APPENDIX B

STUDY PROTOCOL
REVISION 8
INVESTIGATIONAL PLAN FOR
CLINICAL EVALUATION OF
ACORN CARDIAC SUPPORT DEVICE THERAPY
In Patients with Dilated Cardiomyopathy

A Randomized Trial in the United States and Canada

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Table of Contents for Investigational Plan

1.0 INTRODUCTION
   1.1 Device Name
   1.2 Device Description
   1.3 Intended Use of the Device
   1.4 Rationale

2.0 STUDY DESIGN OVERVIEW

3.0 PURPOSE AND PRIMARY OBJECTIVES
   3.1 Purpose
   3.2 Study Hypothesis
   3.3 Study Treatment Modality
   3.4 Objectives

4.0 STUDY ENDPOINTS
   4.1 Primary Efficacy Endpoint
   4.2 Safety Endpoints
   4.3 Secondary Efficacy

5.0 PATIENT POPULATION
   5.1 Selection Criteria
      5.1.1 Inclusion Criteria
      5.1.2 Exclusion Criteria
   5.2 Sample Size and Statistical Considerations
   5.3 Method of Enrollment

6.0 INVESTIGATIVE CENTER SELECTION
   6.1 Number of Investigative Centers
   6.2 Investigative Center Selection Criteria

7.0 INFORMED CONSENT

8.0 STUDY PROCEDURES
   8.1 Summary of Study Procedures
   8.2 Pre-Enrollment Procedures
   8.3 Randomization Procedure
   8.4 Surgery and Device Implant Procedures
   8.5 Follow-up Procedures
   8.6 Study Termination

9.0 ADVERSE EVENTS
   9.1 Reporting Criteria
   9.2 Anticipated Adverse Events
   9.3 Unanticipated Adverse Events
   9.4 Unanticipated Adverse Device Effects

10.0 INDEPENDENT REVIEW COMMITTEES
    10.1 Clinical Events Review Committee (CERC)
    10.2 Data and Safety Monitoring Board (DSMB)
11.0 STUDY DURATION
   11.1 Interim Monitoring

12.0 RISK ANALYSIS

13.0 PROTOCOL MODIFICATIONS AND DEVIATIONS

14.0 STUDY MATERIALS
   14.1 Investigational Product Supplies
   14.2 Investigational Product Storage
   14.3 Investigational Product Accountability

15.0 MONITORING PROCEDURES

ATTACHMENT A: SAMPLE SIZE DETERMINATION
ATTACHMENT B: DATA ANALYSIS PLAN
ATTACHMENT C: PATIENT INFORMED CONSENT
ATTACHMENT D: INVESTIGATOR AGREEMENT
INVESTIGATIONAL PLAN

1.0 INTRODUCTION

1.1 Device Name

The Acorn Cardiac Support Device (CSD) is being used for this study.

1.2 Device Description

The Acorn Cardiac Support Device is a fundamentally new therapy for the treatment of heart failure that is designed to mitigate left ventricular dilation, which is one of the most important pathophysiological mechanisms underlying the clinical syndrome of heart failure. This single-use permanent implant is a biocompatible, mesh-like support that is placed around the heart and adjusted to conform to the heart, supporting the heart without acutely changing hemodynamics. It is constructed using a proprietary knitted polyester fabric designed to optimize circumferential support.

Six device sizes are available to accommodate various patient heart sizes. Sizing is determined by the surgeon based on preoperative estimates and intraoperative confirmation of patient heart size. The device is manufactured by Acorn Cardiovascular, Inc. and will be provided to the investigational sites sterile and individually packaged.

1.3 Intended Use of the Device

The Acorn Cardiac Support Device is intended to support the heart, in order to prevent further dilation that is associated with progressive heart failure, resulting in preserved or improved patient functional status.

1.4 Rationale

The syndrome of chronic (or congestive) heart failure is a growing and costly health problem worldwide. Cardiac medications provide important benefit, but do not uniformly prevent patients' eventual decline. Cardiac transplant has become the accepted method of treating patients who are in severe heart failure. However, the quantity of donor hearts available has limited the number of patients currently being treated. Consequently, the medical research community is seeking increasingly beneficial and cost-effective treatments.

The development of heart failure treatments has paralleled the evolution in heart failure theories. For example, contractile dysfunction was formerly thought to be the major source of heart failure, leading to an emphasis on inotropic therapy. More recently, it has been recognized that heart failure is a complex syndrome that can be initiated by a variety of insults. However, all these insults lead to a long term, progressive remodeling of the heart heralded by continually increasing, deleterious dilation. In the absence of effective means to control or prevent remodeling, continuation of cardiac dilation ultimately results in expression of clinical heart failure. As Jay Cohn, MD, states in an editorial entitled "Structural Basis for Heart Failure"
(Circulation 1995;91:2504-2507), “remodeling, not contractile dysfunction, is the key to the severity” of heart failure.

Since there appears to be a strong causal relationship between cardiac chamber remodeling and heart failure, mitigation or prevention of the deleterious dilation process should serve as an important therapeutic endpoint. Not surprisingly, therapies aimed at preventing, attenuating, or reversing the cardiac remodeling process have become a primary focus of current medical research. Examples of this include cardiac medications (e.g., ACE inhibitors and beta-blockers) as well as surgical therapies (e.g., ventricular reduction and cardiomyoplasty).

Of particular relevance for the therapeutic application of the Acorn Cardiac Support Device is the substantial body of research conducted on cardiomyoplasty, notably as it relates to mechanisms of action. Cardiomyoplasty is a surgical treatment for patients with dilated heart failure in which the sheet-like latissimus dorsi muscle is mobilized while maintaining its vascular supply, internalized into the mediastinum, wrapped around the heart, and stimulated in synchrony with cardiac contractions.

Early researchers postulated that the cardiomyoplasty therapy benefit was derived primarily from the systolic augmentation of the stimulated latissimus dorsi muscle that was timed to be in synchrony with native cardiac contraction. Later, researchers noted that the primary benefits of cardiomyoplasty occurred whether or not latissimus dorsi contractions were evident, a viewpoint summarized by Kass et al. (Reverse Remodeling From Cardiomyoplasty in Human Heart Failure, Circulation. 1995;91:2314-2318). The authors concluded, "While systolic squeezing assist effects of cardiomyoplasty may play a role in some patients, our study found that this was not required to achieve substantial benefits from the procedure. We speculate that cardiomyoplasty may act more passively, like an elastic girdle around the heart, to help reverse chamber remodeling."

The benefits ascribed to cardiomyoplasty come at a price. Whether electrical stimulation is employed following cardiomyoplasty or not, a significant surgical intervention is required to position the latissimus dorsi muscle adjacent to the heart. In addition, a definite period of time is required for healing and remodeling of the latissimus dorsi muscle in its transposed environment. Also, in the case of dynamic cardiomyoplasty, a dedicated implanted myostimulator is required to provide electrical stimulation, and time is required to properly train the skeletal muscle as an assist to cardiac function.

Because of these perceived shortcomings with cardiomyoplasty, investigators have given consideration to substitution of the latissimus dorsi muscle with a synthetic element. Kass et al. (ibid) stated, “Whether skeletal muscle itself is required or whether an artificial elastic ‘sock’ placed around the heart could achieve similar effects remains an intriguing question”. This question has been addressed through recent published reports, in which cardiac binding with a synthetic polymer wrap showed value in restricting deleterious dilation of the heart. The result was improvement in cardiac function compared to controls lacking the synthetic wrap.
The Acorn Cardiac Support Device is a permanent implant designed to provide a non-active support around the heart. It is intended to treat heart failure by controlling deleterious cardiac dilation. The device has been successful in preventing the continual dilation of the left ventricle in two heart failure animal models. Initial human clinical implants have been performed safely. Additional clinical study is warranted to evaluate the safety and efficacy of this new therapy.

2.0 STUDY DESIGN OVERVIEW

This is a prospective, randomized, unblinded, parallel group evaluation of Acorn Cardiac Support Device therapy in patients with dilated cardiomyopathy of either ischemic or non-ischemic origin, who may or may not need mitral valve repair/replacement (MVR). The study is intended to assess the safety and efficacy of the Acorn Cardiac Support Device. Approximately 300 patients (150 treatment and 150 control) will be enrolled in up to 30 US and Canadian centers.

Pre-enrollment baseline patient evaluation will include clinical assessment, blinded central assessment of New York Heart Association (NYHA) functional class, blood tests, chest x-ray, echocardiography, electrocardiogram, cardiopulmonary exercise testing, submaximal exercise testing, and quality of life assessments. After patient informed consent and verification of eligibility, patients who meet the selection criteria will be randomized. Patients assigned to the treatment group will undergo an Acorn device implant. Selection of the device size will be determined by intraoperative measurements at the time of surgery. Acute response to device implant will be monitored intraoperatively via continuous cardiac monitoring, arterial pressure lines, transesophageal echocardiography (TEE), and Swan Ganz catheter.

Follow-up in this study is divided into two distinct phases. During the first phase, henceforth referred to as the “efficacy phase”, repeat testing of patient functional and cardiac structural parameters will be conducted at follow-up visits scheduled at 3 months, 6 months, 12 months, and every 6 months thereafter. Follow-up testing will be supplemented by regular telephone monitoring.

The efficacy phase of the trial will end on a common closing date after a minimum of 12 months of follow-up (i.e., after the last patient enrolled has been followed approximately 12 months). At that point data analysis will be performed and a study report will be generated. Following completion of the efficacy phase, long-term monitoring will continue through each patient’s 5-year visit. This second phase is referred to as the “extended follow-up phase”. During this phase, data collection will be focused on long-term safety and will be conducted at 6-month intervals. Pre-enrollment and follow-up testing is summarized in Table 1, Section 8.

An initial phase of the study was conducted to test the protocol and confirm the short-term safety of the procedure. Patients enrolled during this initial phase continue in follow-up. Their data provide the longest follow-up experience in the trial and will contribute to all efficacy and safety analyses.
The following diagram summarizes the overall design of the randomized trial:

**Figure 1**

All Patients Meeting Enrollment Criteria Including Signed Consent  
*n = 300*

Need MVR?  
**NO**  
*Randomize 1:1*  
Treatment  
Implant

Control

**YES**  
*Randomize 1:1*  
Treatment  
Implant + MVR Surgery

Control  
MVR Surgery

3-Month Follow-up

6-month Follow-up

12-month Follow-up

Follow-up every 6 months until last enrolled patient is followed 12 months  
**Efficacy phase**  
Major efficacy and safety analyses; study report generated

Continued annual follow-up through 5 years  
**Extended follow-up phase**  
Evaluation of long-term safety
3.0 PURPOSE AND PRIMARY OBJECTIVES

3.1 Purpose

The purpose of this study is to evaluate the efficacy and safety of Acorn CSD therapy. This will be accomplished with a randomized, non-blinded, multicenter trial in which patients are randomly allocated to Acorn Cardiac Support Device therapy (CSD implant) plus standard medical therapy (with or without MVR) or to a control group that receives medical therapy (with or without MVR) alone (no CSD implant).

3.2 Study Hypothesis

Acorn Cardiac Support Device therapy will improve patient functional status as measured by a clinical composite consisting of mortality, major cardiac procedures and NYHA class.

3.3 Study Treatment Modality

All patients who qualify for enrollment will be randomized to control (i.e., continued heart failure therapy with optimized standard medical management, and where indicated, MVR), or to treatment (i.e., implant of the Acorn CSD plus continued heart failure therapy with optimized standard medical management and, where indicated, MVR). Thus, it is anticipated that there will be two major subgroups of patients who enter the trial: patients undergoing MVR, and patients without need for MVR.

3.4 Objectives

Primary Objective

- To compare patient functional status after a minimum of 12 months of follow-up for patients randomly assigned to treatment (CSD implant) or control (no CSD implant).

Secondary Objectives

- To determine the rate of death and other serious adverse events experienced by patients assigned to the CSD implant and to compare this rate with that for patients assigned to the control group.
- To compare patient functional status and structural changes in the heart for the treatment and the control groups.

4.0 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint
The primary endpoint for the efficacy phase is a composite ordinal endpoint based on death, major cardiac procedures indicative of progression of heart failure, and blinded assessment of change in New York Heart Association (NYHA) classification of functional class. Major cardiac procedures include the following: heart transplantation, implantation of a cardiac assist or replacement device, coronary artery bypass surgery (CABG), implant of a biventricular pacing device, and subsequent (after the baseline surgery, if applicable) mitral or tricuspid valve repair/replacement surgery (TVR). CABG, MVR, TVR, and implantation of biventricular pacing devices will be counted toward this endpoint only if associated with progression of heart failure, as determined through review by a committee blinded to treatment group.

