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C–Pulse® System

A Heart Assist Device

Investigational Plan

Confidential

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INTRODUCTION

PURPOSE

Sunshine Heart is sponsoring a prospective, multi-center, randomized trial to assess the safety and efficacy of the C-Pulse® System ("C-Pulse").

The purpose of the study is to determine whether the use of the C-Pulse as a treatment for patients in moderate to severe heart failure (HF) has demonstrated safety and efficacy, such that the C-Pulse System merits Food and Drug Administration (FDA) approval to market the device in the United States.

STUDY SIZE AND DURATION

This clinical study is anticipated to commence October 2012. The enrollment and 12 month follow-up duration of the study is expected to be 3.5 years. The primary study population will include 388 subjects enrolled and randomized in up to 40 centers in the United States (US) and potentially additional sites in Canada. The treatment group will include 194 subjects randomized to and implanted with C-Pulse® System and the control group will include 194 subjects randomized to and followed according to the same follow-up schedule as the treated subjects. All patients must be consented prior to performing any study related procedures. A patient is considered enrolled upon signing the informed consent. To minimize the burden to the patient, data collected as standard of care and not for the specific reason for study eligibility may be used for baseline data points as outlined in the informed consent. These tests will suffice for the baseline dataset if collected within the specified baseline data collection timeframe prior to implant. The subjects will be assigned a screening number upon signing the consent.

All subjects who do not meet the eligibility requirements will be promptly study exited. Study exit of these screen failure subjects must be documented. Only the subjects who meet the eligibility criteria will proceed to randomization. The subjects will be assigned a randomization number. The period of subject follow-up will be a minimum of 12 months to assess the safety and efficacy. Post 12 months, subjects will continue to be followed at 18 months and then annually during long-term follow-up to five years.

The study will be conducted in accordance with Code of Federal Regulations (CFR) Parts 11, 50, 54, 56 and 812. A progress report of the clinical outcomes will be given to the Data and Safety Monitoring Board (DSMB) following enrollment of the first forty (40) randomized patients and at least twice annually based on study progress. The recommendation(s) from the DSMB may be circulated to each of the Investigation Review Boards (IRB) and Ethic Committees (if applicable) participating in the study upon request.

BACKGROUND

Heart Failure (HF) represents a major and growing public health concern in terms of incidence, prevalence, morbidity, mortality and economic cost. Chronic HF is predominantly the result of ischemic heart disease or idiopathic dilated cardiomyopathy.

Chronic HF is conventionally treated with drugs. However there are many circumstances where drug therapy is insufficient or where the heart has become refractory to drug therapy. Cardiac Resynchronization Therapy (CRT) is indicated in patients with HF who have ventricular dyssynchrony, commonly evidenced by a widened QRS complex. Resynchronization therapy is suitable for approximately 30% of moderate HF patients, and has been shown to provide significant clinical improvement [as measured by NYHA Class, quality of life (QOL) score, 6 minute walk test, freedom from advanced heart failure treatments, etc][1]. As many as 30% of patients who have CRT implants do not have a satisfactory response ("non-responders"). Further, many patients initially have a good response but then develop more advanced symptoms.

Heart transplantation is an effective therapy for end stage NYHA Class IV patients. The number of donor hearts falls short of meeting the needs of patients and many patients are excluded because of age (the upper limit for transplant being approximately 65 years)[2].

Left Ventricular Assist Devices (LVADs) have been shown to offer the potential for the treatment of end stage NYHA Class IV HF patients. LVADs have been shown to improve survival in patients suffering severe HF and some LVADs have been approved as a bridge to transplant (BTT) and for destination therapy (DT). Because of the blood-contacting nature, these devices have high associated risks such as bleeding, stroke, infection and device failure. Furthermore, despite prolonging life, patients spent more time in the hospital due to these associated complications[3].

There is growing evidence that the unloading actions of LVADs can facilitate significant recovery and reverse remodeling of the heart[4]. However, there is a need for lower risk, lower cost devices that allow for long-term implant in less sick patients. Such a device could provide for partial unloading of the heart such that the patient can be weaned and for the device to not necessarily be removed.

[1] [Abraham 2002]

[2] [Demers 2003]

[3] [Rose 2002]

[4] [Reinlib 2003, Birks 2006]

It is well established that a mode of circulatory support, known as counterpulsation, works by reducing the load on the heart, augmenting heart pump function, and increasing both coronary artery and total body blood flow. Unlike LVADs, counterpulsation devices act to augment native heart function rather than to replace it. While LVADs unload the heart, it is evident that they do not necessarily increase coronary artery blood flow[5]. Unlike VADs, because the C-Pulse System is not located in the bloodstream and does not provide full life support, the C-Pulse may be disconnected for short intervals to allow for personal hygiene, etc. facilitating an improved quality of life. Not being required to tether to a driver for life support allows the patient to return to some normal activities not allowed with VADs.

Counterpulsation has two main benefits to heart function:

- When the aortic valve is closed and the balloon is inflated, diastolic pressure is increased ("diastolic augmentation"): there is augmentation of flow into the peripheral arteries from the aorta, and particularly to the coronary arteries.
- Following the electrical excitation of the left ventricle [electrocardiogram (ECG) QRS complex], the heart contracts and the balloon is deflated. The reduction in impedance reduces aortic pressure and thus the work load of the heart by reducing the pressure-head which the heart has to eject against. This is termed "pre-systolic ventricular unloading" and allows the heart to contract more vigorously and with greater efficiency.

Counterpulsation has been widely used the past 30 years for short term (2 to 7 days) cardiac support in patients with hemodynamic compromise but in whom recovery can be expected, such as after heart surgery or after a major heart attack. These intra–aortic balloons (IABs) are widely used in hospitals. The IAB is inserted via a femoral artery and positioned in the descending aorta. The IAB is attached to a bedside module that inflates and deflates the device based on the R wave of the ECG signal. When the condition of the heart has improved the IAB is removed. IAB counterpulsation a) increases coronary blood flow, b) reduces ventricular afterload to reduce the workload of the left ventricle, and c) increases cardiac output. [6] The level of counterpulsation may affect cardiac performance in the short-term: Cohen et al showed in a limited study of 20 patients a significantly higher velocity time integral across the Left Ventricle (LV) outflow tract resulted when counterpulsated at 1:1 versus 1:8. They did not show any difference with varying the balloon volume from 40 to 32 cubic centimeters (cc)[7].

[5] [Ootaki 2005]

[6] [Cochran 2002, Cheung 1996, Reichart 1993]

[7] [Cohen 1995]

The beneficial effect of counterpulsation in short term situations has stimulated interest in its potential effects when used in longer term situations. Long term counterpulsation may chronically reduce the load on the heart and augment the native heart blood pumping capacity. The devices can be turned on and off as required, particularly if the heart recovers its strength following months of support. Specific examples of investigational long term counterpulsation therapies include the CardioVAD device and a technique known as Aortomyoplasty. Ambulatory IAB (positioned via a graft in the axillary artery) has also been used to support patients as a bridge to transplant[8].

The CardioVAD (LVAD Technology, Inc., Detroit, MI) comprises a pump sewn into the wall of the descending aorta, an access device to allow a gas tube to pass through the skin, and a driver unit worn by the patient to move air into and out of the pump. The CardioVAD has been implanted in a limited number of patients in Class IV heart failure in an Investigational Device Exemption (IDE) Feasibility trial in the USA. Results of the trial to date have shown that the CardioVAD can significantly improve blood flow through the body and reduce HF symptoms[9], though there is a significant surgical risk due to the invasive nature of the surgery.

Aortomyoplasty involves surgically wrapping a muscle from a patient's back around the outside of the aorta and electrically stimulating that muscle to contract in counterpulsation with the patient's heart rhythm using a pacemaker-like device. The results of a series of 15 patients have shown substantial benefits in heart pumping capacity compared to pre-operative measurements, improvement in patient well-being, and an excellent long-term (up to 8 years follow up) safety profile[10]. However, this procedure is associated with a significant surgical risk and lengthy rehabilitation period since the back muscle must be trained over a period of at least 6 weeks before there is effective counterpulsation.

The current need is for a counterpulsation device or method that is effective enough to make its application appealing as a long-term implant to a large number of patients and physicians. It must be simple and safe, with a straight-forward implant procedure, and with long-term measurable patient benefits. Further, it would be advantageous for the counterpulsation device to be smaller, easier to insert, allow for ambulation and disconnection, and not be in the bloodstream. Such a device may be more readily adopted by a wider group of cardiologists and surgeons, and be suitable for a wider group of people in NYHA Class III to ambulatory Class IV heart failure. It is important to point out that a counterpulsation device is intended to augment native heart function and is fundamentally different from total artificial hearts, left ventricular assist devices and heart transplants which are meant to be a total replacement or an alternative to the native heart. Thus, the counterpulsation device is considered non-obligatory and not life-supporting.

[8] [Cochran 2002]

[9] [Jeevananddam 2001]

[10] [Tranini 2002]

Sunshine Heart, Inc. has proposed the C-Pulse® System, a novel ambulatory, non-obligatory, non-blood contacting extra-ascending aortic counterpulsation system[11]. The C-Pulse® System is designed to be implanted without the need for cardiopulmonary bypass or extensive dissection, to be able to be activated immediately, to augment heart function in a safe manner and to provide sustained relief from heart failure symptoms. It can be turned off safely, and similarly, in failure modes, is considered to have an associated low risk of death or disability, other than the recurrence of heart failure symptoms. C-Pulse® System is not an alternative to the heart, it is an augmentation device, and it does not preclude the use of therapies that provide full circulatory support such as heart transplantation or LVADs.

The C-Pulse® System consists of a counterpulsation Cuff secured around the outside of the ascending aorta, the main blood vessel out of the heart. The Cuff and a heart signal sensing wire are attached to an external Driver through a modular lead. The percutaneous interface lead (PIL) is a segment of lead that is designed with a connection point in the subcutaneous layer in the abdomen to allow for exchange if needed without need to access the thoracic cavity. The external Driver inflates and deflates the Cuff in sequence with the ECG signal to assist heart function and improve the pumping capacity of the heart. The Cuff deflects the aorta in a "thumb-printing" manner which has been optimized to minimize aortic wall strain and maximize blood volume displacement per beat. The C-Pulse® System is non-blood contacting, simple to implant, and can be turned on and off as required; all natural blood pathways are maintained – there is no exposure of foreign material to the bloodstream. See Appendix D for a summary of experience to date with the C-Pulse® System.

[11] [Virna, 2010]

C–PULSE DEVICE DESCRIPTION

THE SUNSHINE HEART C-PULSE® SYSTEM

The Sunshine Heart C-Pulse System is an implantable, non-blood contacting, non-obligatory, heart assist device. The system provides cardiac assistance through an extra-aortic balloon Cuff and ECG sense lead connected by means of a Percutaneous Interface Lead (PIL) to an external pneumatic Driver. The PIL is held secure externally, at the exit site, with a simple adhesive clip (C-Patch or similar) for immobilization of the external part of the PIL. The Driver is adjusted using a dedicated notebook computer (Programmer) with specialized software.

The Driver inflates and deflates the Cuff in counter-synchrony to the cardiac cycle. The C-Pulse System has been designed to have simple, effective and safe implantable components (the Cuff and PIL) and external wearable components (the Driver and C-Patch).

The system consists of the following primary components:

- The Cuff is an implantable balloon assembly. The Cuff is pre-shaped to wrap around the ascending aorta. The balloon is inflated and deflated rhythmically in counterpulsation to the heart to assist it to pump blood more efficiently. Counterpulsation on the ascending aorta is efficient because the blood displacement is "unidirectional," and the diastolic and pre-systolic pulse wave propagations versus cardiac systole are well matched. The Cuff does not contact the blood and hence there is; 1) a reduced risk of thromboembolic events, 2) no requirement for cardiopulmonary bypass during the surgery and 3) no requirement for anticoagulation medications related to the device. The C-Pulse System is non-obligatory and is predicated by a long history of counterpulsation therapy. It is intended to provide long term cardiac assistance to improve the patient's quality of life. The ascending aorta presents a minimal risk of disease, has a large capacitance, no branches and is of a predictable helical shape. The aorta is screened using CT scanning to ensure there is no calcification or other significant disease. Three Cuff sizes are available to fit aortae of diameter 28 to 42 mm. The aortic size range and Cuff design have been determined following studies of CT and MRI scans of cardiac patients and clinical experience with C-Pulse System.
- The Percutaneous Interface Lead (PIL) is a separate, exchangeable, silicone percutaneous catheter used for connecting the implanted C-Pulse Cuff and a commercial off-the-shelf ECG sense lead to the C-Pulse Driver. The PIL has a wire-wound silicone-coated construction designed to minimize cross-section area of the lead dual lumen catheter with a gas lumen and an ECG conduction lumen. The PIL is designed to be replaceable with relatively simple surgery in the case of intractable skin infections at the exit site or damage to the Patient Connector. The external PIL connector has a water-tight cap that can be used whenever the C-Pulse System is disconnected, such as for showering.
- C-Patch is a disposable product designed to immobilize the Percutaneous Interface Lead (PIL) at the skin exit site while allowing for connection, disconnection and capping of the patient connector, as well as cleaning and dressing around the exit site. The C-Patch is intended to be worn as long as the C-Pulse System is in place.

- The Driver is an external controller and pump that inflates and deflates the Cuff by means of the PIL. The Driver coordinates inflation timing to the R wave of the ECG signal conducted by the PIL to the Driver. The Driver can be either battery powered to allow ambulation or AC powered to allow for convenient battery management. The Driver (including Battery Pack and Carry Bag) is ergonomically designed to be worn in a shoulder bag with alternative carrying options available. The Driver is programmed by clinicians using the C-Pulse Programmer and incorporates internal parameter validation in addition to the "verification" button used by the clinician to accept any parameter changes made during programming.
- The Programmer is a commercially available computer that operates using an application known as "The Programmer Software". The Programmer allows a physician to observe real time data, make adjustments to a Driver's programmable settings (parameters) and retrieve data from a Driver. The Programmer communicates with the Driver via an infra-red (IR) link.

SYSTEM FEATURES

C-Pulse® Allows Ambulation

It is vital for a device intended to restore a heart failure patient's quality of life that the device can allow the patient to ambulate and to be discharged home. A single battery is used and is easily exchanged and re-charged. The Driver is placed into one small carry bag, for carrying over the shoulder. The Driver has a cable that allows the Driver to be comfortably used in bed. To avoid twisting in the line, the cable can be disconnected to allow it to coil appropriately.

Non-blood contacting

The non-blood contacting feature of the C-Pulse® System is unique for mechanical circulatory support devices. No foreign body material is in the blood stream and thus the risk of blood clotting within the device mechanism is eliminated. There is no requirement for use of anti-coagulants with the C-Pulse® System.

