a critical review of Acorn's pivotal trial data, and other scientific information submitted to the Food and Drug Administration (FDA) in support of approval of the CorCap CSD, which is intended as a new treatment for patients with severe heart failure (dilated cardiomyopathy) that remain symptomatic despite optimal pharmacotherapy. We were asked to consider the extent to which the data provided in the Pre-market Approval (PMA) Application adequately provides reasonable assurance of safety and effectiveness, and further, to consider whether there is sufficient information to resolve scientific and clinical issues raised by the Food and Drug Administration (FDA) and the Advisory Panel convened by FDA on June 22, 2005.

In order to ensure that our opinion on the use of this product is thorough and appropriate, we conducted an independent review of all of the available data (including data from the pivotal clinical trial, the pre-clinical and safety studies, and the CorCap CSD marketing experience outside of the U.S.), participated in a consensus meeting to openly discuss all the clinical issues raised by the FDA and the Advisory Panel, and we thereupon derived a joint opinion based on our findings. Aside from our colleagues specializing in the clinical

management of CHF, we were assisted in our deliberations by two prominent biostatisticians, Drs. Donald Rubin and Steven Piantadosi.

Following our extensive review and discussion of the clinical data, we have reached a consensus conclusion that the CorCap CSD is effective in improving outcomes for patients with heart failure. We believe that the composite endpoint for this study, which FDA supported in its trial design guidance to Acorn and which we, as experts in the field, agree is appropriate and clinically meaningful, was met in a statistically significant manner as specified in the study protocol. This result is supported and strengthened by secondary measures of effectiveness. Based on the safety data from the pivotal trial and other sources of clinical experience with the product, we conclude that the CorCap CSD has a reasonable safety profile in consideration of the benefit provided to patients suffering this chronic and progressive disease. The CorCap CSD is indicated for patients with worsening CHF who do not have other options. We believe that the benefits offered by this device outweigh the risks that may be associated with its use.

Below are specific issues considered by our group, and the basis for our conclusions.

#### **CLINICAL SIGNIFICANCE OF PRIMARY ENDPOINT**

The primary effectiveness endpoint for the CorCap CSD trial was a composite of three clinically meaningful outcomes for this patient population: mortality, major cardiac procedures (MCPs) indicative of progressive heart failure,\* and a blinded assessment of change in New York Heart Association (NYHA) functional classification.

The original CorCap CSD protocol was unconditionally approved with left ventricular (LV) size defined as the primary endpoint. However, FDA requested that Acorn consider selecting an alternate primary endpoint to more directly reflect improvement in patient functional status and well-being. Acorn and FDA ultimately agreed upon a composite endpoint, the concept for which originated from peer-reviewed literature on designs for heart failure trials,<sup>3</sup> as well as from the proposed analyses methods. Further, correspondence indicates that FDA's interest was in verifying that CorCap CSD efficacy did not come at the expense of increased mortality in the treatment group. Besides enhancing statistical power, the advantage of a composite endpoint for a heart failure trial is that multiple outcomes can be simultaneously evaluated as a primary objective. This is especially important for heart failure where the complex pathophysiology of the disease and patient co-morbidities make therapeutic evaluation difficult.

The study was designed and powered specifically for the combined utilization of the three components of the composite endpoint. A trial in which the individual components are evaluated was not feasible due to the large sample size that would be required. For

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\*MCPs include heart transplantation, ventricular assist device (VAD) placement, coronary artery bypass graft (CABG), biventricular pacing device placement, or subsequent mitral or tricuspid valve replacement.

example, detecting even a 30% reduction in mortality due to CorCap CSD implantation at traditional levels of significance would have required a trial with over 2,000 patients. When considered individually, one of the three components (MCPs) achieved statistical significance. As clinicians, we look for clinical tradeoffs and coherence in the changes observed in the elements of the composite endpoint, with changes in the same direction being important, even when not statistically significant.

Additionally, it seems to us that independently considering mortality as an efficacy component (much less anticipating a significant reduction in mortality) does not correspond with the pivotal trial's study design and purpose. FDA's discussions with Acorn (including correspondence in a letter of June 8, 2001) indicate quite clearly that mortality was intended as a safety endpoint, and not as a measure of efficacy. Further, this correspondence indicates that FDA's interest was in verifying that CorCap efficacy did not come at the expense of increased mortality in the treatment group. We agree with the position FDA took in 2001 that mortality should be considered a safety endpoint. Thus, the primary endpoint is most logically viewed as a composite of three outcomes: two efficacy outcomes (change in core-lab NYHA and MCPs), both of which favored CorCap CSD, and one of which achieved statistical significance; and one safety outcome (mortality), which met its success threshold by showing statistically similar mortality in the CorCap CSD and control groups.

Supportive analyses of the primary endpoint were specified in the study protocol to address the robustness of using this composite, as well as to address the secondary major objectives of the study; namely, to assess the structural effects of the device and the associated functional changes. This latter goal was accomplished by comparing structural changes in the heart and patient functional status for the treatment and control groups. These additional analyses were also designed to determine the rate of death and other serious adverse events experienced by patients assigned to the CorCap CSD and to compare this rate with that of patients assigned to the control group.

## **RESULTS FOR SECONDARY ENDPOINTS**

Secondary endpoints were selected for their clinical utility in seriously ill heart failure patients. These endpoints were comprised of structural, functional, physiologic, and serious adverse outcomes.

**Table 1** summarizes results for all secondary endpoints. Each of the secondary endpoints was improved, or statistically neutral, compared to control, with the exception of B-type natriuretic peptide (BNP).

**Table 1**  
**Summary of Secondary Endpoints**

Major Secondary Endpoints	Treatment Difference (T-C)	p-value	
		Nominal	Hochberg
LVEDV	-17.9ml	<0.01	0.03
LVEF	0.83	0.49	0.60
MLHF	-4.47	0.04	0.12
NYHA (Site Assessed)	-0.04	0.60	0.60

Structural Endpoints	Treatment Difference	p-value
LVEDV	-17.9ml	<0.01
LVESV	-15.2ml	0.02
LVEF	0.83	0.49
Sphericity Index	0.042	0.03
Mass Index	-5.9g/m <sup>2</sup>	0.15
LVEDD	-1.8mm	0.02
LVESD	-1.2mm	0.21
Functional Endpoints	Treatment Difference	p-value
MLHF	-4.47	0.04
SF-36 (General Health Domain)	9.13	<0.01
SF-36 (Physical Function Domain)	5.41	0.02
NYHA (Site-assessed)	-0.04	0.60
6-minute Walk Distance	1.27 (odds ratio)	0.24
Cardiopulmonary Exercise Testing	1.37 (odds ratio)	0.15
Other Endpoints	Treatment Difference	p-value
BNP	77.33 pg/ml	0.01
All-Cause Hospitalizations	1.0	0.44
Major Cardiac Procedures	0.46 (odds ratio)	0.01
Mortality or All-Cause Re-hospitalizations	1.02 (odds ratio)	0.88