At the end of the efficacy phase of the study, patients assigned to the treatment group will be compared to patients assigned to the control group for assessment of their functional status as categorized below:

- **Worsened** – patient has died, has experienced a major cardiac procedure, or is classified as at least one category worse on blinded NYHA, 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

### 4.2 Safety Endpoints

The rate of death and serious adverse events overall, and for each specific type of event, will be determined for the two phases of the study: through the common closing date for the efficacy phase, and through the completion of the extended follow-up phase. The following specific adverse events will be considered:

- Allergic response to anesthesia or medications
- Arrhythmia
- Bleeding
- Hemodynamic compromise
- Hepatic compromise
- Infection/pneumonia
- Myocardial infarction
- Neurologic deficit/stroke
- Peripheral thrombus/embolism
- Pulmonary compromise
- Pulmonary embolism
- Renal compromise
- Any unanticipated serious adverse event
In addition to the specific adverse events itemized above, death from any cause, pericardial surgery and a composite endpoint of death, major cardiac procedure, arrhythmia, hemodynamic compromise and myocardial infarction will be evaluated as safety outcomes.

4.3 Secondary Efficacy Endpoints

The following secondary endpoints will be assessed during the efficacy phase of the trial:

- Number of hospitalizations, hospital days and ICU days, for cardiac reasons and overall

- Change in NYHA functional class from baseline to 6 and 12 months as determined by the site clinician and the blinded central assessment clinician.

- Change in exercise status from baseline to 6 and 12 months as measured by 6-minute walk distance

- Change in quality of life from baseline to 6 and 12 months as determined from the Minnesota Living with Heart Failure (MLWHF) and SF-36 questionnaires

- Change in left ventricular end diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD), left ventricular (LV) ejection fraction, LV volumes, mitral regurgitation, sphericity, pulmonary artery pressure, and diastolic function after 6 months and 12 months as measured via echocardiography

- Change in peak oxygen consumption, anaerobic threshold, and exercise time after 6 and 12 months as measured on the cardiopulmonary exercise test (CPX)

- Change in B-type natriuretic peptide (BNP) content in blood plasma from baseline to 6 and 12 months

- All-cause mortality or re-hospitalization

- Incidence of Major Cardiac Procedures
5.0 PATIENT POPULATION

5.1 Selection Criteria

Patients considered for enrollment will meet all of the inclusion criteria in section 5.1.1 below. However, if they meet any of the exclusion criteria in section 5.1.2, they will not be eligible for enrollment.

In general, patients must have left ventricular systolic dysfunction, clinical heart failure and left ventricular dilation. They need to be clinically stable, with cardiac medications considered optimized, and without recent (<1 month) adjustments of cardiac medications other than diuretic therapy. Their surgical risk must be considered reasonable, and they must not have a life expectancy limited to <1 year due to a co-morbid condition.

5.1.1 Inclusion Criteria

Patients must meet all of the following:

♦ Dilated cardiomyopathy of either ischemic or non-ischemic origin.
♦ Stable and optimal medical management including all of the following:
  ➢ Angiotensin-converting enzyme inhibitors (ACE) or alternate if ACE not tolerated.
  ➢ Diuretic at least “prn” (as occasion requires).
  ➢ Treatment with a beta-blocker (unless intolerant) for ≥ 3 months (not required for patients with a mitral valve anomaly that is not likely to respond to medications and requires surgical intervention).
  ➢ Cardiac medications unchanged for ≥ 1 month except for diuretic adjustments (not required for patients with a mitral valve anomaly that is not likely to respond to medications and requires surgical intervention).
♦ Adult (18-80 years).
♦ Left ventricular end diastolic dimension (LVEDD) ≥ 60 mm or LVEDD index ≥ 30 mm/m² as determined by transthoracic echocardiography.
♦ Mitral regurgitation (MR) ≤ 2+ unless scheduled for MVR.
♦ Signed Informed Consent
♦ Left ventricular ejection fraction (LVEF) ≤ 35% via transthoracic echocardiography, cardiac catheterization, radionuclide scan, or magnetic resonance imaging, or LVEF ≤ 45% and planned MVR.
♦ New York Heart Association Functional Class (NYHA) III or IV, or NYHA II if scheduled for MVR.
♦ Baseline 6-minute walk distance < 450 meters (1476 feet).
♦ Acceptable hepatic function with serum glutamic oxalo-acetic transaminase (SGOT or AST) and serum glutamic pyruvic transaminase (SGPT or ALT) < 3x upper limit of normal.

♦ Acceptable pulmonary function as assessed clinically unless there is history of compromise or current evidence of compromise, in which case forced expiratory volume in the first second (FEV1) must be > 50% of predicted normal value.

♦ Geographically available for follow-up

### 5.1.2 Exclusion Criteria

Patients will be excluded should they meet any of the following:

♦ Planned cardiac surgical procedure other than MVR with or without tricuspid valve repair or atrial fibrillation ablation procedure.

♦ Hypertrophic obstructive cardiomyopathy.

♦ Significant cardiomegaly, which is estimated to exceed the largest available size of Cardiac Support Device

♦ Expectation of existing cardiothoracic adhesions that would cause an inability to gain complete circumferential access to the heart.

♦ Any condition considered a contraindication for extracorporeal circulation.

♦ Late-stage heart failure with increased surgical risk as defined by the presence of four or more of the following:
  - LVEDD ≥ 80 mm
  - Peak VO$_2$ ≤ 13 ml/kg/min (cardiopulmonary exercise test)
  - Resting systolic BP ≤ 80 mmHg (on clinical exam)
  - Atrial fibrillation at time of enrollment or paced rhythm with underlying atrial fibrillation
  - Heart failure duration ≥ 8 years
  - Exercise-induced increase in systolic BP ≤ 10% (cardiopulmonary exercise test)
  - 6 minute walk ≤ 350 meters (1148 feet)
  - Previous cardiac surgery
  - BUN ≥ 100 mg/dl
  - Cachexia (clinical impression)

♦ Existing patent CABG.

♦ Candidates for surgical revascularization as determined by an angiogram. Patients with ischemic heart disease who have not had an angiogram within the past 3 years and in whom lesions amenable to revascularization cannot be excluded should have a repeat angiogram.

♦ Receiving an IABP, intravenous inotropic or vasoactive agents, except for immediate pre-operative hemodynamic optimization.
Current or anticipated need for left ventricular assist device (LVAD) or cardiac replacement device.

On active cardiac transplant list or anticipated need for heart transplant within the next two years.

Acute myocardial infarction, unstable angina, or cerebral vascular accident (TIA or CVA) within past 3 months.

Percutaneous coronary intervention or transmyocardial laser revascularization (TMR or PMR) within the past 3 months.

Presence of arrhythmias causing hemodynamic instability, history of resuscitated sudden death without subsequent treatment with implantable defibrillator or amiodarone, or atrial fibrillation with a ventricular rate > 100 bpm on medication.

Co-morbid condition that reduces life expectancy to less than 1 year.

Serum creatinine $\geq$ 3.5 mg/dl or dialysis dependent.

Biventricular (BiV) pacing initiated within the past 3 months or anticipated within the next 12 months.

Active infection.

Pregnancy at the time of enrollment. (Women of child bearing potential must have a negative serum pregnancy test within two weeks prior to randomization, or must be using hormonal contraceptives or intrauterine devices.)

Enrolled in another investigational study that would confound interpretation of trial results, or receiving experimental or investigational drugs.

Unable to comply with protocol-required follow-up (as judged by primary investigator or referring cardiologist).

5.2 Sample Size and Statistical Considerations

Approximately 300 patients (150 treatment and 150 control) will be enrolled. Assumptions used in sample size calculations are provided in Attachment A.

5.3 Method of Enrollment

Patients who have signed an informed consent and are found to meet the inclusion and exclusion criteria will be randomized. Centers are encouraged to complete all required testing and confirm eligibility at least 2-3 days prior to randomization. Baseline eligibility testing should only be conducted after the patient has been stabilized on optimal medical therapy. Randomization will be stratified by those needing MVR and those not needing MVR. Randomization will also be stratified by center. A randomization schedule for each stratum will be generated using random permuted blocks. Patients are considered enrolled in the study when they receive their randomization assignment.
6.0 INVESTIGATIVE CENTER SELECTION

6.1 Number of Investigative Centers

Up to 30 centers in the US and Canada will be included in this study.

6.2 Investigative Center Selection Criteria

All investigative centers will meet the following selection criteria prior to inclusion in this study:

- Center experience (team of cardiac surgeons, cardiologists, anesthesiologists, and ICU staff) that demonstrates established record of low morbidity/mortality and good outcomes after performing cardiac surgery in patients with dilated hearts and low LVEF.

- Clinical research study experience and resources that demonstrate good compliance with study requirements and timely, complete documentation of patient follow-up. Investigational teams must designate a study coordinator to manage the study.

- Willingness to sign Investigator Agreement (Attachment D) and undergo center training.

- Access to the necessary equipment and supplies that are needed to gather the data at baseline, implant, and follow-up evaluations.

- Collaborative team of cardiac surgeon and heart failure cardiologist willing to serve as co-primary investigators.

- Sufficient patient volume to expect enrollment of at least 1 patient per month.

- Willingness to delay presentation or publication of treatment versus control patient efficacy outcomes until agreed to by all contributing centers, and to acknowledge all contributing centers in any subsequent presentations or publications reporting pooled randomized trial data.

- Personnel from Acorn Cardiovascular (or its designee) must have access to the hospital records, investigator’s study records, data, and patient files as they pertain to the study.

Prior to enrolling patients into this study, each center’s primary investigators will sign the Investigator Agreement (Attachment D), or a modification approved by Acorn Cardiovascular, Inc. Prior to his/her initial Acorn CSD implant, each cardiac surgeon will receive surgical training.
7.0 INFORMED CONSENT

Prior to undergoing study-required testing and enrollment, the study will be explained to the patient by the investigator or a trained clinical professional, and an informed consent form will be provided in the patient’s native language. If necessary, a professional interpreter will be utilized to translate the informed consent form, to ensure that communication is complete. The informed consent form must be approved by the institution’s Institutional Review Board (IRB) or ethics committee, and by Acorn Cardiovascular, Inc. All patients will sign an informed consent form prior to undergoing testing for the purpose of determining eligibility for the trial. Tests done for medical purposes and within the window for pre-enrollment testing, but prior to signing an informed consent, will be accepted as baseline study testing provided they meet protocol requirements. A sample of an acceptable informed consent form can be found in Attachment C.

In recognition of the valuable information that can be obtained from an autopsy in the event of a patient’s death following an Acorn device implant, prospective consent for autopsy may be requested, but is not required. An Informed Consent document for autopsy is also included in Attachment C. A copy of the signed Informed Consent document for autopsy should be sent to the patient’s primary physician.

8.0 STUDY PROCEDURES

8.1 Summary of Study Procedures

Pre-enrollment baseline patient testing will include clinical assessment, blinded central evaluation of NYHA functional class, blood tests, chest x-ray, transthoracic echocardiography (TTE), electrocardiogram (ECG), cardiopulmonary exercise testing (CPX), submaximal exercise testing via the six-minute walk, and two quality of life questionnaires. Pre-enrollment testing should only be conducted after the patient has been stabilized on optimal medical therapy. Pre-enrollment data needed to determine eligibility for the trial will be submitted to Acorn Cardiovascular, Inc, for confirmation of eligibility and for randomization. Patients assigned to the treatment group will then undergo Acorn CSD implant. Selection of the device size will be determined by intraoperative measurements performed at the time of surgery. Acute response to device implant will be monitored intraoperatively via continuous cardiac monitoring, arterial pressure lines, transesophageal echocardiography, and Swan Ganz catheter.

Pre-enrollment and follow-up testing is summarized in Table 1. Testing will be supplemented by regular telephone monitoring. Specific instructions for completing the protocol required testing are found in the Operations Manual.

The primary investigators at each study site are responsible for consistency and quality of all data submitted to the Sponsor.
Table 1
Pre-Enrollment and Follow-up Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-enrollment</th>
<th>3 Mo. (61 mo)</th>
<th>6 Mo. (61 mo)</th>
<th>12 Mo. &amp; every 6 Mo. (±3 mo.)</th>
<th>Extended Follow-up Phase: Annually through the 5 year visit (±3 mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Central Blinded NYHA Assessment</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest X-ray (within past 3 mo.)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood Tests</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BNP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Echocardiography (transthoracic)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECG (within past 3 mo.)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>Stop after 12 months</td>
</tr>
<tr>
<td>Cardiopulmonary Exercise (within past 3 mo.)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>Stop after 12 months</td>
</tr>
<tr>
<td>Six Minute Walk</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MLWHF and SF-36 Questionnaires</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Right and/or Left Heart Catheterization</td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

♦ Information regarding vital status and adverse events are reported as they occur during both phases of the trial.
♦ Pre-enrollment testing is required within one month of enrollment except where noted on the table above and should be completed after the patient has been stabilized on optimal medical therapy.
♦ Follow-up testing will be supplemented by regularly scheduled telephone assessment performed according to the following schedule:
  ♦ Every 2 weeks through week 10
  ♦ Monthly between months 4 and 12
  ♦ Quarterly after month 12 (every 3 months)
  ♦ Follow-up telephone assessments every 6 months during the extended follow-up phase
  Telephone assessment is not required during intervals in which the patient is seen for a follow-up visit.

*As required for patients with ischemic heart disease.
8.2 Pre-Enrollment Procedures

The patient will undergo the following assessments to confirm eligibility and provide baseline measurements for post-enrollment comparisons. Clinical assessment, blinded central assessment of NYHA functional class, blood tests, two quality of life questionnaires, six-minute walk and echocardiography must be performed within 1 month prior to enrollment, but after the patient has been stabilized on optimal medical therapy. Chest X-ray, cardiopulmonary exercise testing, if performed, and ECG must be performed within 3 months prior to enrollment, but after the patient has been stabilized on optimal medical therapy.