Non-obligatory

The non-blood contacting feature of the C-Pulse® System also allows the device to be intermittently turned off as tolerated. This allows the patient freedom for personal hygiene. The non-obligatory feature of C-Pulse® System is essential in improving the patient's quality of life and safety. To facilitate the analysis of the therapeutic effect, it is desired that the system be used all the time. The patient must limit disconnection to a minimal amount of time allowed for personal convenience such as hygiene. During the trial period, the patient must not disconnect for longer than 15 minute intervals. The C-Pulse® therapy is intended to facilitate remodeling of the patient's heart over time with chronic use. Although each patient will have a unique progression of heart failure, the device must remain on in order to facilitate having adequate level of therapy to assess the benefits of the chronic therapy and the potential to minimize the progression of heart failure. The Driver records usage and will be monitored throughout the course of the trial.

INDICATIONS FOR USE AND INTENDED USE

The C-Pulse® System is indicated for use in patients with moderate to severe heart failure while on optimal heart failure drug and on device therapies. The C-Pulse® System is intended to relieve the symptoms of heart failure, improve quality of life and cardiac function, and reduce the need for heart failure hospitalization. It is intended for use in hospital and at home. It is not intended as a replacement for heart function; it is not life sustaining or life-supporting therapy. It does not preclude the use of other heart failure therapies, such as valve surgery, heart transplantation or LVAD.

SUMMARY OF IMPLANT PROCEDURE

The C-Pulse® Cuff and Sense Lead are implanted through a chest incision without the use of cardiopulmonary bypass. Only a small pericardiotomy is required, limiting the potential for bleeding and for post-operative adhesions. The ascending aorta is isolated and its circumference measured. The circumferential length is noted on the pre-marked wrap. The Cuff is passed around the aorta such that the inflating aspect of the Cuff is positioned on the outside curvature. The Cuff is then checked to fit the aorta conformably and that the circumferential marks are appropriate prior to securing of the wrap with sutures. Pre-loaded interrupted 'mattress' sutures are placed through the tail of the Cuff at the appropriate circumferential marks with the Cuff 'open', and such that the inflation chamber of the Cuff is always visualized. A bipolar epicardial ECG Sense Lead is placed on the heart, most preferably at the left ventricular free wall. The gas line of the Cuff is trimmed to length and it and the ECG Sense Lead are attached to the intra-corporeal "Y-connector" end of the Percutaneous Interface Lead. The Percutaneous Interface Lead is then tunneled out over the abdomen, the extra-corporeal end of the Lead having a Patient Connector permanently attached. Alternatively, the lines may be tunneled to an intermediary incision for connection, particularly if a less invasive surgical technique (sternal-sparing) is used. The Percutaneous Interface Lead is designed to be exchanged or removed if required, the latter eliminating the exit site. If removal occurs, the Cuff and Sense Lead will remain within the thorax with the gas line of the Cuff and the connector of the Sense Lead capped off and accessible with minimal surgery in the subcutaneous tissue of the abdominal area.

STUDY DESCRIPTION

DESIGN

The study is a prospective, randomized, multi-center trial designed to demonstrate the safety and efficacy of the C-Pulse® System in relieving heart failure symptoms in patients with ACC/AHA Stage C, NYHA Class III to ambulatory Class IV heart failure. Reduction in heart failure symptoms will be demonstrated by increased freedom from heart failure related hospitalization or death in subjects implanted and treated with the C-Pulse System as compared to a concurrent, randomized control group receiving standard optimal medical therapy (OMT).

Patients will be enrolled into the trial upon providing informed consent. Procedures related directly to the study must not be performed prior to informed consent. Following confirmation of subject eligibility, subjects will be randomized to one of two treatment arms, Treatment or Control, in a 1:1 allocation utilizing a random permuted block design stratified by study center. The Treatment group subjects will receive the C-Pulse® System with immediate therapy following implant and OMT while the Control group will continue on OMT. The subjects will not be allowed to cross-over from the assigned group (i.e. a control will not be allowed to receive a C-Pulse). If a treatment subject is explanted, it will be reported in the study analysis per the statistical methods section.

This study will include up to 40 centers in the US and potentially some Canadian centers. The study population will include 388 patients. All subjects who meet eligibility requirements and sign study consent will then be randomized following the baseline testing completion. The follow-up period will be for a minimum of 12 months to assess the safety and efficacy. To facilitate the analysis of the therapeutic effect, it is desired that the system be used all the time. The subject must limit disconnection to a minimal amount of time allowed for personal convenience such as hygiene. The Driver logs subject usage automatically and stores this usage into the system files.

Subjects will be followed for up to five years.

If a subject undergoes anesthesia for the purpose of C-Pulse implantation but does not receive a C-Pulse System, the subject will be followed for 30 days for safety or until they are discharged, whichever occurs first.

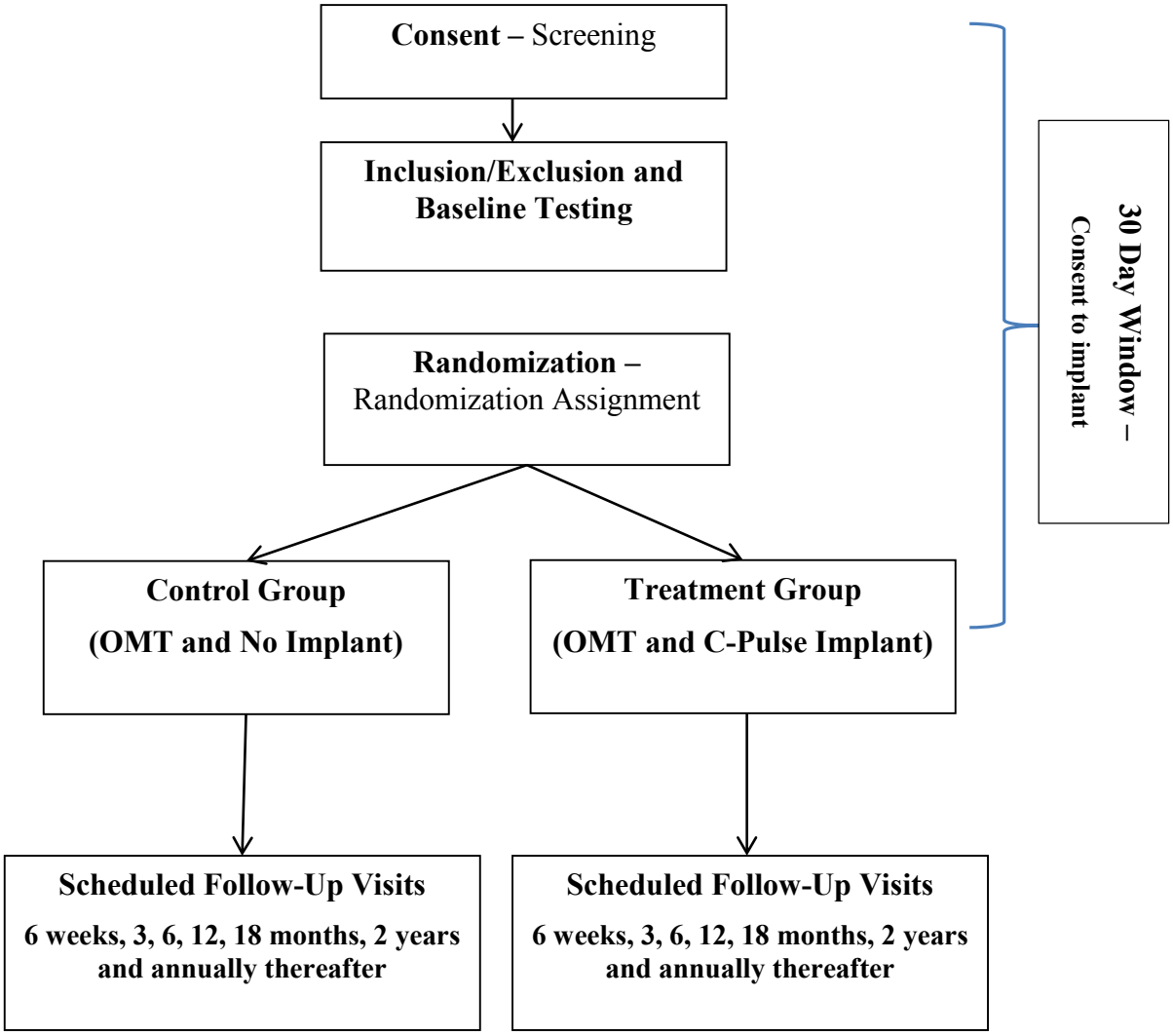

Figure 1. Study Design Flowchart

Patients will be enrolled into the trial upon providing informed consent. Each subject will be randomized after meeting the Eligibility Criteria and completion of baseline testing. Due to time required for baseline testing and scheduling of implant, sites will manage these items within the 30 day window as suited for the individual institution and patient. Procedures related directly to the study must not be performed prior to informed consent. Data collection will be noted prior to implantation of the device and at six months following implant, then long term at 12 and 18 months followed by annually post-implant for five years. Serious adverse events (SAE) will be collected throughout the study until study closure and will be adjudicated by an independent Clinical Event Committee (CEC).

Progress reports of the clinical outcomes will be reviewed by the DSMB after randomization of forty (40) patients and at least twice annually based on study progress. A progress report will be sent to FDA for review as specified in the Statistical Methods and Data Analysis section.

The total duration of the study including the enrollment and 12 month follow-up is expected to be approximately 36-42 months.

OBJECTIVES

Primary Objectives

The primary objectives of the study are to demonstrate the safety and efficacy of the C-Pulse therapy as compared to OMT. Refer to the section on Statistical Methods and Data Analysis for a detailed discussion of the definitions and methodology.

1. Primary Efficacy Objective:

   To demonstrate the superiority of the C-Pulse therapy in increasing survival free from worsening heart failure resulting in hospitalization, LVAD implantation, cardiac transplantation or death as compared to OMT.

2. Primary Safety Objective:

   To demonstrate the safety of the C-Pulse System by evaluating freedom from serious adverse events that are adjudicated as definitely related to device, therapy or procedure and resulting in either surgical intervention or death.

Secondary Objectives

The secondary objectives are as follows:

1. To demonstrate the superiority of C-Pulse therapy as compared to the OMT Control in improvement in 6 Minute Hall Walk score at 12 months post-randomization.
2. To demonstrate the superiority of C-Pulse therapy as compared to the OMT Control in improvement in 6 Minute Hall Walk score at 18 months post-randomization.
3. To demonstrate the superiority of C-Pulse therapy as compared to the OMT Control in improvement in LVEF at 12 months post-randomization.
4. To demonstrate the superiority of the C-Pulse therapy as compared to the OMT Control in improvement in the total days alive out of the hospital for worsening heart failure through 12 months post-randomization.
5. To demonstrate the superiority of the C-Pulse therapy as compared to the OMT Control in improvement in the total days alive out of the hospital through 12 months post-randomization.
6. To demonstrate the superiority of C-Pulse therapy as compared to the OMT Control in improvement in KCCQ scores at 12 months post-randomization.

PATIENT SELECTION

Inclusion Criteria

Patients of both genders who satisfy all inclusion and exclusion criteria are eligible for this clinical study. Patients must meet the following criteria:

1. Left ventricular ejection fraction (LVEF) ≤ 35% (by transthoracic ECHO within 90 days prior to randomization)

2. ACC/AHA Stage C and NYHA III to ambulatory Class IV

3. Age ≥ 18 years

4. Must have cardiac resynchronization therapy (CRT) when clinically indicated, implanted ≥90 days prior to enrollment.

5. Must have an implanted cardio–defibrillator (ICD) when clinically indicated, implanted at least 30 days prior to enrollment.

   Note: If a subject is clinically indicated for an ICD but refuses the ICD, he/she may be enrolled. Please document the refusal of the ICD in the medical record and the eCRFs.

6. Patient must be on stable, up-titrated medical therapy as recommended according to current guidelines (Circulation. 2009; 119 (12): 1977-2016) which minimally includes:

   - *ACE-inhibitor (ACE-I) at stable doses for 1 month prior to enrollment, if tolerated,*

     AND

   - *a beta blocker (carvedilol, sustained release metoprolol succinate, or bisoprolol) for 3 months prior to enrollment, if tolerated, with a stable up-titrated dose for 1 month prior to enrollment.*

   - *This also includes an Angiotensin II Receptor Blocker (ARB) at stable doses for 1 month prior to enrollment, if tolerated, when ACE-I is not tolerated.*

   - *Stable is defined as no more than a 100% increase or a 50% decrease in dose. If the patient is intolerant to ACE-I, ARB, or beta blockers, documented evidence must be available.*

- *In those intolerant to both ACE-I and ARB, combination therapy with hydralazine and oral nitrate should be considered. Therapeutic equivalence for ACE-I substitutions is allowed within the enrollment stability timelines.*

- *Aldosterone inhibitor therapy should be added. Eplerenone requires dosage stability for 1 month prior to enrollment.*

- *Diuretics may be used as necessary to keep the patient euvolemic.*

7. Functional limitation due to heart failure as defined by a 6 Minute Walk test of ≥ 175 ≤ 375 meters, measured within 30 days prior to randomization

8. At least one hospitalization for decompensated heart failure as defined below, while on heart failure medications, within 12 months prior to randomization or BNP level > 300 or NTproBNP > 1500

   Heart failure related hospitalization is defined by the following:

   - *signs and symptoms of worsening heart failure;* ***and***

   - *treatment with intravenous heart failure therapy (including but not limited to diuretic or inotropic therapy)* ***and***

   - *a minimum of one date change in the hospital*

9. Patient understands the nature of the procedure and on-going device therapy, is willing to comply with associated follow-up evaluations, and provide written informed consent prior to the procedure.