Specifically, four secondary endpoints were identified *a priori* in the study protocol as Major Secondary Endpoints: Left Ventricular End Diastolic Volume (LVEDV), Left Ventricular Ejection Fraction (LVEF), Minnesota Living with Heart Failure (MLHF) score, and New York Heart Association (NYHA) classification by study site. The study protocol specified that interpretation of the significance of these four endpoints would be assisted with use of the Hochberg procedure. A strict application of the Hochberg procedure indicates that four distinct adjusted p-values should be provided; these are: LVEDV (0.03), LVEF (0.60), MLHF (0.12), NYHA- site assessed (0.60). A single p-value can be a reasonable summary based on an interpretation of previous FDA panel proceedings using the Hochberg procedure, specifically proceedings leading to the approval of Medtronic InSync Implantable Cardioverter Defibrillator (MIRACLE ICD Trial).<sup>4</sup>

*A priori* success criteria of the other secondary endpoints were not identified in the protocol. The statistical analysis plan specified that data generated from required testing at follow-up visits be summarized at month 6 and at month 12 using analysis of variance, and across all follow-up visits through the end of the efficacy phase using longitudinal regression models. Patients who were treated with a CorCap CSD required fewer additional therapies (such as LVADs and transplants), and they had immediate and sustained improvements in quality of life. Further, patients treated with the CorCap CSD demonstrated improvements in ventricular size and shape, as shown by the substantial and significant decrease in LV volume and improvement in sphericity index. This result is consistent with the therapeutic concept of the CorCap CSD and with a large body of evidence supporting the relationship between cardiac chamber dilation and the progression of CHF. Secondary endpoint results also indicated favorable results in functional endpoints including SF-36 GHD, SF-36 PFD, and MLHF.

Special mention should be made concerning the clinical relevance of changes in ventricular structure because these have been criticized as not being relevant. To the contrary, all drugs shown to improve heart failure morbidity and mortality have been associated with either attenuation (ACE inhibitors, ARBs, aldosterone blockers) or a reversal of ventricular remodeling (beta blockers, cardiac resynchronization therapy). Conversely, therapies that have failed to improve heart failure morbidity and mortality (endothelin blockers, vasopressin antagonists, inotropic agents) have been associated with either no effect or worsening of ventricular remodeling. Therefore, measurement of structural endpoints is of major relevance and importance to outcomes in heart failure patients.

FDA has suggested that most secondary endpoint analyses were not statistically significant under a multiplicity adjustment, although the precise form of that adjustment was not specified. We are of the opinion that this type of multiplicity adjustment for secondary outcomes is not mandatory. Multiplicity adjustments are not required for analyses of secondary variables when those analyses are conducted for the sole purpose of providing supporting evidence to a significant primary endpoint. These kinds of multiplicity adjustments are intended to protect the Type 1 error when many outcomes will be selected based solely on statistical significance and put forward as definitive, which was not true in this circumstance because the primary outcome was protocol-specified. Lastly, variations in statistical significance of secondary endpoints are not unexpected due to the complexity of the disease. Importantly, the large majority of the results in secondary endpoints favor treatment, and the magnitude of the estimated effects are clinically meaningful for this population of patients.

## **CLINICAL SIGNIFICANCE OF SUBGROUP ANALYSES BY MVR STATUS**

The CorCap CSD pivotal trial design was conducted using blocked randomization, after stratification by mitral valve repair or replacement (MVR) surgery, based on clinical considerations. Clearly, the MVR and non-MVR patients are expected to have different baseline characteristics and risk profiles. This design was used to estimate an average

treatment effect across strata, even though the estimated effects could vary from stratum to stratum.

Although the same statistical analyses were performed within strata as in the total group of patients, it was not assumed that analyses of each individual stratum would reach statistical significance because of the smaller sample sizes. Nevertheless, analyses of the primary composite endpoint in the non-MVR stratum showed a statistically significant effect of the treatment (p=0.03). In addition, the CorCap CSD implant reduced the progression of heart failure as evidenced by a statistically significant (p=0.02) decrease in the need for major cardiac procedures. The non-MVR stratum thus offered the purest clinical assessment of the CorCap CSD hypothesis because the comparison was between medical therapy alone (control group) and medical therapy plus the CorCap CSD (treatment group). In this stratum, the CorCap CSD treatment effect is not affected by the MVR procedure.

Failure to reach statistical significance in the MVR stratum is not evidence that the CorCap CSD had no efficacy signal when used as an adjunct to MVR. To the contrary, the CorCap CSD indicates a clinically important treatment effect (OR=1.51) despite a non-significant p-value (0.17) (see **Table 2**). The study was not powered to detect an incremental benefit of the CorCap CSD on MVR surgery alone. It was expected that the benefit of the CorCap CSD in MVR patients may be difficult to observe at 12 months because the benefit of the valve replacement in eligible patients may mask an incremental improvement provided by the device.

**Table 2**  
**Primary Composite Endpoint – Treatment Effect of the CorCap CSD**

<b>Both Strata OR (p-value)</b>	<b>MVR Stratum (n = 193) OR (p-value)</b>	<b>No-MVR Stratum (n = 107) OR (p-value)</b>
1.73 (0.02)	CorCap n = 91 No CorCap n = 102	CorCap n = 57 No CorCap n = 50
	1.51 (0.17)	2.57 (0.03)

**IMPACT OF MISSING DATA FOR THE PRIMARY ENDPOINT**

We understand the rationale for imputing missing baseline NYHA data in this study, which is one of three elements of the composite endpoint. To meet FDA’s requirement for a blinded NYHA assessment, Acorn instituted core-lab determinations of NYHA<sup>5</sup> at each study visit. FDA’s rationale for this request was that this method met a criterion for “clinically meaningful” changes with reduced potential for treatment bias. Missing data arose because the blinded NYHA instrument had not been implemented until over half the patients (174) had been enrolled. The correspondence between Acorn and FDA indicates that FDA was aware that this change, after trial initiation, would result in missing data for some patients.<sup>6</sup>

The results of the primary endpoint analysis were not compromised by multiple imputation. Missing data occurred at baseline, before randomization was conducted, and thus missingness could not be related to patients' clinical outcomes during the trial. There is no reason to doubt the missing at random (MAR) assumption that was made for imputation because missing data arose not due to patient dropout or other potential causal relationships to outcome, but rather from a new study procedure introduced after recruitment had started.

A more thorough statistical evaluation of the impact of missingness conducted by our colleague, Dr. Rubin, showed moreover, that the true statistical effect of missing NYHA data on the composite primary endpoint was comparatively small. A full report of Dr. Rubin's findings is attached at the end of this Memorandum.

Various other imputation methods (sensitivity analyses) with varying appropriate distributional assumptions and sufficiently broad sets of predictor variables all support the conclusion that patients randomized to CorCap CSD had significantly better clinical outcomes, as defined by the primary endpoint, than patients randomized to control. In addition, an independent third-party blinded imputation of the data, designed by Dr. Rubin and performed by Dr. Constantine Frangakis of John Hopkins University, validated the results of the imputation analysis performed by Acorn.

## **SAFETY**

We understand that FDA has expressed concerns about the safety of CorCap CSD, specifically in three areas: risk of perioperative death, particularly four deaths that occurred in the non-MVR strata; risk of re-operation complications due to adhesion formation; and risk of pericardial constriction in the long term.