Clinical Assessment to document clinical status and NYHA functional classification, cardiovascular history, hospitalization information, medications, and overall medical history. The NYHA classification determined at the clinical site pre-enrollment will be used to determine eligibility for the trial.

Central Blinded Assessment of New York Heart Association Functional Class (Blinded NYHA): In addition to the clinical site’s assessment of NYHA class, determination of NYHA class will be made by a cardiologist blinded to randomization assignment. This assessment will be conducted centrally, and will be based on review of a questionnaire that is administered to the patient by a site clinician who is also blinded to the treatment assignment. (Since this assessment was introduced into the protocol after initiation, at least 120 patients will not have this assessment at baseline.)

Blood Tests serum chemistry (at least sodium, potassium, creatinine, blood urea nitrogen, serum glutamic oxalo-acetic transaminase [SGOT or AST], and serum glutamic pyruvic transaminase [SGPT or ALT]), hematology values (at least hemoglobin and white blood cell count), and B-type natriuretic peptide (BNP). A serum pregnancy test is required of women of child bearing potential, if they are not using hormonal contraceptives or an intrauterine device.

Posterior-Anterior and Lateral Chest X-Ray (CXR) to monitor for signs of pulmonary congestion.

Transthoracic Echocardiography / Doppler Ultrasound (TTE) to quantitatively determine heart size, LVEF, and valve function; to assess diastolic function, wall motion, and wall thickness. Note: Transesophageal echocardiography (TEE) is used intraoperatively to monitor device fit.

12-Lead Electrocardiogram (ECG) to assess heart rate, cardiac rhythm, conduction defects, and potential cardiac ischemia.

Cardiopulmonary Exercise Test (CPX) to quantitatively determine maximal exercise tolerance and monitor for stress-induced cardiac ischemia. Note: patients will be accepted for enrollment without a cardiopulmonary exercise test if the principal investigator provides a written rationale and all other inclusion and exclusion criteria are satisfied. Specifically, the patient may be exempted from this requirement if exercise results in potentially life threatening or serious sequelae (e.g. exercise...
induced arrhythmias), the patient is unable to tolerate the exercise equipment (e.g. mouthpiece), the patient is physically unable to walk on the treadmill or pedal a bicycle due to a physical handicap (e.g. amputation or arthritis), the exercise equipment is unable to accommodate the patient (e.g. morbid obesity) or the patient experiences severe PVD with claudication. In these cases, 2 of the 10 relative risk factors listed under the “late-stage heart failure” exclusion criterion will not apply, so patients will be excluded from the study if they have 3 or more of the remaining 8 relative risk factors.

Submaximal Exercise Test (Six-Minute Walk) to quantitatively assess sub-maximal exercise tolerance over a given period of time.

Minnesota Living with Heart Failure (MLWHF) and SF-36 questionnaires to document patient perceptions of health impact on life style.

Right and/or Left Heart Catheterization are done in patients with ischemic heart disease who have not had an angiogram within the past 3 years and in whom lesions amenable to revascularization cannot be excluded. Cardiac catheterization must be completed prior to enrollment.

Note: One of the key features of this study design calls for patients to be receiving maximal medical therapy at the time they are enrolled into the study. Heart failure medications, especially ACE inhibitors and beta blockers, will be titrated to the patient’s individual tolerance prior to enrollment. Principal investigators should consider that dosages at the time of enrollment will remain unchanged during the efficacy phase of the trial. Baseline testing and enrollment should be delayed in patients who are on submaximal therapy and in whom medication changes or bi-ventricular (BiV) pacing is being considered.

BiV Pacing requires special comment since this therapy was approved for patients with heart failure after the first version of the protocol was completed and the study was initiated. As listed in the inclusion/exclusion table, BiV Pacing is permitted pre-randomization. However, patients must have the implant performed at least 3 months prior to enrollment and must still meet all the other inclusion/exclusion criteria. Thus, it is anticipated that patients who have BiV Pacing prior to enrollment will still have disabling, refractory, or progressive symptoms of NYHA class III/early class IV heart failure and therefore be in need of additional therapeutic interventions. Additionally, investigators are strongly encouraged to consider the merits of BiV Pacing in potential patients prior to enrollment into the Acorn trial. If it is anticipated that a patient might be a prime candidate for BiV Pacing within the next 12 months, the investigator should consider delaying enrollment into the Acorn trial until the situation is clarified. In some cases, the preferred sequence is to delay enrollment, implant the BiV Pacer and consider the Acorn trial only if there are disabling, refractory or progressive symptoms after 3 months of pacing.
8.3 Randomization Procedure

The randomized assignment of a patient to either treatment or control group will be made after the study sponsor (Acorn Cardiovascular, Inc) reviews eligibility data. Once Acorn has determined that the patient meets all selection criteria, the patient will be randomized and the randomization assignment will be transmitted to the center. Randomization will be done separately for two strata: patients not requiring MVR, and those requiring MVR. Randomization will also be stratified by center. Once the patient is randomized, he/she is considered enrolled in the trial.

8.4 Surgery and Device Implant Procedures

For control patients requiring MVR, and for all treatment patients, the investigator will make every attempt to minimize the time between randomization and surgery. The surgical procedure for treatment patients includes implantation of the Acorn CSD with or without mitral valve surgery. During surgery but prior to device implant, the surgeon will monitor cardiac geometry, function, and hemodynamic measurements to provide a baseline for acute post-implant comparisons. Standard intraoperative monitoring tools will be utilized including continuous cardiac monitoring, arterial pressure lines, transesophageal echocardiography, and Swan Ganz catheter. Hemodynamic, electrocardiographic, and transesophageal echocardiographic measurements will be recorded on patient case report forms.

The surgeon will place and secure the Acorn Cardiac Support Device onto the heart as described in the Recommended Implant Procedure in the Operations Manual. Every attempt will be made to follow the recommended implant procedure to minimize variance that could potentially impact patient outcomes. Acorn representatives will regularly attend implants to assure compliance with the recommended implant procedure.

8.5 Follow-up Procedures

For purposes of scheduling follow-up visits and measuring changes over time, time zero for patients undergoing surgery (either CSD implant or MVR) is the date of surgery. For patients not undergoing surgery, time zero is the date of enrollment (randomization). Both treatment and control patients will undergo testing at 3 months, 6 months, 12 months and every 6 months throughout the efficacy phase of the trial.

All protocol-required testing is summarized in Table 1 at the end of section 8.1. Follow-up visits during the first 6 months must occur within a time window of ±1 month. Follow-up visits at 12 months and thereafter must occur within a time window of ±3 months. In addition, follow-up will be performed via telephone every 2 weeks for the first 3 months of follow-up; monthly between months 4 and 12; and quarterly (every three months) thereafter through the remainder of the efficacy phase of the trial. Telephone calls are only required during the intervals in which the patient is not seen for a follow-up visit.
Each follow-up visit must include evaluation of clinical status and NYHA functional class, review of medications and hospitalizations, and documentation of all relevant medical events. Clinical status evaluations must include assessment of weight and symptoms of heart failure. Specific guidance on monitoring for potential cardiac constrictive physiology is provided in Monitoring for Constrictive Physiology procedure in the Operations Manual.

Documentation of initial cardiac surgery and related hospitalization, adverse events, repeat surgeries and follow-up visits will be reported on the case report forms.

**Note:** It is important for both the patient and the primary care physician to understand that changes in cardiac medications post-enrollment and initiation of BiV Pacing are strongly discouraged and should be under the control of the investigative center. BiV pacing will be permitted post-enrollment for patients who have progressive, refractory or disabling symptoms of heart failure. It is extremely important to note that the implantation of BiV Pacing for progressive, refractory or disabling symptoms is considered a “major cardiac intervention” in determining the primary outcome for patients. However, it is possible that the clinical threshold for initiating BiV Pacing will be lower than the threshold for other major cardiac interventions. For this reason, the principal investigator will be required to provide a short synopsis of the patient’s relevant background and clinical course, as well as all of the objective laboratory data that document the clear need and expected benefit from BiV Pacing. Data regarding whether or not a patient has deteriorated (i.e., was experiencing refractory or disabling heart failure) will be adjudicated by the Clinical Events Review Committee (CERC). It is understood that BiV Pacing is not normally done under “emergency” situations and that there will be sufficient time to carefully consider this option for patients. Principal investigators will be encouraged to be especially firm when discussing BiV pacing with referral physicians.

_Intravenous inotropic use post-enrollment is restricted to situations where the patient is experiencing occasional exacerbations of worsening heart failure associated with cardiac decompensation refractory to more conservative therapies._

In cases where patients experience major cardiac procedures during the efficacy phase of the trial, the following follow-up requirements will apply:

- Cardiac transplantation, or implantation of ventricular assist or cardiac replacement device: Structural measurements cease at the point of cardiac transplantation or device implant. Other follow-up procedures will continue as long as the patient is willing and able to complete them.

- Other cardiac surgery (e.g., CABG, BiV pacing implant): All follow-up procedures will continue as long as the patient is willing and able to complete them.

At a minimum, any patient undergoing cardiac surgery should be followed for deaths, hospitalizations, and adverse events for the duration of the study.
In the event of a patient’s death, the investigator will request family permission for an autopsy.

Following completion of the efficacy phase, long-term safety monitoring will continue through the extended follow-up phase. During this phase, vital status, and adverse events will be collected through the patient’s 5-year visit. Continued monitoring will also include annual assessment of NYHA functional class and annual echocardiography. Follow-up visits will be supplemented by semi-annual telephone calls.

8.6 Study Termination

Enrollment of patients will be stopped when at least 300 patients have been enrolled. On a common closing date approximately 12 months after the last patient is enrolled, the efficacy phase of the study will end. The database will be frozen and a clinical report will be prepared. Follow-up of patients for long-term safety will continue in the extended follow-up phase through their 5 year visit. Upon completion of the extended follow-up phase, a final clinical report will be prepared and distributed to the investigators. The trial will be officially terminated after all final monitoring activities have occurred.

9.0 ADVERSE EVENTS

9.1 Reporting Criteria

Adverse events are reported as they occur during the course of the trial, irrespective of their perceived relationship to study treatment. All adverse events occurring during the trial, including the date and time of the event, outcome management, and assessed relationship of the event to the study device will be recorded on the appropriate case report form.

**Reportable adverse events** during this study include:

- Any *anticipated* event (defined in Section 9.2)
- Any *unanticipated* event that is either:
  - Serious (see definition below)
  - Device-related (see definition below)

**Serious adverse events**: adverse events which meet any of the following criteria:

- Life-threatening or resulting in death
- Requiring in-patient hospitalization or prolongation of hospitalization (In-patient hospitalization is defined as a hospital stay ≥ 24 hours.)
- Resulting in a permanent disability
Device–related events: events that are likely directly related to the CSD or the act of placing the CSD on the heart. They result from a malfunction (operation not according to design specification) of a CSD, from device-induced arrhythmia, or from interaction between the device and the patient (e.g., biocompatibility problem or cardiac constriction following device implant).

Conditions existing at the time of enrollment do not need to be reported as adverse events unless they increase in severity during the course of the study. Adverse events which resolve and recur should be reported as separate adverse events, as should any repeat hospitalizations. Adverse events which have not resolved at the time of the initial report, and which increase in severity or subsequently resolve, should be reported as adverse event follow-up information rather than as new events.

Adverse events should be classified according to their underlying cause, if known, (e.g., cardiac arrest resulting from ventricular fibrillation should be reported as “arrhythmia”). Concomitant events that are unrelated (in the clinician’s judgment) should be reported as multiple separate events.

Adverse events will be reported during the entire duration of the trial, i.e., during the extended follow-up phase as well as the efficacy phase.

9.2 Anticipated Adverse Events

Anticipated adverse events include those that are expected to occur in this trial because they are associated with:

- cardiac surgery
- invasive or stress-inducing tests (cardiac catheterization, cardiopulmonary exercise)
- placement of the CSD on the heart
- a heart failure patient population over time.