Exclusion Criteria

1. Any evidence, as assessed within 90 days prior to enrollment, of either:

   a. Ascending aortic calcification on posterior-anterior or lateral chest x-ray

   b. Calcific ascending aortic disease as detected by non-contrast CT scan

   c. Ascending aorto-coronary artery bypass grafts, history of aortic dissection, Marfans disease or other connective tissue disorder or repaired aortic coarctation

   OR

   d. Has had an ascending aortic composite graft or root replacement

2. Aorta not conforming to specified dimensional constraints defined by CT scan, most specifically mid ascending aortic outside diameter less than 28 mm or greater than 42 mm

3. Inotrope dependence – inability to wean from inotropic therapy
4. ACC/AHA Stage D heart failure or non-ambulatory NYHA Class IV subject
5. Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, pericardial disease, amyloidosis, active myocarditis, or technically challenging congenital heart disease
6. Clinical signs of severe right heart failure assessed by TAPSE <1.5cm or severe right heart failure precluding LVAD implantation.
7. Reversible cause of heart failure that may be remedied by conventional surgery or other intervention
8. Moderate to severe aortic insufficiency (≥ 2+)
9. Severe mitral or tricuspid valve disease
10. ST elevation myocardial infarction (STEMI) within 30 days prior to randomization
11. Cardiac surgery within 90 days prior to randomization
12. Prior cardiac transplantation, left ventricular reduction surgery, passive restraint device or surgically implanted left ventricular assist device
13. Anticipated concomitant cardiac surgical procedure
14. Estimated Glomerular Filtration Rate < 30 mL/min using the Cockroft-Gault formula within 30 days prior to enrollment; or the need for acute or chronic renal replacement therapy (e.g. chronic dialysis) within 90 days prior to enrollment
15. Evidence of intrinsic hepatic disease as defined as biopsy proven liver cirrhosis; or liver enzyme values (AST, ALT or total bilirubin) that are > 3 times the upper limit of normal within 30 days prior to randomization
16. Patient has severe intrinsic pulmonary disease in judgment of the investigator
17. Body Mass Index (BMI) < 18 or > 45 kg/m2
18. Suspected or active systemic infection
    a. Within 14 days prior to randomization and
    b. Evidenced by positive culture, antibiotics for empiric treatment or elevated WBC > 12K and temperature >38º C
19. Stroke or transient ischemic attack (TIA) within the 90 days prior to randomization; or > 80% carotid stenosis as determined by carotid Doppler ultrasound within 90 days prior to randomization
20. Positive serum pregnancy test, for women of childbearing potential
21. Patient expected survival is less than 2 years

22. Patient is currently enrolled or has participated in the last 30 days in another therapeutic or interventional clinical study
23. Patient demonstrates compliance issues that in the opinion of the investigator could interfere with the ability to manage the therapy (i.e. uncontrolled diabetes, mental health issues, etc.)
24. Patient is not a good surgical candidate

INVESTIGATIONAL CENTER INFORMATION

Number of Sites

It is intended that up to 40 centers in the US and potentially some Canadian centers will participate in this clinical evaluation.

Investigator Agreement/Financial Disclosure

An Investigator Agreement along with a Financial Disclosure Form must be signed by the investigator and returned to Sunshine Heart, Inc. before commencement of the study at a clinical site.

Curriculum Vitae including the investigator's current position and title and medical license will also be required from each investigator and co-investigator(s) participating in this study.

Investigational Review Board

Investigational Review Board approval of the clinical study must be received and the contents of the approval letter approved by Sunshine Heart Inc. before commencement of the study at a clinical site. Required contents are as follows:

- Name of study
- Name/address of IRB
- Date of approval
- Sufficient identification of version/date of the Protocol, amendments and Informed Consent
- An IRB member list or ID number must be provided to Sunshine Heart Inc.

Access to Center and Study Materials

The investigator(s) or his/her delegate(s) and the study coordinator(s) must be accessible to the Sunshine Heart Inc. monitoring staff or designee and Clinical Team. This accessibility is of particular importance for completing and/or correcting the data provided. For the study monitors, access to the patient records for source data verification will need to be granted and prepared prior to the monitoring visit.

Confidentiality

All information generated during the trial is considered highly confidential and must not be disclosed by any method to persons not directly involved in the trial without prior consent from the sponsor or sponsor designee.

Attending Investigator Meetings or Conference Calls

Investigator and/or study coordinator meetings or conference calls may be held to discuss the study protocol, device training, study data or other aspects of trial progress and management. Interim meetings or teleconference calls will be organized as needed to discuss relevant study issues. The investigator must agree to attend these meetings and/or conference calls or send a co-investigator if they are unable to attend.

Required Equipment

The following study equipment will need to be available at each center to support the implant and follow-up of the C-Pulse® System:

- The C-Pulse® System
- Standard cardiac surgery required equipment and facility
- Echocardiography equipment
- CT Scanning equipment

Supply of Study Materials and Device Accountability

All investigators will receive the investigation plan, case report forms and study agreement documents.

Sunshine Heart's Clinical Affairs Department will control the supply of investigational devices, software, and administrative forms necessary to conduct and administer the study. A limited amount of investigational product will be distributed to approved investigators. A site must be approved to store equipment at their center. Approval will require the center to have made provisions for strict control of the investigational devices.

A record shall be maintained at each center to track investigation product information including, but not limited to, the model, serial number of each investigational product, the date used and final disposition. Completed implant data records and device tracking records will be reviewed as part of the device tracking and ongoing site monitoring. Based upon return and review of these forms, additional clinical product will be supplied to the respective investigators within prescribed study limits. Labeling is packaged with each device.

Criteria for Early Termination or Suspension

Reasons for possible suspension of a clinical investigator or a clinical center from enrollment of further patients may at the sponsor's discretion include but are not limited to the following:

- Failure to obtain informed consent
- Non-compliance to the inclusion/exclusion criteria
- Failure to follow through with Investigational Review Board (IRB) for approval or continuation of the clinical study
- Inadequate device tracking or off-label investigator device use
- Failure to follow-up patients per scheduled follow-ups

- Failure to submit data in a timely manner
- Failure to follow-up with findings on a monitoring report

Note that any subjects previously enrolled will continue to be to be followed at this institution by the investigator or a named co-investigator.

Laboratory Accreditation and Normal Values

Appropriate accreditation for all laboratories to be used in the study must be provided to the sponsor. Throughout the study, the Investigator must provide documentation of all renewals of accreditation. The ranges of values considered normal for the laboratory tests being performed for the study must be provided to Sponsor in order to facilitate pooling of the data.

PROCEDURES

Patient Informed Consent and Enrollment

Prior to enrolling patients, each investigational center IRB will be required to approve the study Investigation Plan and the Patient Informed Consent. In addition, patients will be required to provide written informed consent for enrollment.

Patients will undergo a pre-implant baseline assessment to ensure they meet the inclusion and exclusion criteria prior to randomization. The baseline assessment must occur within 30 days prior to implant. Patient informed consent must be signed prior to conducting any screening or baseline testing procedure performed solely for study purposes. A screening number will be assigned upon consent. To minimize the burden to the patient, data collected as standard of care and not for the specific reason for assessing study eligibility may be used for baseline data points as outlined in the informed consent. These tests will suffice for the respective portion of the baseline dataset if collected within the pre-implant evaluation prior to randomization.

When a subject has met all Inclusion/Exclusion Criteria for the study, he/she will be randomized and assigned a randomization number by the center. The treatment subjects must proceed to implant within the window (≤30 days from consent to implant).

If the subject does not meet the inclusion/exclusion requirements, he/she will be study exited.

In accordance with the ethical principles that have their origin in the Declaration of Helsinki, each subject must be informed about the study and the patient or legal representative must sign and date an agreement acknowledging that participation in the study is voluntary. The Patient Informed Consent Form will be provided to the patient in the language he/she is able to read and understand. (Refer to Appendix E for the sample Consent Forms). The original signed Informed Consent will be retained in the individual Participant Study folders, and copies of the signed Informed Consent Form will be provided to the patient and to the hospital medical records of the patient.

Patients shall be consented for follow-up to five years.

Subject Withdrawal or Loss to Follow-Up

In the event a subject chooses to withdraw from the clinical study, the investigational site should attempt to ensure that any adverse events are resolved and documented as such. A Study Exit record must be completed and the subject will no longer be followed in the clinical study.

In the event the subject becomes lost to follow-up, the investigational site should make two documented attempts to contact the subject. A Study Exit record must be completed and the subject will no longer be followed in the clinical study.

Data Collection Overview

A review of patient files is required to determine preliminary eligibility according to patient inclusion and exclusion criteria. Baseline data including functional tests must be collected no more than **30** days prior to randomization. Baseline imaging such as echo and CT scans must be collected no more than 90 days prior to randomization. See the data collection table for details.

Follow-up data will be collected at the time of implant, hospital discharge, at planned follow-ups (6 week, 3, 6, 12, 18-month and annually from the implant date thereafter up to 5 years). All serious adverse events will be collected throughout the study until closure.

All study subjects will follow the prescribed follow-up scheduled despite randomization. Day 0 for the treatment group will be the day of implant. Day 0 for the Control Group will be the day of randomization. Each group will continue with optimal medical therapy for the duration of the study, including all standard of care medications and treatments including transplant, VAD, etc. If the subjects are transplanted or placed on another device they will be censored from the primary endpoint analysis and study exited. Subjects implanted with the C-Pulse will be followed until device removal. If the PIL is explanted and not replaced, the subject will be followed for safety until removal of the entire system.

Data will be collected via electronic data capture (EDC) screens referred to as e-case report forms (eCRFs). Echocardiogram tapes and digital storage media must be documented in the patient medical record for source documentation.

Table 1, below outlines the data collection with the appropriate follow-up time windows.

Table 1. Follow-up Windows

Evaluation	Time Window
Pre–Implant Evaluation	No more than 30 days prior to implant
Randomization	Post Baseline Testing and Pre-Implant
Implant	Day 0 (Treatment Group) – Implant Day 0 (Control Group) – Randomization
Pre-Discharge	Within 36 hours prior to discharge
6 – week follow-up	Days 42 ± 7 Post-Implant
3 – month follow–up	Days 90 ± 14 Post-Implant
6 – month follow–up	Days 180 ± 30 Post-Implant
12 – month follow-up	Day 365 ± 30 Post-Implant
18 – month follow-up	Day 540 ± 30 Post-Implant
Annually Post-Implant	Years 2, 3, 4, and 5 Post Implant (± 30 days of anniversary)

Testing should be conducted at the investigational site. The data collection criteria are summarized in Table 2.

Table 2. Data Collection Summary

Data Collection Requirements							
	Pre-Implant (Baseline)	**Implant**	**Pre-Discharge[2]**	**6 week**	**3 month**	**6, 18 month**	**Annually[1] Yr 1-5**
PATIENT ELIGIBILITY	X						
GENERAL							
Demographic Data	X						
Medical History	X						
General Physical Exam	X	X	X	X	X	X	X
Concurrent Cardiac Meds	X	X	X	X	X	X	X
Weight (Height at enrolment)	X		X	X	X	X	X
Pregnancy test (if applicable)	X						
VITAL PARAMETERS							
Heart rate - (ECG pre-implant)	X		X	X	X	X	X
Blood pressure	X		X	X	X	X	X
Temperature	X		X	X	X	X	X
CARDIOPULMONARY[3]							
CT aorta	X						Year 1
Chest X-Ray	X						X
ECHO	X				X		X
CPX Testing – Sub Study Only	X						X
QUALITY OF LIFE							
NYHA Classification	X				X	X	X
MLWHF/ KCCQ	X				X	X	X
Six Minute Walk /with Gait Speed	X				X	X	X
HEMATOLOGY							
Hemoglobin	X		X		X	X	X
Hematocrit	X		X		X	X	X
Platelet count	X		X		X	X	X
White cell count	X		X		X	X	X
BIOCHEMISTRY							
Serum sodium	X		X		X	X	X
Serum potassium	X		X		X	X	X
Serum creatinine	X		X		X	X	X
BUN	X		X		X	X	X
BNP or NTProBNP	X					X	X
Serum bilirubin	X		X		X	X	X
Serum ALT	X		X		X	X	X
Serum AST	X		X		X	X	X
Estimated GFR	X						
IMPLANT DETAILS		X					
DEVICE LOG		X			X	X	X
DISCHARGE CHECKLIST			X				

1 Annually post-implant for years 2-5
2 At Discharge - within 36 hours prior and as close to discharge as possible (see Appendix)
3 Imaging may be included to Baseline data collection from within 90days prior to implant.

Summary of Required Testing

Data will be collected and recorded into the web-based database. Paper copies of the database pages (eCRFs) will be made available for the sites.

Device Performance Data – (at all scheduled follow–ups and any clinic visit)

Device performance parameters shall be retrieved following implantation on Day 1, at all follow-up periods. Parameters must be retrieved from the Driver using the Programmer and returned to the sponsor by means of web-based secure data upload.

- Device usage between follow-ups
- Cumulative device usage
- Driver Target Inflation Volume (TIV)
- Driver Inflation Hold Pressure (IHP)

Echocardiographic Testing (Baseline, 3, 12 month and annual follow-up visits)

A transthoracic echocardiography test will be performed at Baseline and at the 3, 12 months and annual follow-up visits.

Data will be recorded on the eCRFs, imaging and medical record report will be used for source documentation.

CT Scan (Baseline and 12 month follow-up visit only)

A 1-2 mm slice thoracic CT scan is required at Baseline and at 12 month visit only (12 month visit should be ECG Gated) for treatment subjects. Control subjects only require a baseline CT scan.

Data required from the procedure include:

- Sagittal and coronal images shall be reconstructed at mid-systole and mid–diastole to measure narrowest mid ascending aortic luminal dimensions (i.e. with Cuff inflated and deflated).

Assessment will be made of the aortic diameter and presence of any calcific aortic disease. Data will be recorded on the eCRFs, imaging and medical record report will be used for source.

Six Minute Hall Walk Test (Baseline, 3, 6, 12, 18 month and annual follow-up visits)

The subject must perform a six-minute hall walk test (6MHW) at Baseline and one 6MHW test at 3, 6 12, 18 months and annually thereafter with the C-Pulse. Detailed information is included in the Appendix H.

Two 6MHW tests will be performed at the Baseline visit with at least one hour between the two tests.

During each test, a record will be taken for the time to complete the first 15 feet of the 6MHW as a frailty measure. The time taken for the first 15ft and the distance traveled in 6 minutes will be recorded on the eCRFs and the source records.

Data will be completed on the eCRFs, source documentation will be the worksheet provided by Sunshine Heart Inc. along with the final measurement recorded in the medical record.

Quality of Life Assessment (Baseline, 3, 6, 12, 18 month and annual follow-up visits)

The subject must complete the Minnesota Living with Heart Failure Questionnaire (MLWHF) and the Kansas City Questionnaire (KCCQ) at Baseline, 3, 6, 12, 18 month and annual visits thereafter.

Data will be completed on the Baseline and Follow-up eCRFs. The eCRFs will be used as source documentation for the QoL questionnaires.

NYHA Class Assessment (Baseline, 3, 6, 12, 18 month and annual follow-up visits)

A clinician at each site shall complete the NYHA Classification at Baseline, 3, 6, 12, 18 month and annual visits thereafter.

Data will be completed on the eCRFs. The eCRFs will be used for source documentation.

Concomitant Cardiac Medications (Baseline, implant, pre-discharge, 6 week, 3, 6, 12, 18 month and annual follow-up visits)

All cardiac medications (including diuretics) will be recorded on the Medication eCRF. Doses are required for all cardiac medications including diuretics.

Data will be completed on the eCRFs. The medical record will be used for source documentation.

Clinical Procedures – Pre-implant through discharge

The hospitalization phase is divided into three major parts: (i) Prior to implant, (ii) Implant procedures, and (iii) Post–implant to discharge.

Pre-Implant Considerations

Medication therapy

Prescribed drugs are to be maintained until the time of surgery unless instructed otherwise by the anesthetist. Prophylactic anti-coagulation should be stopped. Pre-medications should be given in accordance with institutional protocol.