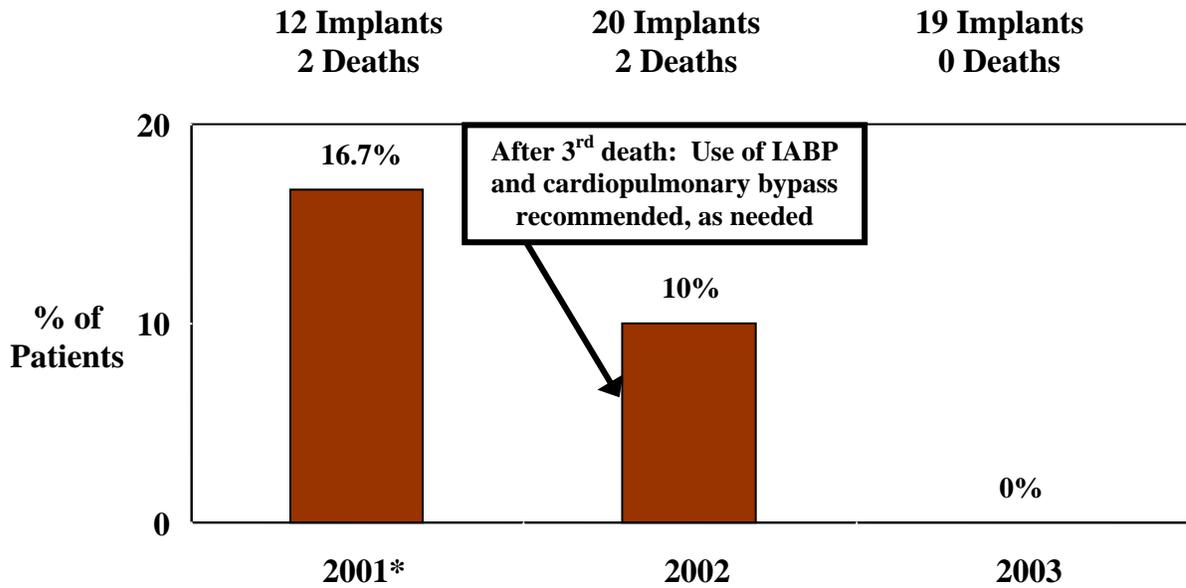
### Risk of perioperative death

As a group, we have focused specifically on the observation that four perioperative deaths occurred in the non-MVR CorCap CSD group compared to none in the non-surgical control during the first 30 post-operative days. For patients who do not qualify for MVR, use of the device is an elective surgery in a very sick population. We wanted to assure ourselves that we completely understood the nature of these deaths and the implications to CorCap CSD safety.

We reviewed the characteristics of the four patients who died in the post-operative period and conclude from our review that all four patients died from cardiac causes probably due to surgical procedure or hemodynamic instability. Clearly, as is observed in many surgical interventions, the procedure and technique used, especially at the beginning of the study, could have contributed to the early deaths. For example, it was found that one consistent feature of all four patients was that the surgeries were started without the use of cardiopulmonary bypass. After the third perioperative death (in 2002), Acorn revised its training program and made several recommendations to all surgeons to reduce peri-

operative risk, including using cardiopulmonary bypass and intra-aortic balloon pump (IABP) if there was evidence of hemodynamic instability. We believe that these changes had an immediate effect since, in 2003, no perioperative deaths were observed out of 19 implants performed (See **Figure 1**). Thus, it appears that the early deaths were due to a “learning curve” associated with the procedure but not with the device directly. The additional experience, as well as the additional training on the use of cardiopulmonary bypass and IABP, were successful in reducing the incidence of perioperative mortality.

**Figure 1**  
**Perioperative Mortality in Non-MVR Stratum**  
**Trial Learning Curve Phenomenon**



Each of the patients that died was extremely ill, as evidenced by very low LVEFs in two patients (9% and 10%, as well as 16% in the third patient), and by hemodynamic instability in three out of the four individuals (see narratives in Appendix A. Consolidated Safety Report). When the experiences with patients at high operative and overall mortality risk were removed from the study, as defined in the exploratory Focused Cohort (described below), mortality in the non-MVR group for the CorCap CSD dropped to 1 patient out of 31, or 3.2%. We believe the risk of perioperative death is effectively mitigated by the modified Instructions for Use, including the revised indications as reflected from the Focused Cohort analysis.

In an attempt to further understand the risk of death in this cohort, we conducted a classic prognostic factor analysis with construction of a risk factor score. All deaths in the entire trial cohort were studied using the proportional hazards model.<sup>7</sup> Twenty-five baseline candidate risk factors were studied, including NYHA classification, age, gender, years since heart failure diagnosis, 6-minute walk distances, MLHF score, MV regurgitation, diastolic blood pressure, sodium, BUN, creatinine, HGB, BMI, ischemic etiology (vs.

other), LVEF, LVEDD, peak VO<sub>2</sub> at baseline, and histories of high blood pressure, angina, CAD, MI, pacemaker, ICD, COPD, diabetes and renal dysfunction.

The model was stratified by treatment group and MVR stratum. Using standard variable selection methods, four factors were identified as predictive of death: LVEF, creatinine, years since diagnosis, and sex. For each study subject, a risk factor score was calculated based on the model coefficients and individual covariate values.

Three of the four early mortality cases were found to have risk factor scores in the highest decile. This indicates that there is some information about early deaths relative to those who died later that is at least partially attributable to subject characteristics in addition to technical procedures. This analysis, when considered alongside the analysis of each case from a clinical perspective, and when combined with the Focused Cohort analysis, adds to the evidence that the risk of perioperative death can be mitigated by proper labeling.

As clinicians and surgeons, it is our experience that surgery in very ill patients is associated with a high risk of perioperative death. For example, the perioperative mortality rate for treatment in the 300-patient cohort (4.1%) was higher than control (which included a non-surgical arm) but still lower than the Society of Thoracic Surgeons (STS) database perioperative mortality rate of 7% for patients with dilated cardiomyopathy.<sup>8</sup> Moreover, one-year mortality is comparable between treatment and control patients in the trial.

Risk of re-operation complications due to adhesion formation

FDA expressed concern that the CorCap CSD leads to an excessive number of adhesions on the heart, which could negatively impact future re-operations. It should first be recognized that dense adhesions can and sometimes do occur following any cardiac surgery, and are not at all unique to this particular procedure. Further, although adhesions were noted in all CorCap CSD re-operation patients, all of the follow-on procedures, including transplantation, were performed safely and with good outcomes (see **Table 3**). Among seven CorCap CSD recipients with extended follow-up who went on to transplant, none have died, whereas two out of 16 control patients died subsequent to cardiac transplantation. The adverse event (AE) rates were similar and the postoperative stay lower in the CorCap CSD group than in control.

**Table 3**  
**Mortality and Morbidity after Transplant – 300 Patient Cohort**

	<b>Treatment</b>	<b>Control</b>
Total # Patients	7	16
Deaths	0	2*
AEs per Patient	1.7	1.9
AEs within 30 days of transplant	4	10
Post-Operative Stay	12.3 days (6-17)	19.6 days (8-46)

\* One patient died within 30 days of transplant

As a group, we are of the opinion that complications due to adhesions at re-operation do not reflect a clinically important risk associated with CorCap CSD. Adhesions are an acknowledged challenge in performing this operation, and are best managed by proper surgical technique and procedure. Two of us, Drs. Acker and McCarthy, have had experience with this as trial investigators. Dr. Acker has consistently compared reoperations in this patient group to standard cardiac reoperations for heart transplant or valve replacement, and concludes that each present equal surgical challenges. Also of note is a letter from Dr. McCarthy (appended at the end of the Clinical Study Summary) where he stated that, while dense adhesions formed around the Acorn device in one of his patients, the implication of this finding is simply that surgeons should be prepared to schedule additional time in surgery to properly remove the device, especially during LVAD explants while waiting for a donor heart for transplantation. Dr. McCarthy was vocal about the fact that he did not deem adhesions to be a specific problem or complication of CorCap CSD implantation.