Anticipated adverse events are reportable if they are serious, as defined in section 9.1 above, or if they meet any of the other criteria given in the following table (Table 2).
<table>
<thead>
<tr>
<th>Anticipated Event</th>
<th>Reporting Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic response to anesthesia or medications</td>
<td>Allergic response to anesthesia or medication that results in a serious event*</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Any arrhythmia that results in the signs or symptoms of vital organ hypoperfusion (e.g., dizziness or syncope) and requires pharmacologic therapy, device implant (e.g., pacemaker), cardioversion or defibrillation (unless associated with CP bypass), or is serious*</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Any episode of internal or external bleeding that is serious*; or peri-operative bleeding resulting in RBC/whole blood transfusion ≥ 3 units within 24 hours following surgery.</td>
</tr>
<tr>
<td>Hemodynamic compromise</td>
<td>Signs or symptoms of vital organ hypoperfusion or deterioration in cardiac performance resulting in a serious* event, excluding hemodynamic compromise events secondary to other defined anticipated events (e.g., arrhythmia, bleeding, MI).</td>
</tr>
<tr>
<td>Hepatic compromise</td>
<td>Increase (greater than 3X above baseline) in any two of the following: total bilirubin, AST, or ALT, measured by standard clinical pathology/laboratory methods and sustained for ≥ 14 days; or any hepatic dysfunction resulting in a serious* event.</td>
</tr>
<tr>
<td>Infection (includes pneumonia)</td>
<td>Localized infection at a surgical incision or site used for invasive monitoring/therapy and treated with systemic antibiotics; pneumonia as diagnosed by standard clinical or laboratory methods; sepsis or other infection resulting in a serious* event.</td>
</tr>
<tr>
<td>Myocardial infarction, acute</td>
<td>Perioperative MI: presence of CK (with positive MB fraction) or troponin &gt; normal range for institution occurring within 48 hours of surgery, together with ECG pattern or changes consistent with acute MI; or non-perioperative MI including at least two: history of chest pain characteristic of MI, ECG changes or pattern consistent with MI, elevated troponin or CK (with positive MB fraction); or any MI that results in a serious* event.</td>
</tr>
<tr>
<td>Neurological deficit/stroke</td>
<td>Any new focal or global neurologic deficit of CNS origin, ascertained by standard neurologic examination or which results in a serious* event.</td>
</tr>
<tr>
<td>Peripheral thrombus/embolism</td>
<td>Any thrombus or embolism which does not effect the heart, lung, or brain, which is confirmed by standard clinical or laboratory testing and which requires intervention or results in a serious* event.</td>
</tr>
<tr>
<td>Pulmonary compromise</td>
<td>Deterioration in pulmonary functioning requiring mechanical ventilation (excluding the first 72 hours post-surgery), oxygen use outside of the hospital setting, or which results in a serious* event. (Report pneumonia under “Infection”.)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Obstruction of pulmonary artery or one of the branches caused by embolus diagnosed by V/Q scan, pulmonary angiogram, or equivalent studies; or symptoms of pulmonary embolism that resolve with treatment; or any diagnosis of pulmonary embolism that results in a serious* event.</td>
</tr>
<tr>
<td>Renal compromise</td>
<td>Abnormal kidney function requiring dialysis or resulting in a serious* event, or creatinine &gt; 2x above baseline and sustained for ≥ 14 days.</td>
</tr>
<tr>
<td>Unanticipated Event</td>
<td>Events not defined above that are serious* or device-related.</td>
</tr>
</tbody>
</table>

* Note: Serious adverse events (defined in section 9.1) are defined as: life threatening or resulting in death, requiring in-patient hospitalization or prolongation of hospitalization or resulting in a permanent disability.
9.3 Unanticipated Adverse Events

Unanticipated adverse events are events that are not considered anticipated, as defined in the previous section. Unanticipated adverse events are reportable if they are serious (as defined in Section 9.1), irrespective of perceived relationship to the study treatment. Additionally, any unanticipated adverse event of lesser severity is reportable if judged by the study investigator to be likely related to the CSD.

9.4 Unanticipated Adverse Device Effects

There are additional reporting requirements for the subset of unanticipated adverse events which meet the regulatory criteria of unanticipated adverse device effects.

Unanticipated adverse device effects (UADE) include any serious adverse effects on health or safety or any life-threatening problem or death caused by, or associated with the study device which are not typically associated with cardiac surgery or invasive, stress-inducing tests, or prospectively identified as potential risks of Acorn Cardiac Support Device therapy.

Any adverse event that is unanticipated, serious, and likely device-related must be reported as a UADE to Acorn Cardiovascular as soon as possible after first learning of the problem. In addition, the investigator must submit a written report to the IRB/ethics committee in accordance with the IRB’s specific reporting requirements (but no later than 10 working days after the investigator first learns of the problem).

10.0 INDEPENDENT REVIEW COMMITTEES

10.1 Clinical Events Review Committee (CERC):

An independent CERC will be formed to review on a case-by-case basis all serious adverse events, including death, and any other adverse events considered device-related occurring in enrolled patients. The CERC may also review adverse events where device relatedness could not be determined by the site. The CERC will be responsible for assessing the relationship of serious adverse events to the CSD.

The CERC will also review, blinded to treatment group, documentation relating to any of the following cardiac procedures that may occur during the course of the trial: CABG, mitral or tricuspid valve surgery (other than that occurring at baseline), or implantation of a biventricular pacing system. Based on their review, the CERC will determine whether the procedure was associated with progression of heart failure. Only those events judged to be associated with worsening heart failure (as compared to baseline) will be counted in the calculation of the primary endpoint.

Members of the CERC will not be employees of Acorn Cardiovascular, Inc, or have any affiliation with the Acorn Cardiac Support Device randomized trial. This committee will be composed of at least two cardiologists specializing in heart failure and one cardiac surgeon. Meetings or conference calls will be held twice yearly and whenever warranted based on event rates and/or types.
10.2 Data and Safety Monitoring Board (DSMB):

An independent DSMB will be formed to regularly review aggregate data summarized by treatment group. Members of the DSMB will not be employees of Acorn Cardiovascular, Inc, or have any affiliation with the Acorn Cardiac Support Device randomized trial. This committee will be composed of at least one cardiologist specializing in heart failure, one cardiac surgeon, and one statistician. The committee's purposes are to review data summaries related to enrollment, data quality, safety, and efficacy outcomes, and to provide recommendations regarding study management or potential early termination of the trial based on safety concerns. Meetings or conference calls will be held at least twice yearly.

11.0 STUDY DURATION

Following approval of the FDA and each center's IRB/ethics committee, it is estimated that this study will require up to 36 months for patient enrollment to be completed. Early termination of enrollment will occur, if warranted, on the basis of medical findings as described under Interim Monitoring below. Patient follow-up will continue through the 5 year follow-up visit, as described in section 8.6, Study Termination.

11.1 Interim Monitoring

Interim analyses will be reviewed by an independent Data and Safety Monitoring Board (DSMB), described in section 10.2. The DSMB will review summaries of enrollment, data quality measures, and efficacy outcomes approximately every 6 months during the course of the trial. Additionally, the DSMB will review safety outcomes quarterly. If the DSMB determines that the rate of adverse events or mortality in the treatment group (patients receiving the CSD) significantly exceeds that in the control group (patients not receiving the CSD), they may recommend trial termination or modification of the protocol.

12.0 RISK ANALYSIS

Patient risks or discomforts that may be expected to include any of the standard risks of a patient undergoing cardiothoracic surgery. This may include: bleeding; development of cardiac arrhythmias; blood coagulation abnormalities potentially resulting in stroke, pulmonary embolism, myocardial infarction, or peripheral embolism; hemodynamic compromise potentially leading to cardiogenic shock and/or neurological deficit; infection; pneumonia; pulmonary, renal, or hepatic compromise potentially leading to failure; reoperation, death; other surgical trauma; and/or allergic response to anesthesia or medications.

Any additional risks for participation in this study have been minimized by careful patient selection and center selection and training, as well as by implementing monitoring procedures to ensure proper conduct and management of the study.

Laboratory and animal experiments, as well as human safety studies, have evaluated a wide range of potential risks due to the Acorn device, and all identified risks are
described in this document. However, the investigational device may still have unknown side effects. There is also the possibility that the device material may not have the correct strength or could develop openings in the material or seams. If these events were to occur, any potential benefit of the device could be compromised.

Additional risks due to the investigational device may include arrhythmias from heart manipulation during device placement. Thrombo-emboli resulting from dislodgment of any intracardiac thrombus during device placement could result in stroke, pulmonary embolism, myocardial infarction, or peripheral embolism. Like all implanted devices, this investigational device may increase the risk of infection.

Hemodynamic compromise could result from an improperly fitted device, from compression or damage to coronary arteries or abrasion of the heart surface during device placement, or from excessive fibrosis or a potential constrictive phenomenon over time. However, animal studies have measured device/fibrosis effects on cardiac compliance and coronary flow, and have found no problems when the device is implanted. Animal testing has also found no abnormal fibrosis formation due to the device implant. Even so, since future surgical procedures will be "redo" surgeries, they will be subject to redo-associated technical compromise. In some cases, they may not be possible due to unexpectedly abundant fibrosis or adhesion formation.

Evaluation of the occurrence of events related to excessive fibrosis or a potential constrictive pattern will be monitored throughout the duration of the study. If the physician determines that cardiac compression or damage related to device placement, subsequent fibrosis formation, or tissue response is resulting in hemodynamic compromise not treatable by cardiac medication alone, the following surgical options are available:

♦ Replacement of device or readjustment of device size (possible during the first few weeks post-implantation).
♦ Removal of device (possible during the first few weeks post-implantation, and in some patients, may be possible later).
♦ Placement of cardiac assist or replacement device (unless the patient has contraindications).
♦ Cardiac transplant (unless the patient is contraindicated for transplant).

The benefits to patients participating in this study will include the recognition that they are contributing to a better understanding of the potential use of the Acorn Cardiac
Support Device therapy. Patients randomized to either the treatment or control group may benefit from closer monitoring of their heart failure. Patients randomized to the treatment group may also benefit from the potential reduction in cardiac dilation that is associated with worsening heart failure. This potential effect on the heart may help to reduce symptoms of heart failure such as shortness of breath with exertion, fluid retention, and breathlessness at night.

13.0 PROTOCOL MODIFICATIONS AND DEVIATIONS

Neither Acorn Cardiovascular, Inc., nor the investigator may modify this protocol without obtaining written concurrence of the other. The investigator in conjunction with Acorn will submit protocol modifications to the IRB/ethics committee as necessary, and Acorn will submit modifications to the FDA as necessary.

Any deviations from this protocol intended to protect the life or physical well-being of a patient in an emergency are to be reported to Acorn Cardiovascular, Inc. as well as the IRB/ethics committee as soon as possible, and no later than five (5) working days after the emergency occurred. Other deviations to the protocol must also be reported to Acorn Cardiovascular, Inc. in a timely manner.

14.0 STUDY MATERIALS

14.1 Investigational Product Supplies

All investigational product, including accessories, will be provided to the investigational site by Acorn Cardiovascular, Inc., once a signed Investigator Agreement and documentation of IRB/ethics committee approval of the protocol and consent forms have been received. Since the Acorn Cardiac Support Device is available in six (6) sizes intended to meet various heart sizes, a range of sizes will be provided.

14.2 Investigational Product Storage

All investigational products, including accessories, will be stored in a secure location with access restricted to study personnel. There are no other special storage requirements for the Acorn Cardiac Support Device beyond standard room temperature conditions.

14.3 Investigational Product Accountability

The investigator will be responsible for the entire inventory delivered to him/her, and must account for all devices and accessories. Study devices will only be placed in patients who meet study criteria, have agreed to participate in the study, have signed an informed consent form, and have been randomized to the treatment group. All devices must either be used or returned. Any contaminated devices must be destroyed using appropriate biohazard precautions, and their disposition must be reported to Acorn. Any opened but uncontaminated devices must be returned to Acorn for device
accountability and safety. All unused devices at the end of the enrollment period will be returned to Acorn Cardiovascular, Inc.

15.0 MONITORING PROCEDURES

Employees of the study sponsor, Acorn Cardiovascular, Inc., or its designee, who have appropriate training and experience will serve as study monitors. Study monitoring activities will include a pre-study site visit, verification of study data to source documents, and review of other study documents. A final monitoring report will be prepared to document that all protocol requirements are satisfied. Monitors may also assume responsibility for communications between the investigator and the sponsor. A primary study monitor will be assigned to each clinical site by the sponsor.

Prior to study launch, the study monitor or designee will ensure that the investigator and research staff understand this investigational plan, case report forms, and required records and reports. The study monitor will ensure that the investigator:

- has appropriate professional credentials, training, facilities, time, and willingness to comply with the study requirements (see section 6.2), and has signed an Investigator Agreement,
- submits this investigational protocol to the IRB/ethics committee for review and obtains approval prior to receipt and implant of any investigational product,
- receives training as per investigational plan and study procedures,
- maintains all study correspondence, the investigational plan and all required records on file, and
- assumes responsibility for the investigation at that center (which may include supervision of some tasks).

A report of the pre-study site visit will be made by the study monitor or designee. Resolution of any concerns and/or completion of any appropriate follow-up activities stemming from the pre-study visit will be documented by the study monitor.

Thereafter, site visits will be scheduled at least annually. These site visits are performed to ensure that the proper medical records are reviewed and that study data is complete and accurate. Samples of completed case report forms or database downloads and study documentation will be compared to source documentation and reviewed for accuracy, completeness, and protocol compliance. The following documents will be audited:

- Informed Consent Forms: An informed consent form must be signed by each patient prior to study-related testing, enrollment into the trial and implantation of the study device (if indicated). These documents will be audited 100% to ensure they are in compliance.
- Case Report Forms: Standardized case report forms must be completed for all patients enrolled into the study. Case report forms will be reviewed for
errors, omissions, internal consistency, and investigator signature and date. Monitoring activities will include verification of study data to source documents.

- **IRB/Ethics Committee correspondence**: All approvals, adverse event and unanticipated adverse event reports, annual reports and other correspondence with the center’s IRB/ethics committee must be up to date and on file.