Cardiac Resynchronization Therapy (CRT)

Per the eligibility criteria a patient should not be enrolled earlier than 90 days following CRT implant. Patients enrolled with a CRT device must have the Cardiac Resynchronization Therapy continued during the follow up period. ICD therapy should remain activated except during the surgical implantation.

Planning for Device and Percutaneous Tube Positioning

Percutaneous Interface Lead exit site should be identified prior to surgery. Pay particular attention to the costal margins, belt line, and impact of sitting and standing and lying, and the exit site when wearing the Driver. The distance of the exit site from the costal margin should be considered in relation to the thickness of subcutaneous tissue in order to prevent the percutaneous tube from rubbing against the costal margin. Also consider patients who inject insulin into the abdominal area. Mark the exit site.

Antisepsis Prophylaxis

Please refer to the Infection Control Guidelines in the Appendices.

Implant Considerations

Implantation of the C-Pulse System will only occur with personnel trained by Sunshine Heart Inc. personnel or designees.

Note: Refer to the Instructions for Use (IFU) for the C-Pulse® Cuff, Percutaneous Interface Lead, Driver, Tunneler, C-Patch™ and C–Pulse® System which outline device preparation, implantation, and operation.

Post–Implant Considerations (prior to discharge)

1. Patient taken to ICU – driver may be disconnected for transport.
2. Extubate patient, when appropriate – move to the telemetry ward when appropriate.
3. Ensure both Drivers are configured with the same settings and verify function of both as above – optimizing settings occurs day 1-3 post-op.
4. Chest and other drains should be removed as soon as practical, at the discretion of the surgeon, and typically within 48 hours, depending on drainage.
5. Heart rates should be maintained below 120 bpm and MAP below 100 mmHg to allow optimal counterpulsation and minimize alarms from the Driver.
6. Blood sugars: An Insulin infusion, titrated to Q1–4hr blood sugar measurement will be established in patients with diabetes or other glucose intolerance until a regular diet and normal diabetic therapy can be re-introduced.
7. Active deep vein thrombosis management includes TED stockings, subcutaneous Clexane or similar and bed leg exercises.
8. Early mobilization and graduated physiotherapy is to be conducted as tolerated from day 1.
9. Heart failure medications should be re-started and drug doses titrated to clinical effect. Diuretics should be re-started immediately, and ACE inhibitors and beta blockers re-started once blood pressure has stabilized.
10. Refer to the infection control guidelines for management of in-dwelling lines and exit sites, etc.
11. Ongoing education to patient and care-givers on general hygiene e.g. regular hand washing and to treat percutaneous line gently and to avoid undue pulling, pushing or torsion.

12. Instruct patient to avoid sleeping on abdomen to avoid gas tube complications.
13. Educate patient and care-giver on how to operate the Driver, per the Patient Manual. Training of the patient and/or caregiver will be documented.

Hospital Discharge

Preparation

Educate patient and care-giver on how to operate and maintain the Driver. Provide the Patient with the C-Pulse® System Patient Manual and contact details for clinical personnel at the clinical site hospital. Refer to Appendix F for discharge checklist.

Discharge Criteria

Discharge should be based on the following criteria, which are based upon initial clinical experience in the US Feasibility study.

- Healing wounds, and with no signs of infection or sepsis
- Patient can walk 30 meters with the device without stopping due to shortness of breath/muscle fatigue/unsteady gait/pain
- Caregiver or patient demonstrates aseptic technique in changing exit site dressing
- Patient and caregiver independently demonstrate connection and disconnection of the Driver, changing and recharging batteries, and to understand and respond to the Driver alerts and alarms
- All scheduled pre-discharge testing is completed

The patient should not be discharged if any of the following issues are present:

- Unresolved system malfunction
- Back-up equipment is not available
- Unresolved adverse event that threatens patient safety
- Patient requires any treatment for disease, illness, mental or physical disability that cannot be provided outside the hospital

Post-Implant Follow-up Testing and Data Collection

Post-Implant Testing and Data Collection Summary

The complete reference list of post-implant testing and data collection that will be performed at each time point is included in Table 3.

Unscheduled Follow-up Visits

If subjects are seen between protocol-scheduled visits because of clinical symptoms requiring readmission, device reprogramming, etc. a follow-up form must be completed with all appropriate sections. In addition, all serious adverse events must be documented throughout the study.

System Modifications

Immediately contact Sunshine Heart clinical support team if a need is suspected for system modification (internal component or system replacement). In the event that the C-Pulse® System requires modification (e.g. Cuff or PIL) data collection must be recorded on the eCRFs along with an adverse event form. Modifications should be done only in communication with Sunshine Heart Inc. clinical personnel, unless the modification is a medical emergency, in which case, Sunshine Heart Inc. clinical personnel should be notified as soon as possible. In addition, the eCRF data collection must be completed documenting the removal of the existing device or component. The explanted C-Pulse® component(s) should be processed according to the Explant Handling Instructions and returned to Sunshine Heart Inc. or designee.

In the event of a system modification, including component removal, reposition or replacement of the entire C-Pulse® System, the follow-up schedule for the subject will remain unchanged (i.e. the subject should continue to be seen for follow-up and associated forms should be completed based on the original follow-up schedule). All serious adverse events should be reported and classified by the investigator. Additionally the CEC will provide further classification of adverse events.

Adverse Event Reporting

Overview

Data collection regarding serious adverse events will be collected throughout the study. Upon identification, the investigator completes the adverse event information via the Adverse Event eCRF. Sunshine Heart Inc. clinical personnel or designee may request further information from the investigator if necessary for review of the event with the Clinical Event Committee (CEC).

The following information will be collected in the database: the date of event onset, the relationship of the event to the implant procedure, device, concomitant medications, patient management, or therapy, other actions taken as a result of the event, and the outcome of the event.

Adverse Event Definitions

Serious Adverse Event is defined as an adverse event that[12];

a) Led to death

b) Lead to serious deterioration in the health of the subject, that either resulted in

   1. A life-threatening illness or injury, or
   2. A permanent impairment of a body structure or a body function, or
   3. In-patient or prolonged hospitalization, or
   4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

[12] ISO 14155:2011 section 3.37

c) Led to foetal distress, foetal death or a congenital abnormality or birth defect

(Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event)

Definitions are listed below for anticipated adverse events. The definitions are consistent with Version 2.2 adverse event definitions for the *INTERMACS*® registry with the exception of Major Bleeding which does not have a minimum standard of transfusion. Aortic Disruption has been added in addition to the *INTERMACS*® registry definitions as an additional screening for safety with respect to the C-Pulse unique application. Worsening Heart Failure has been added due to C-Pulse System not being a heart function replacement rather a heart assist device and based on the definition used by the CEC in the US Feasibility study.

Major Bleeding

An episode of suspected internal or external bleeding that results in one or more of the following:

1. death
2. re-operation
3. hospitalization
4. transfusion of red blood cells.

NOTE: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Cardiac Arrhythmias

Any documented arrhythmia that results in clinical compromise (e.g. oliguria, pre-syncope or syncope) that requires hospitalization or occurs during a hospital stay. Cardiac arrhythmias are classified as 1 of 2 types:

1) Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
2) Sustained supraventricular arrhythmia requiring drug treatment or cardioversion.

Pericardial Fluid Collection

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac output) and those without signs of tamponade.

Aortic disruption

Disruption to the intima of the ascending aorta. Disruption may be partial or complete (i.e. transmural), and the latter may result in contained or free rupture. Typically this would be documented initially by CT scan with or without contrast or by trans-esophageal echocardiography.

Hemolysis

A plasma-free hemoglobin value that is greater than 40 mg/dl, in association with clinical signs associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant. Hemolysis related to documented non-device-related causes (e.g. transfusion or drug) is excluded from this definition.

Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotranferease/ALT) to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

Hypertension

New onset blood pressure elevation greater than or equal to 140 mm Hg systolic or 90mmHg diastolic (pulsatile pump) or 110mmHg mean pressure (rotary pump).

Major Infection

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Percutaneous Site and/or Pocket Infection *(PIL Only)*

A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage or leukocytosis.

Internal Pump Component, Inflow or Outflow Tract Infection *(Cuff, ECG Lead and Gas line not including the PIL)*

Infection of the implanted C-Pulse Cuff or surrounding tissue (e.g. aorta) documented by positive site culture.

Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

Myocardial Infarction

Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction

The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following implant together with ECG findings consistent with acute myocardial infarction.

Non-Perioperative Myocardial Infarction

The presence at > 7 days post-implant of two of the following three criteria:

a) chest pain which is characteristic of myocardial ischemia,

b) ECG with a pattern or changes consistent with a myocardial infarction, and

c) Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

Neurological Dysfunction

Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). The NIH Stroke Scale (for patients > 5 years old) must be re-administered at 30 and 60 days following the event to document the presence and severity of neurological deficits. Each neurological event must be subcategorized as:

1) Transient Ischemic Attack (acute event that resolves completely within 24 hours with no evidence of infarction)

2) Ischemic or Hemorrhagic Cardiovascular Accident/CVA (event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study.

Psychiatric Episode

Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress requiring intervention. Intervention is the addition of new psychiatric medication, hospitalization, or referral to a mental health professional for treatment. Suicide is included in this definition.

Renal Dysfunction

Two categories of renal dysfunction will be identified:

Acute Renal Dysfunction

Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL **(in children,** creatinine greater than 3 times upper limit of normal for age) sustained for over 48 hours.

Chronic Renal Dysfunction

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

Respiratory Failure

Impairment of respiratory function requiring reintubation, tracheostomy or (for patients older than age 5 years) the inability to discontinue ventilatory support within six days (144 hours) post-implant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

Right Heart Failure

Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18 mmHg with a cardiac index <2.0 L/min/m2 in the absence of elevated left atrial/pulmonary capillary wedge pressure (greater than 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD implantation; or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after implantation.

Worsening Heart Failure

A heart failure event that does not require hospitalization but requires visit to Emergency Department or Unscheduled Visit to Clinic including the following (not counted as a primary endpoint event):

- Signs and symptoms of worsening heart failure; and
- Treatment with intravenous heart failure therapy (including but not limited to diuretic or inotropic therapy)

A heart failure event requiring hospitalization including the following:

- Signs and symptoms of worsening heart failure; and
- Treatment with intravenous heart failure therapy (including but not limited to diuretic or inotropic therapy); and
- A minimum of one date change in the hospital or emergency room

Note: Signs and symptoms of worsening heart failure include but are not limited to shortness of breath, persistent cough or wheezing, edema, tiredness, and fatigue.

Arterial Non–CNS Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

1) standard clinical and laboratory testing

2) operative findings

3) autopsy findings

This definition excludes neurological events.

Venous Thromboembolism Event

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Wound Dehiscence

Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

Other

An event that causes clinically relevant changes in the patient's health (e.g. cancer).

Adverse Event Classification

All reported serious adverse events will be classified by the investigator, based on the following categories:

- Relatedness (i.e. device, procedure, concomitant medication, patient management or therapy);
- Status (i.e. ongoing or resolved)

Device Related

An adverse event will be considered device related if it is a direct result of, or is affected by the presence (intended or otherwise) of the investigational device.

Procedure Related

An adverse event will be considered procedure related if it is a direct result of the implant, explant or modification procedure, which cannot be directly attributed to any particular device or implant tool.

Patient Management Related

An adverse event will be considered related to patient management if it is a direct result of the medical complexities and decision making involved in managing co-morbidities.

Concomitant Medication Related

An adverse event will be considered related to concomitant medication when it is reasonable to believe that the event is directly associated with medications used in conjunction with the investigational device and it is not otherwise specific to the device, procedure or patient management.

Therapy Related

An adverse event will be considered therapy related if it is a direct result of, or is affected by the therapy delivered by the device not just the presence (intended or otherwise) of the investigational device.

Unavoidable Events

The events listed in Table 3 are considered minor and if the onset occurs within the timeframe specified, are not subject to adverse event reporting.

Table 3. Unavoidable Events

Event Description	Timeframe (post–implant)
Anesthesia related nausea/vomiting	24 hours
Low-grade fever (<102 degrees F)	48 hours
Minor incision/exit site pain	72 hours
Minor, localized tenderness, swelling, oozing, etc. at incision sites	72 hours
Early post-operative pain associated with endotracheal tube placement and mechanical ventilation	72 hours
Electrolyte imbalance without clinical sequelae	72 hours
Systolic and diastolic blood pressure changes that do not require treatment or intervention	On-going
Chest tube drainage or blood loss not requiring intervention and hematocrit remaining above 25%	72 hours
Sinus bradycardia and tachycardia that does not require intervention	On-going

Adverse Event Reporting to IRB and Regulatory Agencies for Unanticipated Device Events

The investigator must report any unanticipated adverse device effects (UADE) to the Sponsor (Sunshine Heart) and IRB within 10 days after the investigator first learns of the event. The Sponsor must report any UADE to the regulatory agencies, IRBs and all investigators within 10 days of receipt of notice of the event.

An **unanticipated adverse device effect** is defined as:

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects. [21 CRF 812.3 (s)]

Device Deficiency

A device deficiency is defined as; inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety and performance. Device deficiencies must be reported on a device deficiency eCRF.

(Note: Device deficiencies include malfunctions, use errors, and inadequate labelling). [ISO 14155:2011]

Subject Deaths

All subject deaths must be documented in the database. If the subject dies during the study, notify the Sunshine Heart Inc. field support personnel as soon as possible upon first learning of the death. Follow any IRB requirements for reporting of deaths or adverse events.

In the event of a subject death, efforts should be made to retrieve the implanted device and to obtain an autopsy in order to assess the state of the heart and aorta. A sample of the aorta both beneath and adjacent the C-Pulse® Cuff should be collected for analysis. Please call Sunshine Heart Inc. Clinical Support for more instruction. For subjects who do not undergo autopsy, written documentation from the investigator will be required regarding circumstances as to why an autopsy was not performed. The device will be analyzed by local staff and Sunshine Heart Inc. Clinical Support personnel according to a standardized device retrieval protocol.

A death summary and an autopsy report are required. The report should be sent to Sunshine Heart Inc. upon completion and will be provided to the adjudication committee.

Explant Handling and Final Device Disposition

Promptly call Sunshine Heart Inc. Clinical Support for instruction regarding Explant Handling. Cultures should be taken from the device implantation site along with visual analysis and photographs when possible. If a piece of aortic tissue is available from underneath or adjacent to the C-Pulse Cuff, please send to pathology for histological studies. Explanted products should be returned to Sunshine Heart Inc. for analysis.

Report all associated adverse events. Update the device tracking records with all products. If the device is not returned to Sunshine Heart Inc., justification must be provided in the log.

Subject Withdrawal and Study Exit

A Study Exit record shall be completed if subject is unable to or refuses to continue participation in the study. Notify the Sunshine Heart clinical support team as soon as possible upon learning of a subject withdrawal/study exit.