#### Risk of pericardial constriction in the long term

We found no indication from either follow-up or adverse event forms of clinically significant constrictive physiology at any time during the study. Acorn has indicated a commitment to continued monitoring of their IDE cohort patients for evidence of constrictive physiology for 5 years because of the potential that the rate of constriction is low enough that a relationship may only be recognized with time. Thus, while we do not believe that the risk of pericardial constriction in the long term is of clinical significance, we believe this potential complication can be monitored in the post-market period.

#### **ROLE OF FOCUSED COHORT IN REPRESENTING A CLINICALLY MEANINGFUL PATIENT SUBSET**

The Focused Cohort refers to an exploratory analysis conducted by Acorn in response to the not approvable letter sent by FDA on August 12, 2005. In that letter, FDA indicated that a post-hoc analysis of subgroups in the trial may yield a better risk-benefit profile for the device. Results of the sub-group analysis showed an incremental benefit of the CorCap CSD in MVR surgery (OR=1.81) and a significant improvement in the individuals who did not have MVR surgery compared to the standard of care control group (OR=8.33,  $p<0.01$ ) (see **Table 4**).

**Table 4**  
**Primary Composite Endpoint – Treatment Effect of the CorCap CSD**  
**Focused Cohort**

	<b>Both Strata OR (p-value)</b>	<b>MVR Stratum (n = 193) OR (p-value)</b>	<b>No-MVR Stratum (n = 107) OR (p-value)</b>
<b>300-Patient Cohort</b>	1.73 (0.02)	CorCap n = 91 No CorCap n = 102	CorCap n = 57 No CorCap n = 50
		1.51 (0.17)	2.57 (0.03)
	<b>Both Strata OR (p-value)</b>	<b>MVR Stratum (n = 103) OR (p-value)</b>	<b>No-MVR Stratum(n = 56) OR (p-value)</b>
<b>Focused Cohort</b>	CorCap n = 77 No CorCap n = 82	CorCap n = 46 No CorCap n = 57	CorCap n = 31 No CorCap n = 25
	2.45 (0.01)	1.81 (0.16)	8.33 (<0.01)

The questions before us are whether the Focused Cohort represents a clinically meaningful patient subset in which the device is safe and effective, and whether the analysis is clinically meaningful.

It is important to recognize that the Focused Cohort analysis was conducted after a clinically and statistically meaningful positive result was determined for the CorCap CSD in the total cohort. As such, this exploratory analysis, in which a sub-group was identified with a greater benefit-risk profile than the full cohort, provides support for the overall conclusions of the study, and can serve to assist in labeling recommendations, and in patient selection. This subgroup analysis was never intended to supplant the original, protocol-specified, primary cohort analysis.

Development of the Focused Cohort analysis involved collaboration with many clinicians with heart failure expertise: Drs. Abraham, Acker, Burkoff, Cohn, Dowling, Dullum, Jessup, Lorell, Mann, McCarthy, Rose, Ruggio, and Starling. These investigators agreed prospectively that certain parameters are clinically relevant, namely, left ventricular end-diastolic diameter index (LVEDDi). A subgroup analysis from the Valsartan Heart Failure Trial (Val-HeFT) provided additional validation of the concept of different responses among subgroups of patients.<sup>9</sup>

The Focused Cohort analysis is a cumulative trend analysis that was conducted to exclude from the 300-patient cohort individuals with inferior treatment responses attributable to either higher surgical risk or more variable efficacy. An additional analysis of available cases (those without missing data) was also conducted. A combination endpoint of heart failure-related hospitalizations and death was used as an alternative to the primary endpoint of the pivotal study to address the issue of missing data, since there are no missing data with this endpoint. These exploratory results are consistent with results of the primary endpoint in the pivotal trial based on multiple imputation. The primary endpoint and the

alternate primary combination endpoint both achieved significance without imputing the missing NYHA data. Also, the Focused Cohort analysis is of value as a means to guide labeling and improved patient selection.

We agree with FDA that the Focused Cohort analysis provides a hypothesis that can be evaluated with additional research. However, in our assessment, another pre-approval study is not necessary for this device because the primary trial is sufficient to establish safety and effectiveness. Identifying risk factors predictive of a poor outcome with the CorCap CSD can be effectively examined prospectively in a carefully designed and analyzed observational post-market study.

## **RISK/BENEFIT ANALYSIS**

As a group we have carefully considered the potential benefits of this device and weighed the benefits against potential risks to the patients. Heart failure is a life threatening chronic and very serious illness. These patients are in great need of additional therapies, as they currently have very limited options. It is our opinion that, altogether, the data presented by Acorn show that the benefits of CorCap CSD treatment outweigh the potential risks of the procedure.

The known risks of the device are the risks of complications from a surgical procedure, the potential for risks post-operatively, and the remote long-term risk of pericardial constriction. The benefits to the patient are substantial, and include improved function, reduced mortality, improved quality of life, and a reduced risk of transplantation. More specifically, compared to control patients, CorCap CSD patients appeared to experience clinically important benefits as evidenced by:

- Functional Class - 38% improved by one or more NYHA class
- Quality of life - Improved MLHF by 4.5 units
- Need for Transplant or VAD - 55% decreased need for transplant or VAD
- Heart Size - Decreased volume by 17.9 mL

It is our conclusion that the benefits outweigh the risks in these heart failure patients, who experience persistent and advanced symptoms, and for whom no other treatment options exist.

## **CONCLUSIONS**

The data and analyses we reviewed provide what we consider to be a reasonable demonstration that treatment with the CorCap CSD provides a clinically meaningful improvement in patient outcomes.

The 300-patient study succeeded. The *de facto* clinical criterion for success was met with statistical significance and an acceptable benefit-risk profile. The clinically meaningful

and statistically significant primary composite endpoint is supported by analyses of the components of the primary composite endpoint, as well as by secondary endpoints and by the exploratory results of the Focused Cohort of patients not at high risk. In addition, experiences with the device outside the pivotal trial further support these results. The data analyses presented by Acorn in the PMA as amended are, in our opinion, valid and adequate to support conclusions regarding the clinical significance by appropriately qualified clinical and statistical experts.

We appreciate the careful and conservative approach taken by FDA in evaluating the clinical trial results. Upon careful critical review, and based on our combined and extensive experience in this field, we conclude that sufficient data are provided in the PMA submission to address the concerns, and that this device meets the standard of safety and effectiveness required for approval.