These periodic on-site monitoring visits will also be used to assess the proper maintenance of records and reports, assess progress toward meeting study objectives, and identify any concerns that stem from observations of study management documents. Resolution of concerns and completion of corrective actions will be documented by the study monitor in monitoring reports.
Sample Size Determination

Sample Size Assumptions

For this trial, 300 patients (1:1 allocation for treatment and control) will be enrolled and followed to a common closing date, approximately 12 months after the last person is randomized. Sample size was estimated with 90% power at the .05 (2-sided) level of significance.

Several possible distributions of outcomes for the ordinal composite endpoint (described under the Primary Efficacy Endpoint section of the protocol) were postulated. Three different distributions were chosen for the control group, given as Scenarios A, B, and C in Table A-1.

In Scenario A, control group rates are similar to results for the control group in the Val-HeFT study (Cohn, J and Tognoni, G, A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure, *N Engl J Med*, Vol. 345, No. 23, Dec 2001). In the ValHeFT study, 5010 patients with NYHA class II through IV and an ejection fraction of <40% were randomly allocated to receive an angiotensin-receptor blocker (Valsartan) or placebo added to background therapy that could include ACE inhibitors, diuretics, digoxin, and beta-blockers. At baseline, the mean age in the control group (n=2499) was 63 years; 61%, 36%, and 2% of patients were classified as NYHA class II, III, and IV, respectively; and mean ejection fraction was 26.9%. After 18 months of follow-up, approximately 13% of controls had died, and 18% had died after 24 months. By the end of the study, after a mean follow-up of 23 months, 13% had worsened NYHA class and 21% had an improved NYHA class.

In Scenario B, the control group distribution reflects that achieved with a similar endpoint used in the RALES study (Pitt, B, Zannad F, and Remme, W et al, The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure, *N Engl J Med*, Vol. 341, No. 10, Sept 1999). In the RALES study, 1663 patients with heart failure (NYHA class III or IV and left ventricular ejection fraction ≤35%) were randomized to receive either spironolactone or placebo in addition to background treatment with an ACE inhibitor and a diuretic. Treatment with beta-blockers and digitalis was permitted, but not mandated. The 841 patients in the control group had a mean ejection fraction of 25.2% and mean age of 65 years, and the majority (69%) were assessed as NYHA class III at baseline. When the study was halted after a mean follow-up of 24 months, 33% of the control group had experienced an improvement in NYHA class, and 48% had experienced a worsening of NYHA class or had died. For 18% of control patients the NYHA class was unchanged from baseline.

In Scenario C, control rates are hypothesized that are similar to the results of the Miracle Trial (Summary of Safety and Effectiveness for the Medtronic® InSync® Biventricular Pacing System, PMA number P010015). In this double blind study, after implantation of the biventricular pacing device, patients were randomized to either treatment (cardiac resynchronization turned on) vs control (cardiac resynchronization remained off). The primary efficacy endpoints were evaluated at six months, at which time cardiac resynchronization was turned on for patients in the control arm. Entry criteria included NYHA class III or IV heart failure and ejection fraction ≤ 35%. Mean age was 64 years.
and 90% of patients were in NYHA class III at baseline. Of 169 control patients with NYHA measurements at baseline and 6 months, 38% improved from baseline and 4% worsened. After 6 months of follow-up, 8% of control patients had died. After 12 months of follow-up, 15% of implanted patients had died. A distribution for the control group at 18 months was estimated imputing the proportion with improved NYHA class at 6 months and assuming a constant death rate.

For each of the three scenarios for control group rates, various distributions for the treatment group are hypothesized. These distributions were chosen to correspond to three different estimates of the treatment effect as quantified by a proportional odds ratio. Distributions in the top section of Table A-1 correspond to a proportional odds ratio of 2.00. For instance, the odds ratio of improved vs. same or worsened is 2.00 for each of the three control group scenarios; likewise, the odds ratio of improved or same vs. worsened is also 2.00. In the middle panel of Table A1, similar distributions are presented corresponding to a proportional odds ratio of 2.15. The distributions corresponding to a proportional odds ratio of 2.30 are given in the bottom panel of Table A-1.

Sample size for this ordinal composite outcome was then estimated using several different approaches for each of the 9 distributions considered.

For the first approach (labeled Method A on Table A-1), a score was assigned to each category (-1 for improved, 0 for same, and 1 for worsened). Using this scoring system, a treatment difference and corresponding standard deviation were calculated. For example, for a proportional odds ratio of 2.00 and the distribution of scores given under Scenario A, the difference in mean scores is .257 and the standard deviation is .70. Sample size was then calculated to detect a treatment difference of .257, using a standard formula to calculate sample size for two continuous response variables (Fundamentals of Clinical Trials, Friedman, Furberg and DeMets). Using this approach, the required sample size for this hypothesized distribution is 312. Sample size was similarly estimated for the other eight distributions shown.

Method B entailed calculating sample size assuming a proportional odds model, using a method by Whitehead (Statistics in Medicine, 12:2257-2271, 1993). Using this method, the sample size required to detect an odds ratio of 2.00 with 90% power is 308-310, while 214 patients are needed to detect an odds ratio of 2.30.

Finally, sample size was also calculated assuming a Wilcoxon rank statistic for data analysis based on a method developed by Lehmann (O’Brien, RG (1997), “UnifyPow: A SAS Macro for Sample-Size Analysis”, Proceedings of the 22nd SAS Users Group International Conference, Cary, NC: SAS Institute, 1353-1358). Using this approach (labeled Method C), required sample size for 90% power ranges from 240 for a distribution corresponding to a proportional odds ratio of 2.30, to 352 for a distribution corresponding to a proportional odds ratio of 2.00.

The sample size requirements for the three methods (90% power, alpha=.05, two-sided) and nine distributions considered are summarized in the following table (Table A-1). As evidenced from this table, the magnitude of the treatment effect (i.e., the odds ratio) is the primary determinant of sample size, while the choice of the control group distribution has little impact on the number of patients required.
### Table A-1

Sample Size Requirements for Various Scenarios  
Power = 90%, alpha = 0.05 (2-sided)

#### Odds Ratio = 2.00

<table>
<thead>
<tr>
<th>Scenario A</th>
<th>Treatment</th>
<th>Control</th>
<th>Scenario B</th>
<th>Treatment</th>
<th>Control</th>
<th>Scenario C</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>33.3%</td>
<td>20%</td>
<td>50.7%</td>
<td>34%</td>
<td>55.1%</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same</td>
<td>49.1%</td>
<td>50%</td>
<td>17.7%</td>
<td>18%</td>
<td>29.3%</td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>17.6%</td>
<td>30%</td>
<td>31.6%</td>
<td>48%</td>
<td>15.6%</td>
<td>27%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method A</td>
<td>312</td>
<td></td>
<td>312</td>
<td></td>
<td></td>
<td>308</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method B</td>
<td>310</td>
<td></td>
<td>308</td>
<td></td>
<td></td>
<td>308</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method C</td>
<td>352</td>
<td></td>
<td>344</td>
<td></td>
<td></td>
<td>342</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Odds Ratio = 2.15

<table>
<thead>
<tr>
<th>Scenario A</th>
<th>Treatment</th>
<th>Control</th>
<th>Scenario B</th>
<th>Treatment</th>
<th>Control</th>
<th>Scenario C</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>35.0%</td>
<td>20%</td>
<td>52.6%</td>
<td>34%</td>
<td>56.9%</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same</td>
<td>48.4%</td>
<td>50%</td>
<td>17.4%</td>
<td>18%</td>
<td>28.4%</td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>16.6%</td>
<td>30%</td>
<td>30.0%</td>
<td>48%</td>
<td>14.7%</td>
<td>27%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method A</td>
<td>256</td>
<td></td>
<td>250</td>
<td></td>
<td></td>
<td>254</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method B</td>
<td>254</td>
<td></td>
<td>252</td>
<td></td>
<td></td>
<td>252</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method C</td>
<td>288</td>
<td></td>
<td>282</td>
<td></td>
<td></td>
<td>284</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Odds Ratio = 2.30

<table>
<thead>
<tr>
<th>Scenario A</th>
<th>Treatment</th>
<th>Control</th>
<th>Scenario B</th>
<th>Treatment</th>
<th>Control</th>
<th>Scenario C</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>36.5%</td>
<td>20%</td>
<td>54.2%</td>
<td>34%</td>
<td>58.5%</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same</td>
<td>47.8%</td>
<td>50%</td>
<td>17.2%</td>
<td>18%</td>
<td>27.6%</td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>15.7%</td>
<td>30%</td>
<td>28.6%</td>
<td>48%</td>
<td>13.9%</td>
<td>27%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method A</td>
<td>218</td>
<td></td>
<td>212</td>
<td></td>
<td></td>
<td>216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method B</td>
<td>214</td>
<td></td>
<td>214</td>
<td></td>
<td></td>
<td>214</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method C</td>
<td>244</td>
<td></td>
<td>240</td>
<td></td>
<td></td>
<td>244</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Method A = comparison of means  
Method B = Whitehead  
Method C = Wilcoxon

After consideration of the various scenarios, a targeted sample size of 300 was chosen. This corresponds to the most conservative sample size approach (the Wilcoxon approach), an intermediate treatment effect (a proportional odds ratio of 2.15), and an increase of 4-6% for possible missing data.
Power Estimates for Subgroups

Since the subgroup comparison for the MVR and no-MVR strata is an important secondary objective, power was estimated for these analyses considering three different patterns of enrollment. Consistent with the analysis plan for summarizing the interaction between treatment group and MVR stratum, power is calculated to detect a difference in the mean scores between the two treatment groups. Table A-2 summarizes power, in the subgroups and overall, to detect differences of .284 and .32 in scores, with a standard deviation of .70. The difference of .284 correspond to the treatment effects considered for Scenario A in Table A-1, assuming an odds ratios of 2.15. If patients enroll equally into the two strata, power will be 70% to detect a treatment difference of this magnitude. If the treatment difference is modestly larger (i.e., a difference in scores of at least .32), power will be 80% or greater for subgroups of equal size.

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Power to detect treatment difference of .284</th>
<th>Power to detect treatment difference of .32</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVR : no-MVR</td>
<td>MVR</td>
<td>NO-MVR</td>
</tr>
<tr>
<td>200:100</td>
<td>.82</td>
<td>.53</td>
</tr>
<tr>
<td>180:120</td>
<td>.78</td>
<td>.60</td>
</tr>
<tr>
<td>150:150</td>
<td>.70</td>
<td>.70</td>
</tr>
</tbody>
</table>

* alpha = .05 (2-sided)
ATTACHMENT B

DATA ANALYSIS PLAN
Revised Data Analysis Plan

The targeted enrollment of 300 patients was reached on June 20\textsuperscript{th}, 2003. Table 1 gives the number of patients enrolled by site and by stratum.

<table>
<thead>
<tr>
<th>Site</th>
<th>Stratum</th>
<th>MVR</th>
<th>No-MVR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>U of Penn</td>
<td>MVR</td>
<td>27</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>Bryan LGH</td>
<td>MVR</td>
<td>23</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>U of Michigan</td>
<td>MVR</td>
<td>21</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Nebraska Heart</td>
<td>MVR</td>
<td>15</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>U Florida/Shands</td>
<td>MVR</td>
<td>0</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Henry Ford Hospital</td>
<td>MVR</td>
<td>6</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>U of Alabama</td>
<td>MVR</td>
<td>10</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Wash Hosp Ctr</td>
<td>MVR</td>
<td>9</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>MVR</td>
<td>9</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Jewish Hosp, Louisville</td>
<td>MVR</td>
<td>2</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Columbia Pres</td>
<td>MVR</td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>St Louis University</td>
<td>MVR</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>McGill/Royal Victoria</td>
<td>MVR</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Stanford U</td>
<td>MVR</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Albert Einstein</td>
<td>MVR</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Advocate Christ Hosp</td>
<td>MVR</td>
<td>8</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Hershey, Penn State</td>
<td>MVR</td>
<td>1</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Duke</td>
<td>MVR</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Baylor Meth/VA</td>
<td>MVR</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Newark Beth Israel</td>
<td>MVR</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>University of Maryland</td>
<td>MVR</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cedars Sinai</td>
<td>MVR</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Ochsner Clinic</td>
<td>MVR</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>U of Pittsburgh</td>
<td>MVR</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Boston Medical Center</td>
<td>MVR</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>University of Minnesota</td>
<td>MVR</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mpls VA</td>
<td>MVR</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>New England Med Ctr</td>
<td>MVR</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>San Diego</td>
<td>MVR</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Grand Total: 193 MVR, 107 No-MVR, 300 Total

Due to selective enrollment by sites into the mitral valve repair/replacement stratum (MVR), extremely sparse cells result from the cross-tabulation of site and MVR. For this reason, stratification by site will not be performed. Instead, sites will be grouped into three strata of approximately equal size according to their total enrollment (more than 16 patients, 11-16 patients, and 10 or fewer patients). Since site size reflects surgical experience with the CSD, treatment groups will be compared within stratum taking into account that experience.

Table 2 gives the distribution of patients by stratum using this grouping.
All analyses will be stratified by concomitant surgery (MVR vs. No-MVR) and size of clinical site as described above. Analyses based on regression or analysis of variance techniques will include the baseline level of the outcome as a covariate.