If the subject fails to comply with follow-up visits, the study center must make repeated attempts to contact the subject. Each attempt to contact the subject must be documented in the subject's records and in the database.

If the subject officially withdraws from the study, the investigator will document the reason for withdrawal and indicate any relationship of the withdrawal to the study or the device on the eCRF.

If a subject withdraws from the study at any time, there will be no penalty or loss of future medical care.

STATISTICAL METHODS AND DATA ANALYSIS

Analysis Population

All randomized subjects will be included in the evaluation of the primary efficacy objective. Subjects will not be allowed to cross-over. All subjects implanted with the C-Pulse System will be included in the evaluation of the primary safety objective. In the event a randomized subject does not receive the implant or does not receive the randomized therapy, the subject will be analyzed according to the randomized assignment for the primary analyses. Additional supporting analyses of the primary efficacy endpoint will be conducted (as treated and per-protocol) which exclude subjects who do not receive the randomized treatment or those with major protocol deviations. The defined analysis cohorts are:

- Intent to treat: All randomized subject irrespective of treatment actually received (primary efficacy analysis)
- As treated: All randomized subjects receiving treatment as randomized
- Per protocol: All randomized subjects without major protocol deviations

Primary Efficacy Endpoint

The primary efficacy endpoint is defined as freedom from worsening heart failure related hospitalization, LVAD implant, heart transplant, and death.

The primary efficacy endpoint includes all occurrences of worsening heart failure events and will be analyzed utilizing a multiple failure time analysis.

Hypotheses

H_0: HR=1,

H_A: HR≠1,

where HR is the hazard ratio; the ratio of the C-Pulse treatment group worsening heart failure event hazard relative to the Control group worsening heart failure event hazard. This is designed to demonstrate that C-Pulse® therapy increases the freedom from worsening heart failure events as compared to Control as evidenced by a HR that is less than 1 and the upper bound of the two-sided 95% confidence interval for the HR excludes 1. All occurrences of worsening heart failure events will be included in the primary endpoint analysis. Details of the analysis methods can be found in the Statistical Analysis Plan.

Primary Efficacy Endpoint Sample Size

Sample size was estimated using SAS v9.2 software under two sided test for a difference in freedom from worsening heart failure. For the purposes of sample size estimation, a time to first event analysis was used to provide a conservative estimate of the required number of events and subjects. The minimum required sample size and total number of worsening heart failure events was calculated under the following assumptions:

- Significance level = 0.05
- Power = 0.80
- Proportion for 6 month freedom from worsening heart failure event in Control group = 0.72
- Underlying treatment effect on the hazard ratio scale: HR = 0.70
- Accrual time of 2.5 years
- Minimum follow-up of 12 months
- 10% Attrition per year
- 1:1 allocation ratio

Under the above assumptions a total of 265 subjects with at least one worsening heart failure events are required to be observed to ensure adequate power which indicates a total of 388 subjects randomized. As the primary analysis will include all worsening heart failure events in a multiple event analysis, the power for the detection of a difference in freedom from worsening heart failure event may be greater than 80%.

Justification for Primary Efficacy Endpoint Sample Size Assumptions

There is no published study using the same endpoint in a similar heart failure treatment population. The MEDAMACS study has an enrollment population similar to the target population for the C-Pulse System Pivotal Trial and has an endpoint close to the C-Pulse System primary endpoint except that all-cause mortality is included. The study reports a 6-month survival free from LVAD implant, heart transplant or inotrope use of 64%. As this likely represents a higher event probability than the C-Pulse System primary endpoint, a higher freedom from event at 6 months was calculated assuming half the mortality events were not due to worsening heart failure. As the 6 month freedom from all-cause mortality estimate was 84%, an estimate for freedom from worsening heart failure event of 72% is chosen for the Control group estimate. The current proposed study was therefore powered to detect a 30% reduction in the probability of worsening heart failure event (an assumed hazard ratio of 0.70). The C-Pulse System Feasibility Study has an estimated freedom from worsening heart failure event of 95.0% at 6 months and 72.4% at 12 months, however, as this is based on 20 subjects the confidence limits of the estimate are wide and it is therefore not a desirable estimate on which to entirely base the sample size assumptions.

The study is powered to detect a statistically significant difference in freedom from worsening heart failure events favoring Treatment over Control. Worsening heart failure events represent an objective measure of worsening heart failure and an observed reduction would represent a clinically significant and meaningful improvement in heart failure subjects' health. The planned secondary analyses will provide supporting evidence of superiority in the improvement of QOL and other clinical parameters demonstrating the effectiveness of C-Pulse therapy in relieving heart failure related symptoms and associated morbidity.

Primary Safety Endpoint

The primary safety endpoint is 12 month freedom from serious adverse events that are adjudicated definitely related to device, therapy or procedure and resulting in either surgical intervention or death. All serious adverse events that are adjudicated by CEC to be definitely related to device, therapy or procedure and result in either surgical intervention or death will be included in the analysis. Events will be reported by number of event and proportion of subjects with event along with the ninety-five percent binomial exact confidence limits. Only first event counts towards the endpoint for each subject.

The proportion of C-Pulse® subjects free from serious adverse events that are adjudicated definitely related to device, therapy or procedure and result in surgical intervention or death through 12 months following implant and will be compared to the performance goal (PG) of 0.60.

The hypotheses are:

H_0: $\Pi \leq PG$,

H_A: $\Pi > PG$,

where Π is the 12 month freedom from serious adverse events that are definitely related to device, therapy or procedure and resulting in either surgical intervention or death and PG is the performance goal. If the lower, two-sided, 95% confidence bound is greater than 0.6 the objective will be met.

Primary Safety Endpoint Sample Size

Sample size was estimated for a combined freedom from serious adverse events adjudicated definitely related to device, therapy or procedure resulting in surgical intervention (to repair, replace or remove the implanted device) or death. The minimum required sample size and total number of device related deaths and device related surgical intervention events was calculated under the following assumptions:

- Significance level = 0.05
- Power = 0.80
- 12 month freedom from serious adverse events definitely related to device, therapy or procedure resulting in either surgical intervention (to repair, replace or remove implanted device) or death event of 70%.
- Minimum follow-up of 12 months

Under the above assumptions a minimum of 182 subjects are required.

Justification for Primary Safety Endpoint Sample Size

The basis for the primary safety endpoint is from previous studies that had evaluated devices specific to surgical intervention and death.[13,14] The IDE study for the HeartWare® Ventricular Assist System was designed to evaluate non-inferiority of the proportion of study patients alive on the originally implanted device, transplanted, or explanted for recovery at 180 days. This study did not evaluate the impact of surgical intervention and may not be an appropriate comparison. In the Heart Mate II study, survival rate and surgical intervention data was collected in patients throughout the study. Patients were followed to death or pump replacement or repair, whichever occurred first, regardless of whether they were transplanted or explanted. The Heart Mate II study does provide an appropriate safety measure comparison for the C-Pulse System as surgical intervention and death are accounted for. Table 4 outlines the percent survival rate and reoperation repair or device replacement observed in the Heart Mate II study.

Table 4. Heart Mate II Study Rates

Number of cumulative patient deaths*	Survival Rate
43	90/133 (67%)
Reoperation to Repair or Replace the Device	
45	88/133 (66.2%)

*Cumulative deaths included patients that were transplanted, explanted, or had their device exchanged.

Report Following 40 Randomizations and Follow-up to 6 Weeks

A report will be prepared to descriptively summarize early safety and efficacy data and will be prepared after the 20th implanted (treatment) subject has been followed to 6 weeks post-implant and at least 12 treatment subjects have completed the 6-month follow-up or have progressed to VAD, transplant or death by the time of the report. The report will be provided to the DSMB for review for the purpose of making a recommendation to Sunshine Heart Inc. with regards to continuation of study subject enrollment and follow-up. The report and the DSMB's recommendation will be provided to FDA for consideration. It is expected that subject enrollment and follow-up will continue while the DSMB and FDA review this report. This report will include, at a minimum:

- Summary of all adverse events reported within 6 weeks of randomization summarized by treatment group, seriousness, relatedness, type of event, severity and event resolution. All events will be adjudicated.
- Summary of all worsening heart failure events in the report cohort. All events will be adjudicated.

[13] PMA P100047: FDA Summary of Safety and Effectiveness Data HeartWare® Ventricular Assist System : Left Ventricular Assist Device.

[14] PMA P060040/S5: FDA Summary of Safety and Effectiveness Data Thoratec HeartMate® 11 Left Ventricular Assist System (LVAS).

- Summary of baseline demographic, medical history and heart failure related assessments
- Summary of all available follow-up assessments

The initial enrollment period for the IDE study is intended to provide a period of review for safety to ensure that the risk/benefit assessment has not worsened and that the product/procedural/training enhancements have indeed provided the potential for improvement in outcomes such as exit site infections. Specifically, if more than 8 of 20 implanted subjects experience an exit site infection per the protocol definition, within six months of device implant, the enrollment will be halted until a resolution is agreed upon with FDA, the clinical advisors and Sunshine Heart Inc. A stopping rule will also be followed in the event more than 7 of 20 implanted subjects die during device support within twelve months of device implant and the mortality event is adjudicated as possibly or definitely related to the procedure, therapy or device. The company will halt enrollment while FDA, the clinical advisors and Sunshine Heart Inc. come to a resolution on continuing the trial.

Since this interim analysis is only for the purposes of safety and there is no potential for early stopping for efficacy, there is no type I error inflation and no adjustment required to the primary analysis of the protocol.

Interim Analysis

An interim analysis will be conducted when approximately 194 randomized subjects have been followed to twelve months. The interim analysis will evaluate the primary endpoint of a comparison of worsening heart failure events using all accrued, fully adjudicated primary endpoint events of recurrent worsening heart failure. The results of the interim analysis will be evaluated by the DSMB against a futility stopping rule for a finding of efficacy on the primary objective. Details of the analysis methods can be found in the Statistical Analysis Plan.

Additionally, an assessment of early efficacy will be made. The interim analysis will have a significance cutoff for superiority. At the interim analysis, the DSMB may make one of the following recommendations:

1. If the test statistic for the primary endpoint crosses the futility threshold, the DSMB may recommend that enrollment be discontinued for futility.
2. If the test statistic for the primary endpoint crosses the efficacy threshold the DSMB may make one of the following recommendations:
   A. recommend that the trial be stopped for efficacy
   B. recommend that the control arm be dropped as the enrollment of the treatment arm continues in order to achieve a minimum of 12 months of follow-up on a defined number of implanted subjects
   C. recommend that the trial continues as planned to obtain a better precision on the treatment effect.
3. If neither the futility nor the efficacy boundaries are crossed, the DSMB may recommend that trial enrollment and follow-up continue as planned.

Secondary Efficacy Endpoints

The following secondary endpoints will be analyzed according to the objectives and hypothesis tests given below. Testing of the hypothesis driven secondary efficacy objectives will be conducted only in the event the primary efficacy objective and primary safety objectives are met, thereby preserving an overall Type I error rate of 5%. The secondary efficacy endpoints and associated analyses are described below:

1. **Improvement in 6 Minute Hall Walk at 12 months**
   The improvement in 6 Minute Hall Walk will be computed as the difference between the baseline and follow-up value at 12 months. Subjects not evaluated at 12 months due to prior VAD implant, heart transplant or death will have the worst possible outcome imputed for improvement. Subjects unable to perform the 6MHW will have a value of 0 for the 12 month result. Improvement at 12 months will be compared between treatment groups under the following hypotheses.

   Hypotheses

   H_0: DT= Dc

   H_A: DT≠ Dc,

   where DT represents the distribution of improvement in 6MHW for the Treatment and Dc the distribution of improvement in 6MHW for Control. Details of the analysis methods can be found in the Statistical Analysis Plan.

2. **Improvement in** 6 Minute Hall Walk **at 18 months**
   The improvement in 6 Minute Hall Walk will be computed as the difference between the baseline and follow-up value at 18 months. Subjects not evaluated at 18 months due to prior VAD implant, heart transplant or death will have the worst possible outcome imputed for improvement. Subjects unable to perform the 6MHW will have a value of 0 for the 18 month result. Improvement at 18 months will be compared between treatment groups under the following hypotheses.

   Hypotheses

   H0: DT= Dc

   HA: DT≠ Dc,

   where DT represents the distribution of improvement in 6MHW for the Treatment and Dc the distribution of improvement in 6MHW for Control. Details of the analysis methods can be found in the Statistical Analysis Plan.

3. **Improvement in LVEF at 12 months**
   The improvement in LVEF will be computed as the difference between the baseline and follow-up values at 12 months. Subjects not evaluated at 12 months due to prior VAD implant, heart transplant or death will have the worst possible outcome imputed for improvement. Improvement at 12 months will be compared between treatment groups under the following hypotheses.

   Hypotheses

   H_0: DT= Dc

   H_A: DT≠ Dc,

   where DT represents the distribution of improvement in LVEF for Treatment and Dc the distribution of improvement in LVEF for Control. Details of the analysis methods can be found in the Statistical Analysis Plan.

4. **Days Alive and Out of Hospital due to Worsening Heart Failure through 12 Months**
   The total days alive and out of hospital due to worsening heart failure following randomization through 12 months will be computed for each subject in a similar fashion to DAOH except hospitalization days for reasons other than heart failure will not be subtracted from the total possible days. The treatment groups will be compared under the following hypotheses.

   Hypotheses

   H0: DT= Dc

   HA: DT≠ Dc,

   where DT represents the distribution of days alive and out of hospital due to worsening heart failure for Treatment and Dc the distribution of days alive and out of hospital due to worsening heart failure for Control. Details of the analysis methods can be found in the Statistical Analysis Plan.

5. **Days Alive and Out of Hospital through 12 Months**
   The total days alive and out of hospital following randomization through 12 months will be computed for each subject. Each subject will contribute a maximum of 365 days alive and outside of hospital following randomization. Days the subject is in hospital will be subtracted from the maximum. For subjects with a with a death or study exit prior to 12 months, the days from the date of death or study exit to the date at 365 days post randomization will be subtracted from the total. The treatment groups will be compared under the following hypotheses.

   Hypotheses:

   H0: DT= Dc

   HA: DT≠ Dc,

   where DT represents the distribution of days alive and out of hospital for Treatment and Dc the distribution of days alive and out of hospital for Control. Details of the analysis methods can be found in the Statistical Analysis Plan.

6. **Improvement in KCCQ Score at 12 months**
   The improvement in overall KCCQ score will be computed as the difference between the baseline and follow-up scores at 12 months. Subjects not evaluated at 12 months due to prior VAD implant, heart transplant or death will have the worst possible outcome imputed for improvement. Improvement at 12 months will be compared between treatment groups under the following hypotheses.