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**MICHAEL A. ACKER, M.D.**  
**Biographical Statement**

William Maul Measey Professor of Surgery  
University of Pennsylvania School of Medicine  
Chief, Division of Cardiovascular Surgery  
Surgical Director, Cardiac Transplant and Mechanical Assist Program  
Hospital of the University of Pennsylvania  
Philadelphia, PA

Michael A. Acker, M.D., is the Chief of the Division of Cardiovascular Surgery and the Surgical Director of the Heart Transplantation and Ventricular Assist Programs at the Hospital of the University of Pennsylvania. He is also the William Maul Measey Professor of Surgery at the University of Pennsylvania School of Medicine. He is a Board Certified cardiothoracic surgeon who has primarily practiced at the University of Pennsylvania since earning his medical degree from Brown University in 1981.

In addition to significant involvement in cardiac and surgical academic committees and major supervisory responsibilities for both the University hospital and medical school, Dr. Acker maintains an active surgical practice focusing on the care of patients with end-stage heart failure, coronary artery disease and valvular disease. He also has special expertise in mitral valve repair for advanced myxomatous disease or in patients with end-stage heart failure. He is a national leader in the use of mechanical assist devices as a bridge to transplantation or as permanent therapy for end-stage heart failure.

Dr. Acker is a frequent invited lecturer on cardiomyoplasty, cardiac assist devices, heart transplantation, and the treatment of heart failure, mitral regurgitation, and other conditions. With his colleagues, Dr. Acker has contributed numerous case reports and original articles, and numerous textbook and manual chapters on cardiac assist devices, transplantation, and cardiac surgery. From as early as 1992, he has served as a reviewer on the editorial boards of the journals *Circulation*, *Chest*, *Annals of Thoracic Surgery*, *Heart Failure*, and *Journal of Thoracic and Cardiovascular Surgery*. Dr. Acker is Director of an active research laboratory at the University of Pennsylvania investigating both biologic and mechanical ventricular assistance. He has served as a Principal Investigator for several preclinical and clinical studies involving novel cardiovascular devices and cardiac surgical procedures.

Dr. Acker has been recognized as a Best Doctor in America for the years 2003 to 2005, and was awarded the Louis Duhring Outstanding Clinical Specialist Award from the University of Pennsylvania Health System in 2002. He is a Fellow of the American College of Cardiology, the American College of Chest Surgeons, the American Surgical Association, and the American College of Surgeons. He is also an involved member of numerous cardiac and surgical organizations, having served on program committees for the Society of Thoracic Surgeons and the American Association of Thoracic Surgery.

**INDER S. ANAND, M.D., D.PHIL.**  
**Biographical Statement**

Professor of Medicine, Cardiovascular Division  
University of Minnesota Medical School  
Director, Heart Failure Program  
VA Medical Center  
Minneapolis, MN

Inder S. Anand, M.D., D. Phil., has served as a Professor of Medicine at the University of Minnesota, Minneapolis and the Director of the Heart Failure Program at the VA Medical Center in Minneapolis, MN since 1991. He received his medical degree from Punjab University in 1966 and his Doctor of Philosophy degree from Oxford University in 1971. He has significant expertise in the pathophysiology and management of heart failure and in high altitude medicine and physiology.

Dr. Anand is an active member of the cardiovascular research community. Since 1992, he has served as a Principal Investigator in nearly 60 clinical trials that have evaluated pharmacologic, surgical, and/or device interventions for heart failure, atrial fibrillation, and ventricular remodeling. He has also been a member of steering and endpoint committees for many major clinical trials of cardiovascular devices. Dr. Anand's experimental research includes work on isolated myocyte function in human and animal models of heart failure. In addition to his research endeavors and professional responsibilities, Dr. Anand has lectured for numerous national and international audiences at conferences and for organizations on the treatment of heart failure.

He serves on the editorial boards of several peer-reviewed journals, including the *Journal of Molecular & Cellular Cardiology* and *Experimental and Clinical Cardiology*, and he is Associate Editor of the *Journal of Cardiac Failure*. Since 1967, he has contributed to hundreds of manuscripts and book chapters on the treatment and experimental models of cardiac failure.

Dr. Anand is a Fellow of the American College of Cardiology, American Heart Association, and the Royal College of Physicians, London, UK. Dr. Anand serves as Secretary of the World Heart Failure Society and Vice-President of the Indian Section for the International Society for Heart Research. He has twice been the recipient of national honors by the Cardiological Society of India.

**STEVEN F. BOLLING, M.D.**  
**Biographical Statement**

Gayle Halperin Kahn Professor of Integrative Medicine, Section of Cardiac Surgery  
University of Michigan  
Ann Arbor, MI

Steven F. Bolling, M.D. is a Professor in the Section of Cardiac Surgery at the University of Michigan. He also serves on the adjunct staff at St. Joseph's Hospital and on the consulting faculty at the VA Hospital in Ann Arbor, MI. He was recently appointed as the inaugural Gayle Halperin Kahn Professor of Integrative Medicine, and center director for the University of Michigan's Integrative Medicine Center, focusing on traditional and complementary medicine. Dr. Bolling is a Board Certified cardiothoracic surgeon who has served in thoracic and cardiac surgical professorships at the University of Michigan since 1986, where he also received his medical degree in 1979.

Dr. Bolling is an accomplished cardiac surgeon, who has lectured and operated extensively around the world and has developed new techniques, particularly in the area of mitral valve reconstruction. Dr. Bolling is a well-established and supported investigator, not only in the clinical realm, but in the area of myocellular metabolism during myocardial ischemia and transplant immunology. His molecular research has focused on cardiac cell signal transduction as it relates to bioenergetics and myocardial preservation during cardiac surgery.

Since the late 1980's, Dr. Bolling has been a clinical investigator of implanted cardiac devices, such as the artificial heart, a cardiac assist device, and mitral annuloplasty rings and systems. He co-invented the Edwards Lifesciences GeoForm mitral valve repair ring, and has actively taught and presented in national and international forums on mitral valve reconstruction and interventions.

Dr. Bolling has been given multiple awards and honors for his research and professorships, including honors from South African, Korean and Japanese Associations for cardiac and thoracic surgery. He is a Fellow of the American College of Surgeons, the American College of Chest Physicians, the American College of Cardiology, and the American Surgical Association, as well as a member of multiple cardiothoracic surgery organizations, including the American Association of Thoracic Surgeons.

Dr. Bolling is the acting Editor of the *Journal of Investigative Surgery*, and serves as a member of the editorial boards of several journals, including the *Journal of Cardiac Surgery* and *Transplantation* and as a reviewer for a dozen peer-reviewed journals. He is a frequent author of chapters on techniques in surgical texts, and his research has been widely published in manuscripts on the treatment of mitral regurgitation and congestive heart failure, as well as on the pharmacology of Chinese herbs.

**SIDNEY GOLDSTEIN, M.D.**  
**Biographical Statement**

Professor of Medicine  
Wayne State University School of Medicine  
Division Head Emeritus, Division of Cardiovascular Medicine  
Henry Ford Hospital  
Detroit, MI

Sidney Goldstein, M.D., is Professor of Medicine at Wayne State University School of Medicine, and Division Head, Emeritus, of the Division of Cardiovascular Medicine at Henry Ford Hospital in Detroit, MI. Before joining Henry Ford Hospital as Head of the Cardiovascular Division in 1974, he was Head of the Cardiology Division at Rochester General Hospital in Rochester, NY and Associate Professor of Medicine at the University of Rochester. He received his medical degree from Cornell University.