One of the participating sites for this study is in Canada. With the exception that BNP specimens are not collected at this site (due to the complications of shipping frozen specimens across an international border), this site follows the same protocol, and their data will be included in all analyses.

The primary analysis for each endpoint will be by intent-to-treat, and will be carried out on all available data using a .05 level of significance (2-sided). The results of the primary analyses will be presented overall as well as separately for the MVR and No-MVR strata.

Time zero (henceforth referred to as “start date”) for time-to-event analyses will be day of baseline surgery, or day of randomization if baseline surgery was not performed. The hazard ratio, p-value, and 95% confidence intervals will be computed, and Kaplan Meier cumulative event curves and log rank statistics will be generated. Events will be counted in these analyses if they occur on or before the common closing date (July 4th, 2004). For patients with unknown event status, dates provided by the sites on the data collection form completed at close-out will be used for censoring. Specifically, sites will be asked for the date the patient was last known to be alive (if vital status on July 4th, 2004, is unknown) and the date the study coordinator last had contact with the patient (if the occurrence of adverse events, hospitalizations, or major cardiac procedures through July 4th, 2004, is unknown).

The primary analysis for each efficacy endpoint is listed in Table 3. More detail is given in the text that follows.

<table>
<thead>
<tr>
<th>Stratum</th>
<th>MVR</th>
<th>No-MVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large sites (&gt;16 patients)</td>
<td>86</td>
<td>30</td>
</tr>
<tr>
<td>Medium sites (11-16 patients)</td>
<td>53</td>
<td>46</td>
</tr>
<tr>
<td>Small sites (&lt; 10 patients)</td>
<td>54</td>
<td>31</td>
</tr>
<tr>
<td>Type of Endpoint</td>
<td>Outcome</td>
<td>Definition</td>
</tr>
<tr>
<td>------------------</td>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>Primary</td>
<td>Composite endpoint of blinded NYHA, death, major cardiac procedures</td>
<td>1 = improved 2 = same 3 = worsened</td>
</tr>
<tr>
<td>Major secondary</td>
<td>MLHF</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Major secondary</td>
<td>LVEF</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Major secondary</td>
<td>LV volume</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Major secondary</td>
<td>Site NYHA</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Other secondary</td>
<td>6 minute walk</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Other secondary</td>
<td>Sphericity</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Other secondary</td>
<td>BNP</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Other secondary</td>
<td>Hospitalizations</td>
<td>Hospitalizations, hosp days, ICU days, cardiac hospitalizations</td>
</tr>
<tr>
<td>Other secondary</td>
<td>SF-36</td>
<td>Post-pre for PF &amp; GH domains</td>
</tr>
<tr>
<td>Other secondary</td>
<td>LVEDD</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Other secondary</td>
<td>LVESD</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Other secondary</td>
<td>Mitral regurgitation</td>
<td>Post-pre</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Other secondary</td>
<td>Peak VO2</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Other secondary</td>
<td>VO2 at anaerobic threshold</td>
<td>Post-pre</td>
</tr>
<tr>
<td>Other secondary</td>
<td>Mortality or re-hospitalization</td>
<td>Time to 1st event</td>
</tr>
<tr>
<td>Other secondary</td>
<td>Major cardiac procedures</td>
<td>Time to 1st event</td>
</tr>
</tbody>
</table>

**Primary Efficacy Endpoint**

The primary endpoint is a composite ordinal endpoint based on three outcomes: vital status, occurrence of a major cardiac procedure indicative of worsening heart failure, and blinded assessment of change in New York Heart Association (NYHA) classification of functional class. The following events will be counted as major cardiac procedures contributing toward this endpoint: heart transplantation, implantation of a cardiac assist or replacement device, coronary artery bypass (CABG), implantation of a bi-ventricular pacing device, mitral valve surgery, or tricuspid valve repair (TVR).

Using the definitions above, patients will be classified at the end of the efficacy phase into the following categories:

- **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

Mitral or tricuspid valve surgery, CABG, and implantation of a bi-ventricular pacing system will be counted as “worsened” only if judged associated with progression of heart failure, as determined by the Clinical Events Review Committee (CERC) after blinded review. Qualifying MVR or TVR surgery will be counted if occurring after the pre-planned baseline valve surgery (if applicable) and on or before the common closing date for the efficacy phase of the trial. Deaths and other qualifying cardiac procedures will be counted if occurring after randomization and on or prior to the common closing date for the efficacy phase of the trial.

Central assessment of NYHA classification is performed throughout follow-up, blinded to treatment group, at six-month intervals beginning with the 6-month follow-up visit. However,
the central assessment was instituted after the trial had started, and is available for only 126 patients at baseline. Therefore, to calculate change in NYHA, a multiple imputation analysis was used to estimate a core lab-assessed NYHA for the patients who were missing this score at baseline. The primary endpoint was then analyzed using blinded core lab NYHA assessments for all patients at both baseline and during the last available follow-up prior to the common closing date.

Primary Analysis of Primary Endpoint
For the primary analysis, scores of 1 (improved), 2 (no change), and 3 (worsened) will be calculated using the last available blinded NYHA assessment prior to the common closing date.

The resulting score will be compared between treatment groups using a proportional odds model with clinical site size and concomitant surgery as stratifying factors. The odds ratio, 95% confidence interval, and p-value will be reported. Additionally, since this endpoint is based on the patient’s status at the end of the study and the duration of follow-up will differ from patient to patient, the analysis will also be stratified by extent of follow-up. This will be accomplished by dichotomizing patients into two groups based on timing of enrollment. “Late enrollees”, patients enrolled during the last year of the trial (start dates after July 4th, 2002) will have potential follow-up through the 12 or 18 month visit, while patients with a start date before July 4th, 2002 (“early enrollees”) will have potential follow-up through month 24 or greater.

Table 4 shows the number of patients in the 12 cells that result from this stratification.
Table 4

Cross-tabulation of Patients by Size of Site, Stratum, and Period of Enrollment

| Size of Site | MVR Stratum | | No-MVR Stratum | |
|-------------|-------------| | | |
| | Early Enrollment | Late Enrollment | Early Enrollment | Late Enrollment |
| Large       | 37          | 49 | 13           | 17 |
| Medium      | 27          | 26 | 29           | 17 |
| Small       | 22          | 32 | 9            | 22 |

This analysis will be repeated separately for the MVR and No-MVR strata with stratification by clinical site size and extent of follow-up, as described above.

Supportive Analyses of Primary Endpoint

Several supportive analyses will be performed. These will include:

- The composite endpoint will be evaluated using the central blinded assessment during follow-up as compared to the central blinded assessment of pre-enrollment NYHA status, in the subgroup of 126 patients for whom the baseline blinded assessment is available.

- The composite endpoint will be analyzed as status at the end of the efficacy phase rather than change from baseline. Deaths will be considered as “class V”, and qualifying cardiac procedures will be considered “class IV”. Using this 5-level ordinal scale, treatment groups will be compared using CMH, with stratification by size of clinical site, MVR, and baseline NYHA class (Lehmann, E.L. (1975). Nonparametrics: Statistical Methods Based on Ranks, San Francisco: Holden-Day, pp 132-137, 145). For baseline NYHA, patients will be classified into three categories according to whether the central assessment of NYHA was class 4, class 1 to 3, or missing. Patients for whom the NYHA is missing are patients who were enrolled during the earlier part of the trial; therefore, this categorization also provides stratification by duration of follow-up.

- The consistency of the treatment effect over time will be assessed by comparing the scores for the primary endpoint categories (as described in the previous bullet) at each follow-up visit using longitudinal regression models with an interaction term for treatment and follow-up visit. Treatment differences could be reduced with increasing follow-up if concomitant use of other heart failure therapies are offered to more patients in the control group than the device group. This could result as a consequence of the unblinded nature of the trial and the desire for control patients to find alternative treatments.
• The composite endpoint will also be analyzed comparing the last core lab blinded assessment of NYHA to the baseline NYHA classification assessed by the site clinician using the Cochran-Mantel-Haenszel test for ranked row means scores (CMH).

• If an imbalance is found between the treatment groups in mean values of prognostic baseline variables, adjustments will be made for these baseline covariates as well as stratifying variables in the proportional odds model.

• A “per protocol” analysis will be performed which excludes:
  
  o Treatment patients who did not receive the CSD.
  
  o Patients who were enrolled into the MVR stratum, but who did not undergo mitral valve surgery at baseline.
  
  o Patients who experience a major cardiac procedure prior to or within 30 days following the start date. This is motivated by the fact that clinical procedures that occur very early during follow-up are unlikely to be associated with heart failure that has progressed since baseline. For instance, a left ventricular assist device might be implanted as a consequence of an emergent event during surgery.
  
  o Patients who did not meet inclusion/exclusion criteria.
  
  o Central NYHA assessments for which the blinded grader answered “no” to the question “Was the questionnaire completed appropriately?”

• Supportive analyses of the primary endpoint will also consider the impact of missing data. The following sensitivity analyses will be performed: imputing worst case (“worsened” for treatment patients, “improved” for control patients) for unknown outcomes; and imputing no change from baseline (“same”) for unknown outcomes.

• Additionally, the proportion of patients improved and the proportion worsened will be compared between the treatment and control arms to verify that improvement in the treatment group did not come at the expense of a greater number of patients worsened.

**Major Secondary Efficacy Endpoints**

Four secondary endpoints have been designated a priori as “major secondary outcomes” by virtue of their clinical significance. These endpoints represent a spectrum of functional, physiologic, and structural changes by which by the medical community will evaluate the effectiveness of the CSD.

The four endpoints considered major secondary outcomes include:
To estimate the overall treatment effect throughout the efficacy phase, these four outcomes will be analyzed using longitudinal regression methods. Longitudinal analyses of MLHF and NYHA will include all follow-up visits through the end of the efficacy phase. Due to the length of time required for echocardiographic review by the central laboratory, the longitudinal analysis of left ventricular volume and LVEF will be truncated at the 18 month visit for the analysis of the efficacy phase data. For echocardiographic outcomes, follow-up visits after 18 months will be summarized when the data from the extended follow-up phase are analyzed.

Changes in each of these endpoints will be summarized at months 6 and 12. Changes in NYHA (as assessed by the site) will be summarized using the stratified CMH procedure. Analysis of variance techniques will also be used to summarize changes in major secondary outcomes.

Graphical representations of mean levels of the major secondary efficacy endpoints throughout follow-up will be based on estimates obtained from the longitudinal analyses.

In addition, Hochberg’s method will be applied to the four major secondary endpoints to evaluate their statistical significance at a family-wise type I error rate of 5%.

The following section gives additional detail on several of the major secondary endpoints.

**Minnesota Living with Heart Failure Questionnaire**

In keeping with the guidelines provided with the MLHF copyright agreement, if the answer to an individual item is omitted from a baseline questionnaire, that particular question will be omitted from analyses of follow-up data for that patient. When the answer to an individual item on a questionnaire completed during follow-up is missing, the value from the previous visit (baseline or follow-up visit) will be carried forward for that question.

**Left Ventricular Ejection Fraction**

LVEF is estimated in two ways by the core laboratory. One method calculates LVEF from left ventricular dimensions; the other method calculates LVEF from left ventricular volumes. The volume-based measurement is considered the optimal of the two. Therefore, the primary analysis will be based on change in LVEF summarized among the patients who have volume-based LVEF measurements at both baseline and during follow-up.

**Supportive Analyses of Major Secondary Efficacy Endpoints**

Supportive analyses as described below will be carried out to fully explore the treatment effect on the major secondary outcomes. Unless otherwise specified, the outcomes will be summarized at 6 and 12 months.
• “Per protocol” analyses will be conducted which exclude patients who did not receive the CSD implant, if randomly assigned to treatment, and exclude patients who did not undergo baseline mitral valve surgery, if enrolled into the MVR stratum.

• Because of the difficulty in interpreting patient functional and structural results following additional therapy, an analysis will also be performed limited to patients who have not experienced a major cardiac procedure prior to the measurement of the endpoint. Specifically, the procedures defined as major cardiac procedures for the primary endpoint will be considered censoring events. However, for this analysis, patients will be censored irrespective of the outcome of the CERC review of the procedure.

• Sensitivity analyses will be performed on treatment differences obtained at the end of the study using three separate approaches. The first approach will use last value carried forward (LVCF). In LVCF analyses, the value from the previous follow-up visit will be imputed for missing data at the end of the efficacy phase; baseline values will not be carried forward. In a second analysis, worst case will be imputed for missing data; specifically, the worst outcome will be assumed for missing data in the treatment group, and the best outcome will be assigned for missing data in the control group. Finally, the baseline value will be imputed for missing data at the end of the study. Van Elteren’s test will be used for significance testing in these analyses.

• If an imbalance is found between the treatment groups in prognostic baseline variables, secondary analyses based on analysis of variance techniques will be conducted with additional adjustment for these baseline covariates.

• Because the primary analysis of LVEF eliminates patients who do not have the volume-based LVEF but who may have a dimension-based measurement, the primary analysis of LVEF will be repeated imputing the change based on dimension-based LVEFs for patients in whom the volume-based LVEFs are missing.