   Hypotheses

   H_0: DT= Dc

   H_A: DT≠ Dc,

   where DT represents the distribution of improvement in Overall KCCQ Score for Treatment and Dc the distribution of improvement in Overall KCCQ for Control. Details of the analysis methods can be found in the Statistical Analysis Plan.

Additional Supportive Analyses

1. **Components of primary efficacy endpoint**
   The components of the primary endpoint will be summarized individually by treatment group. The proportions of subjects with heart failure related hospitalization, LVAD implant, heart transplant, and death due to worsening heart failure will be reported and the time to each event will be described by Kaplan-Meier curves. The number and proportion of subjects with hospitalization due to worsening heart failure as well as the rate per patient year will be summarized.

2. **All-cause mortality**
   All-cause mortality will be summarized by treatment group by number and percent of subjects as well as by Kaplan-Meier curves.

3. **Major cardiac events**
   The proportions of subjects within each randomization group with major cardiac events (myocardial infarction, heart failure and stroke) and the composite of major cardiac events or death will be computed. Ninety-five percent binomial exact confidence limits will be calculated and time to each of these endpoints will be described by Kaplan-Meier curves.

4. **Adverse events**
   The frequency and rate (based on the Poisson distribution) of all adverse events will be summarized for each randomization group overall and by seriousness, severity, relatedness and expectedness. Differences in the incidence of adverse event rates will be compared between randomization groups using Poisson regression. Ninety five percent (95%) confidence intervals (based on the Poisson distribution) for the risk ratios will be computed. The number and proportion of subjects with adverse events well as the rate per patient year will be summarized.

5. **Quality of life**
   Quality of life and changes from baseline as measured by the MLWHF and KCCQ assessments will be summarized by treatment group.

6. **Device Performance and Usage**
   The device performance and subject usage will be summarized. The exchange of implanted components that did not result in a device malfunction adverse event will be reported. Device usage will be summarized as the percent of follow-up time with device use. This will be summarized as both a continuous outcome and in quartiles of use defined as 0-25%, 26-50%, 51-75% and 76-100%. The impact of device usage on the primary and secondary efficacy outcomes will be assessed within the C-Pulse arm by summarizing outcomes by quartile of use.
7. **Reduction of diuretics**
   The dose of diuretics pre-implant and during support will be summarized for control and treatment groups.
8. **ICD discharges**
   The frequency of ICD discharges will be summarized for control and treatment groups.
9. **Summary of outcomes – Transplant, VAD Implantation, Recovery or Death**
   A competing outcomes summary will be completed demonstrating the occurrence of time to transplant, VAD implantation, Recovery or Death. Recovery will be defined as NYHA Class I/II and an Ejection Fraction greater than 40%. The data will be summarized for both the control and treatment groups.

Assessment of Poolability

The poolability of the primary efficacy endpoint across clinical sites will be assessed using a covariate adjusted proportional hazards regression model including an interaction term for clinical site and treatment group. In the event statistical evidence of a difference in treatment effect by site is found, an analysis utilizing a random effects model with a random effect for site will be conducted.

Type I Error Control for Secondary Objectives

The secondary efficacy objectives will be tested in a hierarchical fashion in the order listed only in the event the primary efficacy objective is met, thereby preserving an overall Type I error rate of 5%.

Handling of Missing Data

For the primary efficacy analysis, subjects lost to follow-up or explanted will be censored at the date of the last assessment.

Additional analyses of the follow-up assessments of KCCQ, six minute walk and LVEF will be conducted to assess the impact of missing data at month 12. The Wilcoxon Sign-Rank test with the worst rank imputed for data missing due to death, LVAD transplant, heart transplant or explant (in order of time to outcome) will be used to assess treatment differences in the continuous parameters while including subjects who withdrew from randomized treatment prior to the 12 month assessment. Multiple imputation analyses will be conducted to assess the robustness of the study results against data missing due to losses to follow-up and study non-compliance or un-interpretable test results.

Impact of Covariates on the Potential Treatment Differences

Additional exploratory statistical analyses of the primary and secondary study results will be conducted to assess for impact of selected baseline and follow-up parameters on the observed treatment differences. This will involve the stratification of results by categorical parameters and covariate adjusted regression analyses for the assessment of interaction with randomization assignment. Of particular interest will be an assessment for any treatment differences in the efficacy or safety parameters by gender. Other baseline covariates of interest will include classification based on race/ethnicity, age at implant, INTERMACS profile, NYHA, etiology (ischemic/non-ischemic), CRT/ICD therapy, angina, arrhythmia, hyperlipidemia and diabetes and the continuous covariates of baseline six-minute walk, KCCQ and MLWHF.

Additionally, the impact of device compliance on the efficacy outcomes will be assessed. This will be a single arm (within C-Pulse arm only) assessment for evidence of association between device compliance and the primary and secondary efficacy outcomes. This will involve the quantification of each subject's compliance with instructed use with a continuous outcome of percent of follow-up time with device on. Covariate adjusted regression analyses will be used to assess for evidence of statistical association between device use and outcome.

RISK ANALYSIS

Sunshine Heart Inc. has evaluated the potential risks and benefits (listed below) associated with the C-Pulse® System and its appropriateness for therapy for symptomatic Stage CHF patients with NYHA Class III to ambulatory Class IV symptoms. Evaluation is based on the preclinical and clinical experiences to date. The adverse event definitions in the previous sections highlight and expose a standard level of expected risks. Any unanticipated risks and associated events will be captured through the adverse event reporting.

Potential Risks

Risks Related to the Implantation Procedure

Surgical risks along with mitigations specific to the C-Pulse® System include:

- Damage to Cuff on implantation not detected
- Misplacement of ECG lead – not able to sense 'R' wave appropriately
- Improper placement of the implantable components

Implantation is an invasive procedure requiring a median sternotomy or other thoracic incision and the use of general anesthesia and mechanical respiratory support. The potential risks associated with the implant procedure also include those associated with any cardiothoracic surgery, including implantation of devices and include the following:

- Bleeding
- Infection
- Neurological Dysfunction
- Renal Dysfunction
- Cardiac Arrhythmias
- Pericardial Fluid Collection
- Aortic disruption
- Device Malfunction
- Hemolysis
- Hepatic Dysfunction
- Hypertension
- Myocardial Infarction
- Psychiatric Episode
- Respiratory Failure
- Right Heart Failure
- Worsening HF
- Arterial Non-CNS Thromboembolism
- Wound Dehiscence
- Death

There may be other unforeseen risks.

Risk Related to the Investigational Device

The C-Pulse System is designed to allow implantation with a satisfactorily low hospital mortality risk and to allow intermittent use to augment native cardiac function as well as to improve the quality of life in patients in Stage C, Class III to ambulatory Class IV heart failure. Avoiding or minimizing surgical risk factors such as blood contact, anti-coagulation, bleeding, thromboembolism, prolonged operating time, and device-dependent circulation are important when considering the design of C-Pulse System, the operative mortality risk associated with implanting the device and the potential for long-term benefit to a patient's quality of life and heart function. C-Pulse has undergone extensive component and system testing. Potential failure modes that Sunshine Heart Inc. was not able to mitigate through testing have undergone individual risk analysis. Key risks associated with the device and how they have been minimized or mitigated are detailed as follows.

Lack of effect – insufficient relief from heart failure symptoms

Given the natural toroidal shape of the ascending aorta, the greatest opportunity for displacement of blood from the ascending aorta with the least amount of aortic wall strain is for inward displacement of the outer curvature of the ascending aorta – a so-called "thumb-printing" action that results in a rolling back and forth of the outer aortic wall. The C–Pulse Cuff actuator is positioned on the outer curvature of the aorta, pre-shaped like a cap when deflated – the inflation/deflation port is positioned radially in the central aspect of the outer part of the balloon. A circumferential polyester wrap holds the actuator in place. As the actuator inflates the outer ascending aortic wall is pushed toward the posterior inner arc of the ascending aorta. The wrap stays circumferential, and the actuator takes on a 'lens' shape as it fills, and displaces blood in the ascending aorta. The ascending aorta provides for a relatively large volume of blood displacement, which is key to effective counterpulsation.

Counterpulsation is proven to be more effective the closer this occurs to the aortic valve.[15,16,17] The pre-systolic unloading action at the level of the ascending aorta is more direct on the left ventricle. In the descending aorta, there are diffusive losses, with multiple branches, bi-directional blood volume displacement, and less precision of timing to aortic valve opening and closing. Diastolic counterpulsation on the ascending aorta, against the closed aortic valve, may also contribute more directly to forward cardiac output by creating unidirectional flow.

[15] [Furman 1970]

[16] [Gitter 1998]

[17] [Davies 2002]

The C-Pulse Cuff has a maximum target volume setting of 20–26c, dependent on Cuff size. The degree of efficiency of counterpulsation on the ascending aorta is of the order of 2-3 times compared to the descending aorta. As such, a displacement volume in the ascending aorta of 16–20 ml might be comparable to a 40 ml descending thoracic aortic IAB. Although not validated by FDA clinical trials, aortomyoplasty displacement volume may be as little as 15 ml, and counterpulsation is run at 1:2 and has good clinical effect. In addition, the Kantrowitz counterpulsation device is positioned in the descending aorta and has a maximum capacity of 60 ml but operates clinically at a maximum of 50–55 ml at 1:1 counterpulsation with good clinical effect.

The dimensions of the ascending aorta were determined by literature review, and by cadaveric, intra-operative, and radiology studies. The Cuff dimensions were based on these measurements; to allow a certain inflation profile that would fit aortas in the range of outside diameter 28-42mm, but if over-inflated would not allow the intimal surfaces to touch and to at least match an equivalent counterpulsation volume to those achieved in humans with predicate devices with clinically significant results[18]. The C-Pulse Cuff is thus supplied in three sizes designed to fit to a range of aortic dimensions and to minimize absolute strains and rates of change of strains in the Cuff and aorta during inflation and deflation, while allowing significant blood volume displacement in the aorta.

The ascending aorta was selected over the descending thoracic aorta because of:

- surgical access
- counterpulsation on ascending aorta is unidirectional and more efficient
- ascending aortic diameter is greater than the descending thoracic therefore less wall movement is required for a given volume displacement
- no side branches such as intercostal and spinal arteries
- uniform ascending aortic anatomy
- low incidence of calcific disease in the ascending aorta

The wrap design allows for minimal axisymetric expansion of the aorta during systole yet containment of the actuator ensures the proper inward inflation profile for effective diastolic counter-pulsation.

R wave detection by the Driver is highly specific and sensitive to ensure the Driver is able to deflate the balloon effectively in relation to the onset of systole and to not remain inflated during any systolic event, including from ventricular premature beats, paced beats or other arrhythmias. The gas line is designed for high air flow rates, thus ensuring rapid balloon inflation and deflation. These features are key in ensuring the C-Pulse System is able to effectively counterpulsate.

[18] [Legget 2005]

If the left ventricular failure is severe, counterpulsation may not prove adequate to support the patient in the short or long term. The device is not intended to fully support the systemic circulation. The C–Pulse System is not indicated in INTERMACS status 1 and 2 heart failure patients; those that are not ambulatory, are hemodynamically unstable and/or have severe multi-organ failure.

Improving left heart function may reduce the load on the right heart, however if the right heart failure is severe, or is secondary to primary pulmonary hypertension, then there exists a risk that C-Pulse counterpulsation will not be as effective.

Device Failure

The pre-shaped extra-aortic non-blood contacting design of the Cuff significantly reduces any consequence of device failure.

The Cuff actuator has been designed for maximal durability by designing to minimize strain in the flexing membrane. Finite element analysis (FEA) of the current design was iterated using ABAQUS FEA software to reduce the strain to an acceptable level. The greatest area of strain is around the moving membrane. Key elements of strain related to the thickness of the membrane and to its edge radius. Varying aortic wall thickness between 1.5–2 mm had no significant effect. Membrane material thickness and the edge radius are most critical in minimizing strain in the C-Pulse Cuff.

The membrane edge radius gets compressed to less than its molded edge radius when assembled on the aorta and assumes the wall tension of the pressurized aorta. It does not crease. The rolling edge design has the further advantage of allowing the Cuff better conformation to the slight variations in individual aortic dimensions.

The Cuff needs to comply with the natural shape of the ascending aorta to not cause local pressure. The wrap is designed to maintain the actuator in position on the aorta, and to ensure it deflects inward. A pre-shaped wrap made of woven polyester and with some strain relief feature in the top and bottom edges of the cuff to better transition from the cuffed aorta to the non-cuffed aorta has been used. Woven polyester has proven long-term use clinically as both a peri-vascular wrap and as a graft replacement, and has less than 5% stretch long-term *in vivo*. It is secured to itself using standard suturing.

The inflation fluid is filtered room air. Accelerated over-pressure device testing indicates that the balloon is very unlikely to fail within the first four years of continuous use. Premature failure may occur if the inflation membrane of the Cuff migrates under the wrap and causes a crease line and counterpulsation is continued. The expected consequences of a persistent leaking balloon may include surgical emphysema or pneumothorax. Leakage of non-sterile air may also predispose to mediastinal infection. There is negligible risk of air embolism if the aorta is not compromised.

There is a risk of a needle puncture hole being made intra-operatively. The Cuff is pre-loaded with sutures to mitigate against risk of balloon puncture. Surgeons are required to perform implantations of the Cuff on a mock inflated ascending aorta prior to their first implantation. There are intra-operative procedures to check for and discover any such hole and thus replace the Cuff.

The Driver is designed to detect air leaks and will immediately alarm and stop if a major leak occurs.

The electronic system is also used to detect impending malfunctions by performing diagnostic tests on the system. Safety features built into the Driver are designed to protect the patient in the event of system failure as well as to protect the integrity of the system. Safety features include protection against current leakage, defibrillating voltages, failure of the microprocessor and power supply and over-inflation of the Cuff.

Device stoppage for any reason is not immediately dangerous to the patient, but the symptoms of heart failure may return. The Driver is engineered to resume a deflated state if there is a power loss or malfunction, thus the natural blood pathways of the heart and vasculature are preserved.

Aortic Rupture

There are several examples of extra-aortic banding or counterpulsating, using different materials and in different species. In humans, wraps have been used to support primary ascending aortic aneurysm repair as described in a number of clinical series, with 10 year follow–up[19,20,21]. Note that patients requiring an aorto-coronary graft had it placed via a hole cut in the wrap. There has been no reported instance of aortic dilation above or below the wrap. However, a poorly fitted or not well secured wrap may migrate and this may cause aortic erosion and subsequent false aneurysm formation[22].

The pre-shaped C-Pulse Cuff is designed to minimize the risk of migration – it is anatomically designed to conformally fit the toroidal ascending aorta between the sinotubular junction and the brachiocephalic artery. The Cuff cannot fully occlude the aorta thus there is negligible risk of any abrasion of aortic wall surfaces.