Dr. Goldstein's research has focused on clinical trials for ischemic heart disease and prevention of sudden cardiac death and the treatment of heart failure. He served as chairman of the steering committee of the Beta-Blocker Heart Attack Trial and was a Principal Investigator in the Aspirin Myocardial Infarction Study, the Cardiac Arrhythmia Suppression Trial and the Asymptomatic Cardiac Ischemia Pilot Study. He has carried out extensive research on the mechanism and prevention of sudden death, supported by the National Heart, Lung and Blood Institute. His current interests are directed at understanding the basic mechanism of heart failure. Most recently, he served as co-Principal Investigator of the Metoprolol CR Randomized Interventional Trial in Heart Failure. He has served as chair for Data and Safety Monitoring Boards in multiple clinical trials investigating pharmacological and device interventions in heart failure.

Widely published in the fields of ischemic heart disease, prevention of sudden cardiac death, and treatment options for heart failure, he has authored or co-authored editorials, book chapters, and published extensively in peer-reviewed journals. He is co-editor of *Heart Failure Reviews*, a journal examining the spectrum of research in heart failure from basic science to clinical research. He is medical editor of *Cardiology News* and currently serves on the editorial boards of several journals, including the *American Journal of Cardiology*, *American Journal of Geriatric Cardiology* and *Internal Medicine News*.

Dr. Goldstein is a Fellow of the American College of Cardiology and a past member of its board of trustees and chairman of the Workforce and Credential Committees. He is also a member of the Council of Clinical Cardiology and Epidemiology of the American Heart Association, a Fellow of the American College of Physicians, and a member of the American Federation for Clinical Research, the Central Society for Clinical Research, and the Association of University Cardiologists. Dr. Goldstein has received the Walter Bleifeld Memorial Award from the International Society of Heart Failure, and the Life Time Achievement Award from the American Heart Association of Michigan.

**MARIELL JESSUP, M.D.**  
**Biographical Statement**

Professor of Medicine  
University of Pennsylvania School of Medicine  
Medical Director, Heart Failure & Cardiac Transplantation  
Hospital of the University of Pennsylvania  
Philadelphia, PA

Dr. Mariell Jessup is the Director of Heart Failure and Cardiac Transplantation at the Hospital of the University of Pennsylvania, and Professor of Medicine at the University of Pennsylvania School of Medicine. Dr. Jessup is also Director of Cardiovascular Medicine Special Projects and Associate Director of the Penn Cardiac Care Outreach Program with the University of Pennsylvania Health System. She is certified in internal and cardiovascular medicine. Dr. Jessup received her medical degree at Hahnemann Medical College (Drexel University). She is certified by the American Board of Internal Medicine and in the subspecialty of cardiovascular medicine.

Dr. Jessup's research interests include diastolic heart failure, ventricular assist devices, and heart failure outcomes. She is a frequent lecturer for national and international audiences on heart failure treatments and heart transplantation, having delivered over 75 presentations at conferences and symposia in the past five years alone.

Dr. Jessup is an involved member of multiple national professional and scientific cardiology organizations. She is a Fellow of the American College of Cardiology and a current member of its Heart Failure and Transplant Committee, a Fellow of the American Heart Association and Vice Chair of its Committee of Scientific Sessions Program, and on the Board of Directors for the International Society for Heart and Lung Transplantation. She is a founding member of the Transplant Cardiology Research Database, and serves on the American Board of Internal Medicine's Subspecialty Board of Cardiovascular Disease. Dr. Jessup has been recognized by Best Doctors in America from 2003 to 2006.

Her contributions to scientific literature include manuscripts and book chapters on mechanical ventricular assistance, transplantation, and treatment of heart failure. She serves on the Editorial Advisory Boards of *Heart Failure*, *Journal of Cardiac Failure*, and *Journal of Heart and Lung Transplantation* journals, and is a reviewer for *Circulation*, *New England Journal of Medicine*, and *Journal of the American College of Cardiology*.

**PATRICK M. McCARTHY, M.D.**  
**Biographical Statement**

Chief of Cardiothoracic Surgery  
Feinberg School of Medicine, Northwestern University  
Co-Director, Bluhm Cardiovascular Institute, Northwestern University  
Chicago, IL

Patrick McCarthy, M.D., is the chief of the division of Cardiac Surgery and Co-Director of the Northwestern Memorial Cardiovascular Institute, as well as professor of surgery at Northwestern University's Feinberg School of Medicine. He is a Board Certified cardiothoracic surgeon and earned his medical degree from Loyola University, Strich School of Medicine, in Maywood, IL. His areas of interest include cardiac tumor resection, ventricular myectomy, and coronary artery bypass and valve surgeries.

Dr. McCarthy has achieved national and international recognition in the field of complex adult cardiac surgery, including valves, cardiac transplantation, mechanical ventricular assist devices, coronary artery bypass, minimally invasive surgery, and atrial fibrillation ablation. An innovator in his field, Dr. McCarthy developed the Edwards three-dimensional annuloplasty system for the repair of tricuspid regurgitation and recently adapted it for mitral valve use. He has also been the primary investigator in testing the efficacy of these as well as other cardiac devices. His work on surgical therapies for heart failure has been profiled on television programs such as "Nova" and "20/20" and featured in the *New York Times*, *Time*, *Newsweek*, and *Discover*. Dr. McCarthy has been consistently named both one of America's Top Doctors and America's Surgeons yearly since 2002.

Dr. McCarthy has lectured extensively on the subjects of dilated cardiomyopathy, mitral valve replacement surgery, partial left ventriculectomy, and left ventricular volume reduction. He is a Fellow of the American College of Cardiology and a member of numerous societies including the American Association for Thoracic Surgery. Dr. McCarthy also sits on the steering committee of the Society of Heart Valve Disease, and is Chair of the Workforce on New Technology for the Society of Thoracic Surgeons.

He is widely published on subjects such as ventricular assist devices, nonischemic dilated cardiomyopathy, mitral valve repair, heart transplantation, and partial left ventriculectomy. He is currently writing a book entitled *A Combined Medical and Surgical Approach to Heart Failure* and co-authored *The Stanford Manual of Cardiopulmonary Transplantation*. He serves on the editorial boards of the *Journal of Heart and Lung Transplantation*, the *Journal of Cardiac Surgery*, the *Annals of Thoracic Surgery*, and the *Japanese Journal of Thoracic and Cardiovascular Surgery*.

**DOUGLAS L. MANN, M.D.**  
**Biographical Statement**

Chief, Section of Cardiology  
Director, Winters Center for Heart Failure Research  
Baylor College of Medicine  
Don W. Chapman Chair of Cardiology  
St. Luke's Episcopal Hospital and Texas Heart Institute  
Houston, TX

Douglas Mann, M.D., serves as Chief of the Section of Cardiology, as a Professor of Medicine and a Professor of Physiology and Biophysics at the Baylor College of Medicine. He is also the Don W. Chapman Chair of Cardiology at St. Luke's Episcopal Hospital and Texas Heart Institute, the Director of the Winters Center for Heart Failure Research, and a staff physician at the Michael E. DeBakey VA Medical Center. Dr. Mann received his medical degree from the Temple University School of Medicine and is Board Certified in cardiology and internal medicine.