• The primary analysis of MLHF will be repeated separately for the physical and emotional components of the instrument. The physical components are defined as items 2 through 7, 12 and 13 on the MLHF questionnaire. The emotional components are defined as items 17 through 21.

Other Secondary Efficacy Endpoints

This section of the data analysis plan details the analyses that will be performed for other secondary efficacy endpoints. Unless otherwise specified below, data that emanate from required testing at follow-up visits will be summarized at month 6 and 12 using analysis of variance, and across all follow-up visits through the end of the efficacy phase using longitudinal regression models.

Components of Primary Composite Endpoint
Each of the components of the composite primary endpoint is considered a secondary endpoint. Thus, in addition to summarizing the primary endpoint as an ordinal composite endpoint as described above, the components of the endpoint will also be summarized individually. Time-to-event methods will be used to compare the individual events that are components of the primary endpoint (deaths and qualifying major cardiac procedures), and the NYHA classification component will be analyzed using a proportional odds model analogous to that performed for the composite endpoint, excluding patients who died or experienced a qualifying major cardiac intervention as defined in the primary endpoint analysis.

**Hospitalizations**

Number of hospitalizations, overall and for cardiac reasons, through the common closing date of the efficacy phase of the study will be compared using van Elteren’s test, with stratification by size of clinical site and concomitant surgery. The number of hospital days will be compared for total days hospitalized and ICU days. Both total hospitalizations (including the baseline hospitalization) and re-hospitalizations (excluding the baseline hospitalization) will be considered. Re-hospitalizations will be counted in these analyses if the admission date occurs after time zero (as defined above) and the hospitalization entails at least an overnight stay.

To quantify the effect of treatment on all re-hospitalizations during follow-up (i.e., subsequent events as well as the first event), multivariate failure time analyses using the PWP method will be performed (Prentice, R.L., Williams, B.J., and Peterson, A.V. (1981), “On the Regression Analysis of Multivariate Failure Time Data,” *Biometrika*, 68, 373-379).

**Cardiac Sphericity**

Sphericity is defined as the ratio of ventricular length to width. It will be computed using the 2D apical 4-chamber estimate of width. If this view is not available, the 2D parasternal long axis view will be substituted.

**BNP**

BNP will be log-transformed for analysis to normalize the data.

The collection of BNP samples was instituted after the study started, and is therefore not available for all patients. The primary analysis will consider changes from baseline, with the baseline value as a covariate, in the subset of patients who had BNPs measured at enrollment. Patients who had baseline BNPs drawn after enrollment or on the day of surgery will be excluded.

To take advantage of the larger data set with BNP values during follow-up but not at baseline, mean values of BNP during follow-up will also be compared without consideration of the baseline value.
SF-36
Items on the SF-36 will be rescaled according to the procedure described by Ware (SF-36 Health Survey Manual & Interpretation Guide). Treatment differences will be summarized for the physical functioning and general health domains, using analysis of variance techniques. In addition, the afore-mentioned O'Brien procedure will be used to compute a global test statistic across all eight quality of life domains.

Exercise Testing
Patients who cannot tolerate cardiopulmonary exercise (CPX) testing are exempted from baseline CPX testing. Therefore, the analysis of changes in performance as assessed through CPX will be restricted to patients for whom the baseline assessment is available. Since this assessment is performed prior to randomization, no bias will be introduced by restricting the analysis to patients with complete baseline data.

Peak VO2 and VO2 at anaerobic threshold will be summarized as efficacy outcomes, using analysis of variance techniques. These measurements will also be summarized at months 6 and 12 using longitudinal regression to provide an average treatment effect over these two visits.

Peak VO2 will be analyzed for all patients for whom the data are available. The analysis of VO2 at anaerobic threshold will be limited to those patients who achieved anaerobic threshold, as indicated by a respiratory exchange ratio of 1.0 or greater. In addition, the number of patients achieving anaerobic threshold will be summarized by treatment group for each visit.

Six-Minute Walk
Due to the competing causes of decreased exercise capacity over time (e.g., arthritis, hip fractures, claudication), a longitudinal analysis of 6-minute walk distance will take into account only follow-up visits through month 12.

Other Echocardiographic Measures
LVEDD and LVESD are assessed by a core laboratory using both 2D and M-mode imaging methods. The 2D parasternal anterior-to-posterior short axis view (PSAX) is considered optimal, and the M-mode is regarded as an adequate substitute. At baseline, 258 (86%) patients have at least one of these measurements. This optimal view cannot always be evaluated due to quality of the echocardiographic technique or physical traits of the patient. Therefore, LV dimensions will be assessed two ways.

The analysis at months 6 and 12 will consider changes calculated by comparing follow-up to baseline measurements of the first available pair of views according to the following hierarchy:
- 2D PSAX (if not available, substituting M-mode);
- 2D parasternal long axis;
- 2D parasternal short axis (septal to lateral);
- 2D apical 4-chamber.
For the longitudinal regression analysis, the average of the 2D PSAX and M-mode measurements will be used. These analyses will be restricted to follow-up visits through month 18. Follow-up visits after that timepoint will be analyzed when the data from the extended follow-up visit are analyzed.

Frequency distributions of mitral regurgitation, as assessed from the central blinded review of echocardiograms, will be compared across treatment groups at months 6 and 12. Treatment group differences will be quantified using the stratified CMH procedure.

**Combined endpoint of death or re-hospitalization**

Time-to-event methods (stratified proportional hazards models, log rank tests, and Kaplan-Meier cumulative event curves) will be used to summarize the combination endpoint of death or re-hospitalization through the common closing date of the efficacy phase.

**Primary functional status measures**

The three primary measures of patient functional status—six minute walk, MLHF, and blinded NYHA assessment—will be jointly summarized at the end of the study using a procedure described by O'Brien to compute a global test statistic (O'Brien, P, Procedures for comparing samples with multiple endpoints. *Biometrics*, 1984, 31:511-529). Because the blinded baseline NYHA assessment is missing for a large number of patients, the last available blinded NYHA classification will be used for this endpoint, while the six minute walk and MLHF components will be based on change from baseline.

**Subgroup Analyses**

An important secondary objective is to evaluate the treatment differences for the two subgroups defined according to whether MVR surgery was carried out at the time of randomization. The treatment groups are not expected to differ qualitatively for the MVR and no-MVR groups; however, treatment with CSD is expected to result in greater structural improvements, compared to control, for those in the no-MVR group than those in the MVR group. These greater relative improvements may result in greater treatment vs. control functional changes for the no-MVR group.

In order to quantify the treatment by subgroup interaction, the consistency of the treatment differences in patient functioning for each subgroup will be assessed by comparing the mean scores corresponding to the primary endpoint categories using analysis of variance techniques. An interaction term for treatment and MVR stratum will be included in the model. Consistency of the results across the other strata (size of clinical site) will be similarly assessed, and evidence of heterogeneity across site will be documented.

The following other subgroups will also be evaluated: etiology of heart failure (ischemic vs. non-ischemic), gender, race, age, classes of cardiac medications used at baseline, common baseline co-morbidities (e.g., diabetes, atrial fibrillation), and subgroups defined by the median baseline assessments of LVEDD, LVESD, left ventricular diastolic volume, LVEF, BNP, peak VO2, MLWHF, and six-minute walk. Separate analyses will be carried out for each subgroup and evidence of heterogeneity between subgroups will be documented.
Further analyses of heterogeneity will be conducted to verify the poolability of patients at one Canadian site with those at U.S. sites, and to test the poolability of patients enrolled under revision 2 of the data analysis plan, versus those enrolled under revisions 3 and 6.

**Safety Endpoints**

Time-to-event methods (stratified proportional hazards models, log rank tests, and Kaplan-Meier cumulative event curves) and stratified Mantel-Haenszel chi-square will be used to summarize deaths and serious adverse events (SAEs).

The proportion of patients experiencing specific types of SAEs will be compared across treatment groups in two ways. In the intent-to-treat analysis, all SAEs on or after the day of randomization will be included. This analysis will then be repeated, excluding patients who did not receive the CSD (if assigned to the treatment group) and excluding patients who did not undergo baseline mitral valve surgery (if entered in the MVR stratum). In this analysis, only adverse events occurring on or after time zero, as defined above, will be included.

Comparisons of SAEs will be 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.

Analyses will be performed to quantify the surgical morbidity associated with the device implant. Proportions of patients dying or experiencing an adverse event during the operative period will be compared across treatment groups for patients who receive the protocol-defined surgery. Events will be characterized as occurring during the operative period if they occur after the initial surgery and before hospital discharge or within 30 days following surgery. Additionally, deaths and common specific SAEs occurring early (within 30 days of surgery/randomization) and late (greater than 30 days from surgery/randomization) will be compared for all patients across treatment groups.

Stratified multivariate failure time analyses will be used to summarize multiple SAEs experienced during the follow-up period using the afore-mentioned PWP method.

The CERC assessment of death and SAE causality will be summarized by treatment group. The outcome of the CERC’s review of cardiac procedures will be tabulated. While not reviewed by CERC, surgical procedures to drain pericardial fluid are collected as cardiac events, and will also be tabulated.

Time-to-event methods will be used to summarize the composite endpoint of death, a major cardiac procedure (as defined above for the primary endpoint), or occurrence of any of the following serious adverse events: arrhythmia, hemodynamic compromise, or myocardial infarction. Death will also be combined with SAEs and with AEs of any severity for time-to-event analyses. Both these analyses will be performed by MVR stratum, and for early/late events as defined above.

Reporting criteria for adverse events and the definition of “serious” have been modified since the original version of this protocol. The reporting criteria have been standardized and more clearly defined to ensure consistent adverse event reporting. Because of this change, all adverse events reported under previous versions were internally reviewed to re-evaluate
severity and to ascertain whether the adverse event meets reporting criteria for the current version. Treatment comparisons of adverse events will be summarized using the definitions given in the May 2002 version of the protocol. Pre-operative hospitalizations for hemodynamic optimization prior to surgery (e.g., implantation of an intra-aortic balloon pump) are not considered adverse events.

The central blinded review of echocardiograms during follow-up provides an opportunity to assess the incidence of constrictive physiology. The percent of patients with echocardiographic findings indicative of constriction will be summarized across treatment groups using stratified Mantel-Haenszel chi square procedures.
ATTACHMENT C

Patient Informed Consent Form
Randomized Trial of Acorn Cardiac Support Device Therapy
In Patients with Dilated Cardiomyopathy

Patient Informed Consent Information

**Purpose and Background:**
You are being asked to participate in this research study because you have dilated cardiomyopathy (heart disease with a stretched out, poorly pumping heart). The purpose of this clinical research study is to assess the safety and efficacy of the Cardiac Support Device manufactured by Acorn Cardiovascular, Inc. The Cardiac Support Device is intended to support the heart, preventing further dilation that is associated with progressive heart failure, thereby preserving or improving functional status. The Acorn Cardiac Support Device is an investigational device not yet approved by the US Food and Drug Administration. It has the appearance of a loosely knitted cap and is made of a polyester fiber. Similar material is currently used for blood vessel and heart defect repairs. The device is placed around a dilated or enlarged heart, and is intended to limit how far the heart will stretch. Patients in the study will be monitored for changes in the size and functioning of their heart, changes in their quality of life and ability to perform daily activities, and any new or recurring health problems. Approximately 300 patients will participate in this study.

In preparation for this clinical study, the Cardiac Support Device has been tested in animals to demonstrate its performance and safety. In addition, the Cardiac Support Device has been tested for strength, flexibility and material stability in engineering studies. The Cardiac Support Device has undergone special testing to ensure that the material is compatible with the tissues in the body and that it will not cause infections. Based on these test results an initial patient safety study was initiated outside the United States in April 1999 and the last patient was enrolled in July 2000.

The investigators in charge of this study are ______________________ and ______________________.

**Study Procedures:**
If you agree to be in this study and give your written consent the following will happen. Baseline information such as age, gender, medical history, and medication use will be collected. Tests that are routine for evaluating heart function will be performed, if not already done within the past 1-3 months. These tests include blood tests, pregnancy test if applicable, chest x-ray, echocardiography (heart ultrasound), electrocardiogram (ECG), exercise (treadmill test and six-minute hall walk), two quality of life questionnaires, and an interview with a nurse or physician regarding your ability to perform daily activities. Some of these tests will also help determine what size device is appropriate for your heart. In some cases patients with very large hearts may need to undergo a cardiac MRI to make certain that the heart size does not exceed the largest size device available. In some cases you may be have a right or left heart catheterization to determine if you are eligible for this trial. If you meet all the study criteria and give your consent, you will be entered into the study. A process called randomization (similar to flipping a coin) will be used to determine your study assignment to the treatment group (receiving the device) or the control group (not receiving the device). All enrolled patients will continue to get optimal medical management and, if warranted, cardiac valve surgery under the close observation of the study investigators.
Half the enrolled patients will be randomly selected to also receive Acorn Cardiac Support Device implants (the treatment group). If you are randomized to receive the Cardiac Support Device, your surgeon will implant the appropriately sized Acorn Cardiac Support Device. He/she will monitor your heart function during surgery to make sure the device fits correctly, and will oversee your recovery from surgery. There will be no charge for the device.