An infected Cuff may cause aortitis. If the infection is aggressive or left untreated, subsequent erosion of the aortic wall resulting in contained or free aortic rupture may result (see below).

Device–related Infection – Intra–thoracic and Exit–site

There exists the risk of mediastinal infection involving the implanted Cuff. This may occur as a result of inoculation at the time of implantation or arise at long-term follow-up; the latter may be due to seeding of circulating microbes, breach of the implanted gas-line or balloon or from infection ascending from the exit-site.

Perforation of the Cuff at the time of surgery is of concern as the air used to inflate the Cuff is filtered but not sterile. There is negligible risk of air-leak and thus no risk of infection if the Cuff is not damaged. Cuffs are 100% checked during the assembly process and following complete assembly to confirm integrity. Bench testing of the Cuffs has demonstrated very high confidence of reliability beyond 6 years of cycling at significantly higher pressures than required clinically. However, there remains the risk that a leak could be made at the time of implant and this may potentially cause

[19] [Barnett MG 1995]

[20] [Carel 1991]

[21] [Rubiscsek 1994]

[22] [Bauer 2003]

mediastinal infection. Thus diligence is required to ensure a needle-hole is not made at the time of surgery and if it is that it be recognized and the Cuff replaced prior to closing the chest. To this end, the methodology to implant the Cuff has been revised to allow visualization of the balloon at all times when placing sutures into the wrap and intra-operative testing is a mandatory part of the procedure. Furthermore, bench and *in vivo* models have been developed to provide surgeon training prior to implantation.

Infection of the Cuff may lead to erosion of the aorta, with subsequent risk of septic thromboemboli and poses a significant problem. Early recognition of an infected Cuff and aggressive treatment will likely limit potential complications. Chest pain and/or fever of unknown origin should be thoroughly investigated. Removal of the Cuff is an option, which allows also surgical debridement and drainage as well as long-term antibiotic therapy. Other methods of cardiac support may be required in the interim.

Infection risk may be reduced by careful selection of patients: excluding non-ambulatory patients or those in hospital on intravenous inotropic support, those who are severely cachectic or have severe chronic renal failure may improve early healing post–surgery and reduce the risk of early device infection. Similarly, optimal implant techniques, appropriate use of antibiotics and avoiding nosocomial infections in indwelling catheters peri-operatively will minimize implant infection rates. The protocol is specific to reducing the risk of peri-operative infection.

The presence of a percutaneous line creates a risk of long-term infection at the exit-site and the risk of ascension to the Cuff. Strict immobilization for the first 6 weeks post-operatively is mandatory to allow effective fibrotic ingrowth and thus anchoring of the subcutaneous flocking. Specific guidelines are also given to care-givers and patients for managing this wound site long-term. The Percutaneous Interface Lead has been specifically designed to reduce the risk of infection – the outside diameter is approximately 6 mm, the material is Silicone, and the tubing is soft and flexible. Flockings exist subcutaneously to anchor the percutaneous lead in a manner similar to Tenkhoff and Hickman catheters[23]. There is no device 'pocket' created.

The Cuff and ECG lead can be terminated subcutaneously and sealed if the Percutaneous Interface Lead is chronically infected or otherwise damaged and needs removal.

Risks Related to the Study Conduct

The methods for data collection involve only standard, well-established methods and do not differ from normal mechanical circulatory support device implantation and heart failure management follow-up practice. Therefore, the clinical study requirements of C-Pulse® pose no additional risk to the patient.

Risk Minimization

Sunshine Heart has attempted to minimize the risk of implanting the C-Pulse® System through careful design and pre–clinical testing. Pre-clinical testing includes bench and animal testing to verify performance, software validation testing, destructive analysis and shock tests, and packaging qualifications.

[23] [Ash 1990]

Risks normally associated with cardiac devices and their implantation will be minimized by selecting investigators who are experienced in the diagnosis and treatment of patients with end-stage heart failure. In addition, investigators will be trained on the device operation and protocol prior to participating in the study. Product labeling is also provided which further addresses risk mitigation.

Prior to implant patients should go through a complete cardiac evaluation. After implantation, subjects will be followed at regular intervals to confirm that the device parameters are appropriate and to monitor the status of the C-Pulse® System. Frequent follow-up will promote faster identification and resolution of adverse events. The severity of system related events will be minimized by restricting use of the C-Pulse® System to hospitals equipped with redundant systems and staffed by qualified, trained personnel.

C-Pulse® System Potential Benefits

Anticipated benefits of the C–Pulse® System may include:

- Relief of symptoms
- Improved QOL
- Enhanced mobility
- Home discharge
- Freedom to disconnect from the external driver for short periods of time before noticing return of symptoms, particularly shortness of breath
- Anti-coagulants not required
- Increased diastolic coronary artery blood flow
- Reduced systolic pulmonary artery pressures and mitral regurgitation
- Increased cardiac index
- Straightforward implant surgery
- No cardio-pulmonary bypass
- Avoid risk of lung and right heart complications associated with cardiopulmonary bypass – critical in patients with HF
- Preserved pericardial sac around ventricles
- Modular design
- Implanted device is very small
- There is no ‘pocket’ created
- Device can be removed and infection treated if necessary
- Subcutaneous line is long, and multiple flocking anchors are provided
- Line exiting skin is made of biostable and biocompatible materials, is soft and flexible, and can be removed and/or replaced

Overall advancement of medical and scientific knowledge that may benefit future patients may also be realized from this study.

There may also be other benefits that are unforeseen at this time.

Justification for the Investigation

The ethical conduct of a clinical trial of a new therapy relies on the promise the therapy has some benefit, but its efficacy to achieve this benefit is unknown and the new therapy always carries some risk (clinical equipoise). A careful and complete presentation of the scientific merit for the trial, including evidence both for and against the investigational treatment, forms the ethical basis for the study design and conduct.

Clinical Need

There are over 1.5M people in the USA in Class III heart failure. Biventricular pacemakers are indicated in patients with a wide QRS – approximately 30% of this population. Approximately 2200 heart transplants are done per year. A similar number might receive an LVAD as either a bridge to transplant or as destination therapy.

There remain a very large number of people that may benefit from an improvement in their clinical status from NYHA Class III/IV to Class I/II. The targeted patient population is defined by the expected natural history of heart failure. **Figure 1** highlights the trend of heart failure, and the relationship of severity of heart failure with repeat hospitalization and with mortality.

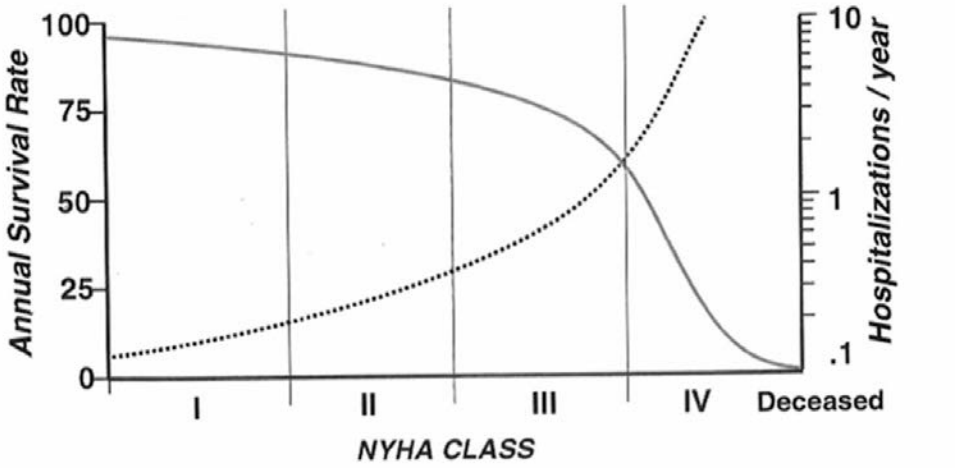

Figure 2 Annual Survival versus Hospitalization versus NYHA

It can be seen from the figure that repeat hospitalizations, on a logarithmic scale on the right hand side, changes at a much greater rate compared to the mortality curve, with any change in the NYHA Class. In the patient group indicated for C-Pulse System, i.e. NYHA Class III to ambulatory Class IV, patients are characterized as beginning to have more frequent admissions to hospital or increasing length of stays, with significant cost burden, but remain ambulatory. Patients in late Class IV have a more rapidly escalating mortality rate, and are generally not ambulatory at all.

As the severity of disease increases, there is greater certainty regarding imminent death, and less certainty is required regarding the device performance and patient outcome after implantation. However, generally, increasing disease severity also increases the risk of adverse outcomes attributable more to the patient than the device. At lesser grades of severity, when death is not imminent, details regarding the expected function and quality of life with mechanical circulatory support become more critical. Patient preference for

quality of life versus survival shows remarkable variation at every level of disease severity.

From a practical standpoint, apart from those with high predicted in-hospital mortality (i.e. Cardiogenic Shock or Class IV with risk factors such as multi-organ failure) many patients exhibit a dynamic state that fluctuates over months, with exacerbations related to dietary indiscretion, seasonal viral infections, and other exogenous factors.

Ambulatory heart failure patients on oral therapy are generally not as sick, but experience discomfort during any physical activity and may have discomfort while at rest. The hypothesis is that a mechanical circulatory support device will provide such patients with an improved physiologic and functional quality of life. The probability of survival at a specific time is not well established. End-points of interest include quality of life, all-cause and cardiac-related mortality, and morbidity, whereby a sustained improvement in quality of life and significantly less morbidity may be considered a significant benefit even if survival is equivalent. For ambulatory heart failure patients, a large component of the decision to receive investigational therapy is the degree to which the current clinical status is unacceptable.

The objective of the C-Pulse® System is to provide an effective, low risk and low cost mechanical heart assist device for use in patients in NHYA Class III to ambulatory Class IV. Basic safety has been demonstrated in the US Feasibility IDE Study. Significantly, there was no surgical-related mortality and while there were indicators for device performance in relation to heart failure symptoms and cardiac function, there was an incidence of exit site infection. The infection control guidelines and lead stabilization techniques are now incorporated.

STUDY OVERSIGHT AND INTEGRITY

DESIGNATION OF SPONSOR, DATA MANAGER, AND MONITOR

Table 5. Study Oversight Contact Information

Role	Organization	Address	Contact Numbers
Sponsor Study Monitor Clinical Events Committee Data Management and Reporting DSMB COUNTER HF Subject Eligibility Committee	Sunshine Heart, Inc.	12988 Valley View Rd Eden Prairie MN 55344	1-952-345-4200

MONITORING PROCEDURES

The Sunshine Heart C-Pulse study will be monitored according to the guideline summarized below.

SUMMARY OF MONITORING PROCEDURES AND RESPONSIBILITIES

It is the responsibility of the study sponsor (Sunshine Heart Inc.) to ensure that proper monitoring of the investigation is conducted and that IRB review and approval of the investigation is obtained. Monitoring visits will occur based on implant volume at the center or at least annually. Adequately trained Sunshine Heart Inc. or delegates appointed by the study sponsor will do study monitoring in order to ensure that the investigation is conducted, recorded and reported in accordance with:

- The signed Investigator Agreement
- The Investigational Plan
- Applicable laws and regulations

Monitoring will be planned at the study site to assure compliance with the study protocol. The sponsor (or appropriate designee) must therefore be allowed access to the subjects' files as per the informed consent at the investigator's site when so requested.

Sunshine Heart Inc. will monitor investigational sites to ensure that the study is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOPs) and applicable regulatory requirements.

Monitoring visits will be conducted by trained Sunshine Heart Inc. personnel or designated representatives. A Monitoring Plan will be completed for the study and will identify the frequency of monitoring and further identifies the names of monitors.

INTERIM MONITORING VISITS

Routine monitoring visits are made periodically to assess the Investigator's adherence to the Investigational Plan, IRB review of the progress (if appropriate), maintenance of the records and reports and selection review of source documents for accuracy, completeness, legibility and omissions. The following factors will be taken into account when determining the frequency of the monitoring visits: subject accrual at each center, total number of subject enrolled at each center, and protocol compliance at each center. Each participating institution will be monitored once per year, at a minimum.

The monitors will acquire information to assess the progress of the study (toward meeting study objectives) and identify any concerns that stem from observation of device performance and/or review of the investigator's subject records, study management documents, device tracking and Subject Informed Consent documents. Resolution of concerns and completion of assigned tasks may be documented by the monitors. Source data verification and review of any ongoing finding may occur during monitoring visits.

STUDY CLOSURE

Study closure is defined as a specific date that is determined when Sunshine Heart Inc. regulatory requirements have been satisfied per the Investigational Plan (IP) and/or by a decision of the business leaders for Sunshine Heart Inc. Study closure visits will be conducted at all clinical sites in order to review record retention requirements, device disposition requirements, etc. with site personnel. A telephone contact may take the place of a study closure visit if appropriate (e.g. low subject enrollment, recent monitoring visit, etc.).

STUDY SAFETY

Counter HF Subject Eligibility Committee

A Subject Eligibility Committee will be established by Sunshine Heart. The committee will be comprised of at least one CTS and one HFC. These physicians will be trained on the COUNTER HF study protocol and enrollment criteria. The committee will receive baseline study enrollment information and source documents for all subjects submitted by sites for randomization approval/denial. A charter will be established for the committee and approved by the sponsor and the committee.

Information or factors the physician Subject Eligibility Committee will review, includes but is not limited to:

1. Verification that subject meets the study entry criteria.
2. Subject source documents submitted to verify classification of NYHA class III or ambulatory class IV AND INTERMACS 4-7.
3. Subject comorbidities to identify those that would preclude a subject's ability to benefit from the C-Pulse System (if randomized into the study and assigned the treatment arm). Specifically, comorbidities including renal dysfunction and predominant right heart failure.
4. Verification that subject is a viable surgical candidate based on prior history or calculated STS surgical risk score.

Clinical Events Committee (CEC)

A CEC will be established by Sunshine Heart or designee to assess, review, and classify all adverse events and deaths during the clinical study. Classification will include relatedness and onset/resolution dates. The committee will consist of a minimum of three physicians including a chairperson appointed by Sunshine Heart Inc. or the CEC committee. The CEC will regularly review and adjudicate reported adverse events including deaths.

At the onset of the study, the CEC, along with support from Sunshine Heart Inc. will establish a charter outlining the minimum data required and the algorithm followed in order to classify an event. This charter will be approved by the committee during the first round of meetings. Members will be provided data summaries from the clinical study in a blinded fashion without site, subject or physician identification.

Data and Safety and Monitoring Board (DSMB)

A DSMB will convene, composed of a least one heart failure cardiologist, cardiac surgeon and a biostatistician who are not directly involved in the trial. The DSMB will review the study data after the 20th implanted subject has completed the 6 week follow-up. Enrollment of further subjects will occur as the DSMB reviews the data. The DSMB will provide a report following the review and may recommend to Sunshine Heart Inc. to continue, modify or stop the trial based on their findings.