The focus of Dr. Mann's laboratory research has been to define the basic cellular and molecular mechanisms that are responsible for disease progression in the failing heart, and in translating novel findings obtained in the basic research laboratory into multicenter clinical trials. In addition to pursuing his research interests in the areas of cardiac cellular and molecular physiology, innate immunity and inflammation, and heart failure, Dr. Mann also holds a patent for "Novel Therapeutics for Heart Failure and Aging."

Dr. Mann is a Fellow of the American College of Cardiologists and the American College of Chest Physicians. He is an active member of multiple professional and scientific organizations and task forces, such as the National Heart, Lung, and Blood Institute's Committee on Strategic Planning on Heart Failure and Cardiomyopathy, and a program committee chair for the Heart Failure Society of America.

He has published extensively on the topics of cardiology and heart failure, and has also edited several books on these subjects. Dr. Mann has lectured extensively on immunological responses and inflammation mediators in heart failure. He served as Deputy-Editor of *Chest* and Associate Editor of *Circulation* for most of the past decade. Currently, Dr. Mann serves on the editorial boards of *Circulation*, *Heart and Vessels*, *Cardiology Today*, the *Journal of the American College of Cardiology*, *Heart Failure Reviews*, *Heart Failure Monitor*, the *Journal of Molecular and Cellular Cardiology*, the *Journal of Cardiac Failure*, and *Congestive Heart Failure*, and as an editorial consultant for over twenty additional periodicals.

Dr. Mann has received multiple awards for excellence in clinical and laboratory research, teaching, and as an editor.

**STEVEN PIANTADOSI, M.D., Ph.D.**  
**Biographical Statement**

Director of Biostatistics  
Professor of Oncology  
The Johns Hopkins University School of Medicine  
Joint Appointment in Biostatistics & Epidemiology  
The Johns Hopkins University Bloomberg School of Public Health  
Baltimore, MD

Steven Piantadosi, M.D., Ph.D., is the Director of Biostatistics and a Professor of Oncology at the Johns Hopkins University School of Medicine, and a Professor of Epidemiology at the Johns Hopkins University Bloomberg School of Public Health. As Director of Biostatistics, his primary objective is to provide the statistical design, analytical tools, and guidance necessary to ensure methodologically sound research. He received his Ph.D. in Biomathematics from the University of Alabama and his M.D. from the University of North Carolina. His specialties include mathematics, mathematical models of tumor growth, and statistical methods for the design and analysis of clinical trials.

In addition to his educational activities, he has served as principal statistician for the New Approaches to Brain Tumor Therapy Consortium since 1994, and as Principal Investigator of the Coordinating Center and Vice-Chairman for the National Emphysema Treatment Trial since 1996.

Dr. Piantadosi's current professional memberships include the Society for Clinical Trials, the American Statistical Association, the American Society of Clinical Oncology, and the American Association for Cancer Research. He has served on several FDA Advisory Committees, including the Oncologic Drugs Advisory Committee and the Neurologic Devices Advisory Committee. He currently sits on the Antiviral Drugs Advisory Committee and the CBER Vaccines and Related Biological Products Advisory Committee. He is a frequently invited lecturer on biostatistics and is a Fellow of the Foundation for Promotion of Cancer Research.

Dr. Piantadosi is the author of *Clinical Trials: A Methodologic Perspective* and more than 200 articles on clinical trial methods and analysis as well as the genesis, screening, and treatment of cancer. He has co-authored numerous book chapters on subjects including the identification of endpoints, statistical issues arising in clinical trials, and factor design in clinical trials. He has also developed clinical trial design software.

**DONALD B. RUBIN, Ph.D.**  
**Biographical Statement**

John L. Loeb Professor of Statistics  
Department of Statistics  
Harvard University  
Cambridge, MA

Donald B. Rubin, Ph.D., is the John L. Loeb Professor of Statistics at Harvard University and has been a professor at Harvard since 1984. He earned his M.S. and Ph.D. from Harvard University in Cambridge, MA. His research interests include causal inference in experiments and observational studies, inference in sample surveys with non-response and in missing data problems, application of Bayesian and empirical Bayesian techniques, and development and application of statistical models to data in a variety of scientific disciplines.

Dr. Rubin is the recipient of two of the most prestigious awards available to statisticians: the Samuel S. Wilks medal of the American Statistical Association and the Parzen Prize for Statistical Innovation. He received The Parzen Prize for Statistical Innovation for his work and innovations in statistical theory and methodology in the fields of missing data analysis (EM and related algorithms, method of multiple imputation), causal inference for observational data, design and analysis of experiments and sample surveys, Bayesian statistical computation, and use of statistical techniques to obtain interesting information in education, psychology, medicine, economics, sociology, and census data. In addition to delivering the keynote address at the 5<sup>th</sup> Annual Hawaii International Conference on Statistics, Mathematics, and Related Fields in 2006, Dr. Rubin also served as the Chair-Elect of the American Statistical Association's 2006 Section on Epidemiology.

He is a Fellow of the American Statistical Association, the Institute for Mathematical Statistics, the International Statistical Institute, the Woodrow Wilson Society, the John Simon Guggenheim Society, the New York Academy of Sciences, the American Association for the Advancement of Science, and the American Academy of Arts and Sciences.

Dr. Rubin has published more than 300 scientific articles and six books and monographs on the subjects of computational methods, causal inference in experiments and observational studies, survey methods, techniques for handling missing data, Bayesian methods, multiple imputation, matched sampling, and applications in many areas of social and biomedical science. He is among the most highly cited mathematical scientists in the world.

**HANI N. SABBAH, Ph.D.**  
**Biographical Statement**

Director, Cardiovascular Research  
Department of Medicine  
Henry Ford Health System  
Professor of Medicine  
Case Western Reserve University  
Cleveland, OH  
Professor of Medicine  
Wayne State University  
Detroit, MI

Hani Sabbah, Ph.D., is the Director of the Cardiovascular Research Laboratories at the Henry Ford Health System and is a Professor of Medicine at both Case Western University and Wayne State University. He received his Ph.D. in Biomedical Sciences and Medical Physics from Oakland University.

Dr. Sabbah specializes in heart failure treatment research, in understanding the pathophysiology of heart failure, and on the development and testing of novel therapeutic modalities. He directs laboratory research including traditional biochemistry, molecular biology, cell electrophysiology, pathology, immunohistochemistry, and organ and whole body physiology.

Dr. Sabbah is a Fellow of the American College of Cardiology, the American College of Chest Physicians, and the American Heart Association. He is a member of numerous medical societies primarily devoted to cardiologic-related studies, such as the Executive Council of the Heart Failure Society of America. He is a senior member of the Biomedical Engineering Society. Dr. Sabbah has chaired numerous scientific sessions, specifically focusing on the pathology of cardiovascular disease, and novel and experimental diagnostic and therapeutic methods.

Dr. Sabbah has published extensively and has presented abstracts at numerous national and international scientific conferences on the subject of heart failure. In addition to his position as Co-Editor-in-Chief of *Heart Failure Reviews*, Dr. Sabbah also serves on the editorial boards of the *Journal of Clinical and Basic Cardiology*, the *Journal of Heart Disease*, the *Journal of Cardiac Failure*, *The Journal of Heart Failure*, *Cardiovascular Drugs and Therapy*, and *Current Cardiology Reviews*. He is a reviewer of numerous peer-reviewed scientific journals.