**Follow-up:**
Both the treatment group and the control group will undergo identical follow-up evaluation and testing. Pre-enrollment testing will be repeated at:
- √ 3 months: (at least clinical assessment, blood tests, echocardiography, electrocardiogram, six-minute walk exercise test, and quality of life questionnaires).
- √ 6 months: (at least clinical assessment, blood tests, an interview with a physician or nurse about your ability to perform daily activities, echocardiography, electrocardiogram, six-minute walk exercise test, cardiopulmonary exercise test and quality of life questionnaires).
- √ 12 months: (at least clinical assessment, blood tests, an interview with a physician or nurse about your ability to perform daily activities, echocardiography, electrocardiogram, six-minute walk exercise test, cardiopulmonary exercise test and quality of life questionnaires).
- √ and every 6 months thereafter (at least clinical assessment, blood tests, an interview with a physician or nurse about your ability to perform daily activities, echocardiography, six-minute walk exercise test, and quality of life questionnaire).

In addition, you will be asked to answer telephone questions from the study center regarding symptoms, medications, daily activities, and new or recurring health problems at the following intervals: every 2 weeks for 3 months, monthly between months 4 and 12 and quarterly (every three months) thereafter. Telephone calls are only required during the months in which no follow-up visit occurs.

- √ The follow-up schedule described above, called the efficacy phase of the trial, will continue until the last enrolled patient has completed the 12-month follow-up (expected to take up to 36 months from the time you are enrolled).
- √ After the efficacy phase is complete, you will continue to receive at least telephone calls every 6 months regarding your health status and any serious medical events. You will also continue to receive an echocardiogram and an assessment of your functional status yearly at the study center for a total of five years from the time you are entered into the study.

**Potential Risks/Discomforts:**
Risks or discomforts that may be expected include any of the standard risks of a patient undergoing heart surgery. These may include bleeding, development of an abnormal heart rhythm, a blood coagulation abnormality that may cause small blood clots to be released into the blood circulation possibly clogging blood vessels or causing stroke or heart attack, a (usually temporary) deterioration in heart function, infection, pneumonia, problems with lung, kidney, or liver function, accidental injury during surgery or need for reoperation, an allergic reaction to anesthesia or medications, or death.
Additional risks due to the investigational device may include abnormal heart rhythms during device placement.

Laboratory and animal experiments, as well as human safety studies, have evaluated a wide range of potential risks due to the Acorn device. All identified risks are described in this document. However, the investigational device may still have unknown side effects. There is also the possibility that the device material may not have the correct strength or could develop openings in the material or seams. If these events were to occur, any potential benefit of the device would be minimal. Like all implanted devices, it may increase the risk of infection. The device may cause the heart to become stiffer, it may reduce blood flow, or it may cause excess tissue to grow from the heart to surrounding tissues. All these things could lessen the pumping capability of the heart. The excess tissue growth could make future cardiac procedures or surgery more difficult, and may make some surgeries impossible. However, preliminary animal studies have measured heart stiffness, blood flow, and heart healing responses, and have found no problems due to a correctly implanted device. To help manage potential risks, your doctor will be monitoring your health and providing appropriate care during this study.

**Benefits:**

The potential benefits you may experience if you participate in this study are improvements in your symptoms of heart failure.

If you are randomized to the control group, you will receive the best medical care your physicians can provide throughout the clinical study. In addition, the tests you receive during the study may assist your doctor with the treatment of your illness. If needed, you will receive mitral valve surgery. You should know that many patients in other randomized trials have shown some clinical improvements as a result of this close medical management, regardless of which group they are in.

If you are randomized to receive the Acorn device, it may reduce or prevent continued heart dilation. You may benefit directly from a maintained or reduced heart size. This potential effect on the heart may help to reduce symptoms of heart failure such as shortness of breath with exertion, fluid retention, and breathlessness at night.

Even if you receive no direct benefit from participating in this study, hopefully the information gained from this study will help in the treatment of future patients with conditions like yours.

**Alternative Therapies:**

You do not have to participate in this study. Alternatives available to you may include continuation of your standard cardiac medications. Some patients may be eligible for biventricular pacing devices. Your physician may also consider other investigational therapies or medications for you.
Costs:
You will not be charged to enroll in this study, and if you are randomized to receive the Cardiac Support Device, you will not be charged for the device. Costs for study-related travel, testing and surgery should be discussed with your physician.

Questions / Study Related Injury:
If you have questions about this study or your rights as a patient, or if you believe that participation in this study has resulted in personal injury to you, you may contact the following person(s), who will review the matter with you, identify any resources that may be available, and assist you in obtaining appropriate medical care.

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

A Decision Not to Participate:
Your participation in the study is entirely voluntary. If you decide not to participate in the study, it will not affect your present or future medical care in any way. You may withdraw from participation at any point. If you are not interested in participating or you change your mind about participation, simply tell your doctor.

Confidentiality of Records:
The records of this study will be kept confidential. You will not be identified by name or description in any reports or publications about this study. Only persons directly involved with this clinical study will be given access to the medical records pertaining to your pre-existing heart condition, the surgical procedure, your follow-up care and hospital charges for the services provided to you. These persons include your doctor and associated study investigators, authorized IRB/ethics committee staff, Acorn Cardiovascular staff, and regulatory agencies including the US Food and Drug Administration (FDA).

Conclusion:
I have had my questions answered and have been given a copy of this form for my own records. I agree to participate in this study, as indicated by my signature below:

________________________________________________________________________
Patient Name (please print) Date
________________________________________________________________________
Signature of Patient Date
________________________________________________________________________
Signature of Physician Date
________________________________________________________________________
Signature of Witness Date
Randomized Trial of Acorn Cardiac Support Device Therapy
In Patients with Dilated Cardiomyopathy

Patient Informed Consent for Autopsy

I understand that valuable information can be gained from an autopsy following the death of a patient involved in clinical research. Therefore, I hereby give my permission for the performance of an autopsy on me in the event of my death either during the time I am a participant, or after the conclusion of my participation, in the study entitled Randomized Trial of Acorn Cardiac Support Device Therapy In Patients with Dilated Cardiomyopathy. I hereby give my permission to Acorn Cardiovascular, Inc., its successors and assigns to use the results of the autopsy for research purposes, regulatory submissions, and presentations or publications related to the research or development of Acorn therapy. I hereby release Acorn, its subsidiaries, successors and assigns from any and all liability to me, my heirs, personal representatives, administrators and/or executors with may arise from the rights granted herein.

Signed this __________________ day of ________________________, _________.

Patient Name (please print)  Date

Signature of Patient  Date

Signature of Physician  Date

Signature of Witness  Date
Clinical Evaluation of Acorn Cardiac Support Device Therapy in Patients with Dilated Cardiomyopathy

INVESTIGATOR AGREEMENT

_________________ and _____________ MD (hereinafter together referred to as “Investigator”) wish to participate in the clinical trial, Clinical Evaluation of Acorn Cardiac Support Device Therapy in Patients with Dilated Cardiomyopathy – A Randomized Trial in the United States (the “Investigational Plan”), sponsored by Acorn Cardiovascular, Inc., 601 Campus Drive, St. Paul, MN 55112, USA (“Acorn”) and involving investigation of Acorn’s proprietary Cardiac Support Device (“CSD”). In exchange for such participation and other consideration, Investigator specifically agrees that:

Investigator is familiar with the Investigational Plan for the clinical trial and is qualified by training and experience to perform the Investigational Plan.

Investigator will conduct the clinical investigation in accordance with this Investigator Agreement, the Investigational Plan, all applicable governmental regulations including the FDA’s IDE regulations, and conditions of approval imposed by the reviewing IRB/ethics committee and/or government agencies.

Investigator will maintain direct supervision of all use of the CSD involving human subjects. Investigator will not supply the device to any person other than patients meeting all trial requirements or other physicians responsible to Investigator, unless Investigator has prior written authorization from both Acorn and the IRB/ethics committee.

Investigator will ensure that an adequate Informed Consent process is used when recruiting potential patients for the trial and written Informed Consent is obtained from each patient who participates in this clinical investigation, prior to implant of the device. In order to meet these requirements, Investigator will (check one):

- Use the Informed Consent materials provided by Acorn and approved by the IRB/ethics committee.
- Use alternative Informed Consent materials that have been approved by Acorn and the IRB/ethics committee. A copy of the alternative Informed Consent materials must be provided to Acorn for review and approval.

All information obtained from Acorn about the CSD and all information, including, without limitation, the terms and conditions of this Agreement and all information relating to Acorn’s past, present, or future research, technology, designs and products, and any knowledge or information developed by the participating center (“Institution”) or Investigator, either alone or with others, as a result of their work under this Agreement, excluding patient data, shall be considered the confidential and proprietary information of Acorn. Investigator shall not use such confidential information for any purpose other than the performance of the Investigational Plan and shall not disclose such confidential information to any third party without written permission of Acorn or prior public disclosure by Acorn. Investigator agrees to submit to Acorn all trial-related abstracts, presentations, press releases, and manuscripts 30 days prior to submission or presentation so that Acorn can review them for accuracy and Acorn confidential-proprietary information. Investigator agrees to delete all Acorn
confidential-proprietary information from any proposed abstracts, presentations, press releases, and manuscripts.

All patient data generated by Investigator at their center is considered to be shared between Acorn and the Investigator. The Investigator will maintain it in confidence and not release it to anyone without informing Acorn or prior public disclosure by Acorn.

To protect Acorn's patent rights, Investigator will not release the Acorn CSD to anyone other than those individuals participating in this clinical trial without written consent from Acorn.

Investigator will send Acorn a copy of the written IRB/ethics committee approval when Investigator has obtained it for this clinical investigation.

Investigator will include a copy of his curriculum vitae with this Investigator Agreement.

As an investigator for this trial and as a result of participation in this trial, Investigator or Investigator’s staff may conceive or reduce to practice an invention, discovery or improvement to the CSD or tools or procedures for its use. Investigator agrees to keep any records of such inventions as may be necessary to obtain patents and to report any inventions promptly to Acorn. Investigator agrees that such invention, discoveries or improvements in the CSD or tools or procedures for its use, of whatever form or nature, will be the sole and exclusive property of Acorn. Institution and Investigator agree to assist Acorn in obtaining any patents relating to such inventions. Acorn will compensate Investigator for the costs of any time incurred by Investigator required to maintain records documenting the inventions or obtaining the patents.

All clinical experience data collected on the Acorn CSD is available for use for regulatory submissions. Investigator will make his premises and procedures, clinical data and trial-required paperwork available for audits and inspection by Acorn staff, Acorn's representatives, or governmental agencies. Investigator will maintain trial-related records in a secure location for a period of 5 years after completion of the trial, and will contact Acorn prior to disposal of trial records.

If Investigator leaves his current Institution, or if Investigator fails to fulfill the obligations of this agreement, this agreement shall immediately terminate. Upon such termination, obligations of confidentiality and any rights otherwise accrued under this agreement shall continue. In addition, Acorn may terminate this Agreement at any time upon thirty days prior written notice.

The law of the State of Minnesota, without reference to its choice of law provisions, shall govern this Agreement and its interpretation and construction. Minnesota is a convenient forum for the resolution of any conflicts and personal jurisdiction in Minnesota is admitted by all parties to this agreement.

Investigator represents and warrants that at no time preceding this Agreement, and throughout the term of this Agreement, neither Investigator nor any of Investigator's staff providing services under this Agreement, has been or will be debarred, excluded, or subject to limitations on the management or conduct of clinical trials by the FDA, other regulatory authority, any institution’s IRB/ethics committee or any sponsor of such activity for reasons of non-compliance.
INVESTIGATOR REQUIREMENTS -- Investigator will be responsible for the following:

Attend Investigator meetings or conference calls when requested. During these meetings and calls, the Investigator will also represent his colleagues participating in the testing and monitoring of trial patients.

Serve as a contact between Acorn and his colleagues participating in the testing and monitoring of trial patients and be sufficiently familiar with his/her patients such that he/she can make an informed judgment when signing case report forms reporting patients’ status and test results.

Complete all pre-trial agreements required by the protocol prior to trial start, and return them to Acorn in a timely manner.

Ensure trial case report forms are completed with all information requested, including Investigator signature, and are returned to Acorn in a timely fashion.

Upon receipt of Final Closure Report(s) from Acorn, immediately review and return to Acorn in a timely manner to facilitate reporting to regulatory agencies for trial closure.

Immediately inform Acorn of any Acorn therapy- or device-related issues, including without limitation any adverse events.

The Investigator will provide to Acorn sufficient accurate financial disclosure information to allow submission of the appropriate certification or disclosure statements as required by 21 CFR §54 - financial disclosure by Clinical Investigators. The Investigator agrees to update this information if any relevant changes occur during the course of the trial and for 1 year following trial completion.

Investigator affirms that he/she has read the Investigator Agreement for the clinical evaluation of the Acorn CSD and agrees to abide by the guidelines set forth in this agreement, as indicated by the signature(s) below.

INVESTIGATOR:  ACORN CARDIOVASCULAR, INC

Signature:________________________  Signature:________________________

Print Name:_______________________   President and Chief Executive Officer

Date:_____________     Date:_____________

Signature:________________________

Print Name:_______________________

Date:_____________