Dr. Sabbah is the recipient of the 2005 American Heart Association Seymour Gordon Award for Distinguished Achievement and the 2002 Albrecht Fleckenstein Award for Distinguished Contribution in the Field of Basic Research in Cardiology from the International Academy of Cardiology.

**RANDALL C. STARLING, M.D., M.P.H.**  
**Biographical Statement**

Head, Section of Heart Failure & Cardiac Transplantation Medicine  
The Cleveland Clinic  
Medical Director, Kaufman Center for Heart Failure  
The Cleveland Clinic  
Cleveland, OH

Randall Starling, M.D., M.P.H., is the Section Head for Heart Failure & Cardiac Transplantation Medicine and the Medical Director of the Kaufman Center for Heart Failure at The Cleveland Clinic Foundation, a Staff Physician at the Clinic's Multi-Organ Transplantation Center, and a Professor of Medicine at the Clinic's Lerner College of Medicine. He has previously served as the Medical Director of the Cleveland Clinic Foundation Transplant Unit. Dr. Starling is Board Certified in cardiology and internal medicine. He received his medical degree from Temple University.

Dr. Starling has been a Principal or Co-Principal Investigator of numerous clinical trials for mechanical ventricular assistance devices and pharmacologic therapies in heart failure, including trials funded by the National Institutes of Health. Dr. Starling is also a current member of multiple institutional and steering committees. He has served as a television editorial consultant for ABC's 20/20 segment on ventricular remodeling and the NOVA (PBS) segment "Cut to the Heart," and was interviewed during CNN's "Heroes in Medicine" segment and the PBS/The Learning Channel's segment on ventricular remodeling surgery. He has particular interest in transplantation and mechanical support devices and other forms of surgical therapy for the treatment of heart failure, having published extensively in this area.

Dr. Starling is also the International Editor in Chief of the *Greek Journal of Heart Failure*, a member of the editorial boards for the American College of Cardiology Foundation Cardiosource Clinical Trials, the *Journal of the American College of Cardiology*, an invited editorial consultant for *The American Journal of Cardiology*, *The American Journal of Medicine*, the *American Journal of Transplantation*, *The Annals of Thoracic Surgery*, *Catheterization and Cardiovascular Diagnosis*, *Circulation*, *Cardiovascular Research*, and *The Journal of Heart and Lung Transplantation*.

He is a Fellow of the American College of Cardiology and a member of the Board of Directors of the International Society of Heart and Lung Transplantation. Additionally, Dr. Starling served on the Guidelines Committee of the Heart Failure Society of America, and is a member of the American Heart Association Council on Clinical Cardiology, the American Society of Transplantation, and the Heart Failure Society of America. Dr. Starling has been listed as one of the Best Doctors in America several times from 2002 to the present.

**MARTIN GRAHAM ST. JOHN SUTTON, M.B.B.S.**  
**Biographical Statement**

John W. Bryfogle Professor of Medicine,  
Director, Cardiovascular Imaging Program  
Director, Cardiovascular Fellowship Program  
University of Pennsylvania School of Medicine  
Philadelphia, PA

Martin St. John Sutton, M.B.B.S., is the Director of the Cardiovascular Imaging Program and of the Cardiovascular Fellowship Program at the Hospital of the University of Pennsylvania. He has previously served as a consultant cardiologist to the Royal Brompton National Heart & Lung Hospital in London, England; as a staff cardiologist and Director of the Non-invasive Cardiology Laboratories of Brigham & Women's Hospital at Harvard Medical School; and as a staff cardiologist and Co-Director of the Non-invasive Cardiac Laboratory at the Hospital of the University of Pennsylvania. Dr. Sutton earned his M.B.B.S at Guys Hospital Medical School, London, England, and is certified by the American Society of Echocardiography.

Dr. Sutton was recognized as one of the Best Doctors in America from 2005 to 2006. He is a member of the Royal College of Physicians, the American Federation for Clinical Research, the Association of Subspecialty Professors, and a member of over ten additional cardiology-related societies. Dr. Sutton serves as a task force member for the ACC/AHA Writing Group for Guidelines for Use of New Radionuclear Cardiology, the ASE Writing Group for Quantification of Ventricular Function, and a member of the advisory board of Medtronic for the Triple Chamber Pacing Trial. He is also an abstract reviewer for the American Society of Cardiology Annual Scientific Sessions, the American Heart Association Annual Scientific Sessions, and the American Society of Echocardiography.

Dr. Sutton serves as an editor for the *American Journal of Non-Invasive Cardiology*, the *International Journal of Cardiology*, the *European Heart Journal*, and *Heart*. He is also a reviewer for the *New England Journal of Medicine*, *Circulation*, the *Journal of the American College of Cardiology*, the *American Journal of Physiology*, the *American Journal of Cardiology*, the *Journal of the American Society of Echocardiography*, the *European Heart Journal*, *Heart*, the *International Journal of Cardiology*, *Annals of Internal Medicine*, the *Journal of Thoracic and Cardiovascular Surgery*, and *Pediatric Research*.

Dr. Sutton has published extensively in his area of expertise, including articles in peer-reviewed journals, over sixty editorials, reviews, and book chapters, and twelve books, which focus on his research in left ventricular function and remodeling, echocardiography, non-invasive cardiac imaging, and adult congenital heart disease.

**JAMES B. YOUNG, M.D.**  
**Biographical Statement**

Chairman, Division of Medicine  
Cleveland Clinic  
Professor, Department of Medicine  
Lerner College of Medicine of Case Western Reserve University  
Cleveland, OH

James Young, M.D., is the Chairman of the Division of Medicine at the Cleveland Clinic Foundation; a Professor of Medicine and Academic Chairman of the Department of Medicine of the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University; and has a joint appointment at the Multi-Organ Transplant Center. He has previously served as Medical Director of the Kaufman Center for Heart Failure, Head of the Section of Heart Failure and Cardiac Transplant Medicine, and as Vice Chairman of the Department of Cardiovascular Medicine. Dr. Young has recently been named the Study Chairman of the NIH, FDA, and CMS Interagency Mechanical Circulatory Device Support Registry (INTERACS). Dr. Young completed his medical degree, internship, residency, and fellowship at the Baylor College of Medicine and its affiliated hospitals, and is certified as a Diplomat of the American Board of Internal Medicine as well as in the subspecialty of Cardiovascular Disease.

He serves on the editorial boards of the *Journal of Evidence Based Cardiovascular Medicine*, the *Journal of the American College of Cardiology*, the *American Heart Journal*, and *Cardiology Today*, and *Graft: Journal of Organ and Cell Transplantation*. Dr. Young also serves as an associate editor of the *Journal of Heart and Lung Transplantation*, *The Heart.org*, the *Transplantation and Immunology Letter*, the *United Network of Organ Sharing Transplantliving.org* and the *Cleveland Clinic Journal of Medicine*. He is a member of numerous societies, including the American College of Cardiology Foundation, the American College of Chest Physicians, the American Federation for Clinical Research, the American Medical Association, the American Society of Transplantation, the Heart Failure Society of America, the Heart Rhythm Society, and the International Society for Heart and Lung Transplantation. He is also a founding member of the Cardiac Transplant Research Database.

Dr. Young has served as the Principal Investigator or Co-Principal Investigator for many major, multi-center clinical trials and has published extensively on the molecular biology of cardiac remodeling, allograft arteriopathy, and transplanted heart rejection.