TRAINING PROCEDURES

Site training is required at all investigational sites. Each study site will be trained on all aspects of the protocol, device implantation and operation, as well as subject training in preparation for discharge. At the end of the training course, all participants should be competent in ensuring optimum care of the subject. In addition, each site will have identified a local expert user to provide continuing training to team members.

The training program will be conducted according the Sunshine Heart Inc. standard operating procedures and quality system requirements.

PROTOCOL DEVIATIONS

A Protocol Deviation is defined as an event where the clinical investigator or site personnel did not conduct the study according to the investigational plan, protocol or the investigator agreement.

Prior notification to the SHI study manager is expected in those situations in which the investigator anticipates, contemplates, or makes a conscious decision to depart from the procedure specified in the Investigation Plan, except when necessary to protect the life or the physical well-being of a subject in an emergency. Prior notification is not required in situations where the unforeseen circumstances are beyond the control of the Investigator (e.g. inadvertent mistakes, equipment failure, subject ill and unable to perform testing, etc.).

Protocol deviations must be recorded in the database. Include a description of the deviation, justification for the deviation, corrective action and whether the SHI study manager was notified prior to the deviation.

Deviations will be reported to the SHI study manager regardless of whether medically justifiable or taken to protect the subject in an emergency. Protocol deviations should be reported as soon as possible upon discovery of the deviation. Study deviations may be discovered through variety of sources, such as during the data review, telephone conversations, and site monitoring. Report protocol deviations to your IRB in accordance with IRB policies and/or local laws.

FDA regulations require the investigators to notify the sponsor and reviewing IRB within 5 working days for the following deviations:

Deviation from the investigational plan to protect the life or physical well-being of a patient in an emergency.

"An investigator shall notify the sponsor and the reviewing IRB (see 56.108(a)(3) and (4) of any deviation from the investigational plan to protect the life or physical well-being of a patient in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred." 812.150(a)(4)

No informed consent prior to device use.

"If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs." (21 CFR 812.150(a)(5))

A Protocol Deviation record is to be completed for each study protocol deviation, including but not limited to:

- Failure to obtain informed consent
- Incorrect version of informed consent document used
- Patient did not meet inclusion/exclusion criteria
- Missed follow–up visit
- Follow–up visit out of window
- Failure to adhere to protocol required testing
- IRB approval not obtained prior to implant
- Implant occurring during IRB lapse of approval

RECORDS AND REPORTS

INVESTIGATIONAL RECORDS

The Investigator is responsible for the preparation (review and signature) and retention of all records cited below. All of the below records, with the exception of case history records, should be kept in the Investigator Site File, i.e., the study binder provided to the Investigator. The following records are subject to inspection and must be retained for a period of two year (or longer as local law requires) after the study closure.

- All correspondence that pertains to the investigation.
- Subject's case history records, including the signed subject informed consent form; all relevant observations; observations of adverse events; medical history; implant and follow-up data; documentation of the dates and reasons for any deviations from the protocol.
- Device Accountability Documentation, containing Site delivery dates of devices, implant dates and returned to Sponsor dates, quantities and serial/lot numbers of devices delivered at the site, quantities and serial/lot numbers of devices returned to Sponsor, and subject IDs of the subjects implanted.
- Signed Clinical Trial Agreement and current curriculum vitae.
- IRB documentation and correspondence.
- Center personnel training documentation forms.

INVESTIGATOR REPORTS

The Investigator is responsible for the preparation (review and signature) and submission to the sponsor of all eCRFs, all death and adverse events (except unavoidable adverse events) and any deviations from the investigational plan; other reports are listed in Table 6. All reports are subject to inspection and to the retention requirements described above for the Investigator records.

If an IRB takes any action as a result of this study, copies of all pertinent documentation must be forwarded to the sponsor.

Table 6. Investigator Reporting Responsibility

Report	Submit to:	Description
Unanticipated Adverse Device Effect	Sponsor and IRB	If an unforeseen complication is determined to be related to the device, this information must be reported to FDA, IRB, and Sponsor.
Withdrawal of IRB Approval	Sponsor	The investigator must report a withdrawal of the reviewing IRB approval within 5 working days.
Progress Report	Sponsor and IRB	The investigator must submit this report if the study lasts more than one year on an annual basis.
Deviation from the Investigational Plan	Sponsor and IRB	The IRB and sponsor must be notified within 5 working days of the event of an emergency deviation from the IP to protect the life or physical well-being of a subject. Except for the deviations under emergencies, prior notification must be submitted to Sunshine Heart Inc.
Failure to Obtain Informed Consent	Sponsor and IRB	The Investigator must make notification within 5 working days after device use. The report must include a brief description of the circumstances justifying the failure to obtain informed consent and include written concurrence by a licensed physician not involved in the investigation.
Final Report	Sponsor and IRB	A final report must be submitted within 3 months after termination or completion of the study.

SPONSOR RECORDS

Sunshine Heart Inc. will retain the following records:

- All correspondence pertaining to the investigation.
- Device disposition records containing site delivery date of device, implant device serial numbers, expiration dates, quantities of devices shipped and returned.
- Signed Clinical Trial Agreements, financial disclosure forms, and recent CV of investigators.
- All adverse events (except unavoidable adverse events), deaths and complaints.
- All eCRFs that are submitted, samples of the informed consents, investigational plans, and report of prior investigations.

SPONSOR REPORTS

Table 7. Sponsor Reporting Responsibility

Report	Submit to:	Description
Unanticipated Adverse Event – Device Related	FDA, all IRBs and all Investigators	Sunshine Heart Inc. will report any and all unanticipated device–related adverse event evaluation within 10 working days of receipt of notice.
Withdrawal of IRB Approval	FDA, all IRBs and all Investigators	Notification will be made within 5 days.
Withdrawal of FDA Approval	All IRBs and Investigators	Notification will be made within 5 working days.
Current Investigator List	FDA	Sunshine Heart Inc. will submit a list of names and addresses of all participating investigators at 6–month intervals (starting at 6–month after FDA approval).
Progress Report	FDA, all IRBs and all Investigators	A progress report will be submitted at least yearly.
Recall and Disposition	FDA, all IRBs and all Investigators	Notification will be made within 30 working days and will include the reasons for any request that an investigator return, repair or otherwise dispose of any devices.
Final Report	FDA, all IRBs and all Investigators	Sunshine Heart Inc. will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted within 6 months after completion or termination.
Failure to Obtain Informed Consent	FDA/IRB	A copy of the investigator's report will be submitted within 5 working days of the notification.

PUBLICATION STRATEGY

Sunshine Heart Inc. will form a publication committee that includes participating investigators. The committee will finalize a publication plan. The scientific validity and timing of publications will be evaluated in order to maximize the benefits derived from the publication of the North American clinical data of the study. In general, publications utilizing worldwide data will be managed as described below.

PUBLICATION COMMITTEE

The publication committee will be defined by the time enrollment for the primary objective is completed. Sunshine Heart Inc. will form a publication committee that includes the National Principal Investigator and participating investigators (as needed), the Sunshine Heart Inc. VP of Clinical Research, or designee, and other Sunshine Heart Inc. personnel.

The publication committee is responsible for overseeing the development of case reports, manuscripts, and abstracts according to the Publication Strategy, identifying and appointing the manuscripts/abstracts first author(s)/writer(s) and identifying Sunshine Heart Inc. personnel responsible for assisting the first author. The publication committee will meet approximately annually to refine the publication strategy.

The publication committee reviews not only the main publications, but also ancillary publications. If necessary, specified authorship criteria may be applied for ancillary publications. The Committee may decide that no case reports, publications or abstracts will be prepared prior to the end of the study, or not on individual center data.

Being a member of the subcommittee gives no privileges for authorship selection.

Centers will be appraised of the objectives of the Publication Committee. Participating centers will agree that publication of the aggregate data from this multi-center trial takes precedence over results from an individual center.

AUTHORSHIP SELECTION

The first author will be selected on the basis of the following:

- A significant contribution to the design of the study and/or development of the product;
- A significant contribution to subject enrollment into the study;
- High procedure volume and high quality of data as determined by the clinical study requirements;
- Demonstration of a high level of interest in the performance of the product and/or the unique product features, applications, and the ability to write, review, edit, and present the publication;

- A demonstration of a good publication history;
- A willingness to contribute to the publication;

Appropriate geographic representation, if a geographic region enrolls a significant number of patients. The Publication Committee recommends the number of authors per region.

Appropriate Sunshine Heart Inc. personnel or representatives (e.g. clinical study personnel, statistician, and field personnel) are considered based on substantive contributions to the study or publication effort.

All investigators not listed as co-authors will be acknowledged as the "Sunshine Heart C-Pulse Investigators" and will be individually listed according to the applicable scientific journal.

REVIEW AND COMMUNICATION GUIDELINES

Investigators will receive a communication regarding the authorship selection, the publication co-authors and to which scientific platform the publication will be submitted.

Prior to the submission of a publication (abstracts and manuscripts), the Sunshine Heart Inc. study team, publication committee and all co-authors will review and approve the contents and scientific platform. No individual center or individual investigator publications will be permitted for the Sunshine Heart Inc. C-Pulse System study unless agreed upon by the Publication Committee, to ensure consistency of methods, data integrity, and appropriate publication timing.

Investigators who contribute patient data will be provided a copy of the final manuscript/abstract.

For publication of investigator's own data, Sunshine Heart Inc. will limit its review to a determination of whether or not confidential information is disclosed or if technically incorrect statements are made and will not attempt to censor the data or conclusions.

ANCILLARY PUBLICATIONS

The publication committee will review ancillary requests. Ancillary publications include those reporting on a subset of the patient population or reporting a specific aspect of the study.

Requests for publications using regional data beyond the North American study results will be evaluated for scientific validity and the ability of Sunshine Heart Inc. to provide resources. The publication committee must approve requests and will need to ensure that requests do not present conflicts with other geographical regions. If multiple geographies contribute to data, co-authorship will be representative, using the guideline for authorship selection described above.

APPENDIX A: ABBREVIATIONS AND ACRONYMS

CEC	Clinical Events Committee
MAB	Medical Advisory Board
AE	Adverse Events
DSMB	Data Safety and Monitoring Board
HF	Heart Failure
ECG	Electrocardiogram
BTT	Bridge to transplant
VAD	Ventricular Assist Device
TTE	Transthoracic echocardiography
FDA	Food and Drug Administration
TEE	Transesophageal echocardiography
CRT	Cardiac Resynchronization Therapy
NYHA	New York Heart Association
QOL	Quality of Life
LVAD	Left Ventricular Assist Device
DT	Destination Therapy
IAB	Intra-Aortic Balloon
IDE	Investigational Device Exemption
ICP	Implantable Counterpulsation Pump
PIL	Percutaneous Interface Lead
IR	Infra–red
CPX	Cardiopulmonary Exercise Testing
IRB	Investigational Review Board
MLWHF	Minnesota Living With Heart Failure
KCCQ	Kansas City Cardiac Quality of Life Questionnaire
CXR	Chest X-ray
ECHO	Echocardiogram
eCRF	Electronic Case Report Form Template
ICU	Intensive Care Unit
IV	Intra–venous
PRBC	Packed Red Blood Cells
MCSD	Mechanical Circulatory Support Device
GFR	Glomerular Filtration Rate
TAPSE	Tricuspid Annular Systolic Excursion
CTS	Cardiothoracic Surgeon
HFC	Heart Failure Cardiologist

APPENDIX B: SUMMARY OF PREVIOUS STUDIES

Experience to date by Sunshine Heart Inc. provides evidence of safety and performance. These include:

INTRA-OPERATIVE CLINICAL FEASIBILITY STUDY

The aim of this study was to determine the safety and performance of a new method of non-blood contacting counterpulsation utilizing an inflatable Cuff (C-Pulse) around the ascending aorta.

In 6 patients undergoing first time off pump coronary bypass surgery via sternotomy, the C-Pulse was secured around the ascending aorta and attached to a standard counterpulsation console. At baseline, and with 1:2 and 1:1 augmentation, hemodynamic and echocardiographic parameters of ventricular function and coronary flow were measured. High intensity transient signals (HITS) were measured using transcutaneous Doppler over the right common carotid artery.

No complications occurred.

With C-Pulse there was no significant change in heart rate and blood pressure, and no increase in HITS. There was a 67% increase in diastolic coronary blood flow (mean left main diastolic velocity time integral 15.3 cm unassisted vs. 25.1 cm assisted, $p<0.05$). Measurements with transesophageal echocardiography, at baseline and with 1:1 counterpulsation, demonstrated a 6% reduction in end diastolic area ($p = NS$), 16% reduction in end systolic area ($p < 0.01$), 31% reduction in LV wall stress ($p < 0.05$), and a 13 % improvement in fractional area change ($p < 0.005$). It was concluded that C-Pulse System counterpulsation augments coronary flow and reduces left ventricular afterload.[24]

LONG-TERM EXTRA-AORTIC BALLOON COUNTERPULSATION IN SHEEP

This study was undertaken to examine the effect of chronic counterpulsation with C-Pulse on the integrity of the ascending aorta in sheep at 5 and 10 months.

A pre-shaped cuff, consisting of a polyurethane balloon and polyester wrap, was implanted around the ascending aorta via a left mini-thoracotomy in 11 adult sheep. An endocardial ECG sensing lead was implanted via the right external jugular vein. The balloon's gas line and the sensing lead were brought out percutaneously over the back and connected to a Datascope 90 IABP console.

[24] Legget 2005

Sheep were counterpulsated for approximately five and ten months. Prior to post-mortem, intra-aortic ultrasound examination was completed to examine balloon function. Following euthanasia, an autopsy was conducted in all sheep; particular attention was paid to the heart, brain and kidneys. Detailed histology was completed on the heart and great vessels with the attached device, from each sheep.

Intra-aortic ultrasound showed each cuff to be inflating and deflating in a normal pattern following 5 and 10 months operation. Sheep were terminated at five months (6) and 10 months (5).

One sheep was euthanized at 5 months because it became ill over several days; at autopsy it was found to have a bacterial infection involving the cuff and the aorta resulting in a contained aortic rupture. In two other sheep (at 5 and 10 months, respectively) non–disruptive aortitis was noted at post-mortem and this was confirmed by microscopic pathology.

Hence the thoracic aorta was assessed microscopically in 8 sheep; 4 at 5 months and 4 at 10 months. Histology of the aortic wall at the root and arch appeared normal. Sections through the mid-ascending aortas revealed the peri-aortic implants were well incorporated by the adventitial peri-aortic tissues and that there was no disruption to the endothelial surfaces. Histology demonstrated that for each of the 8 sheep the intima and inner half of the media, measuring 0.6–0.9 mm thick, appeared normal. Findings in the outer one third to one half of the aortic wall included muscular atrophy, thin-walled blood vessels, petechial hemorrhages, small focal strips of coagulative necrosis (0.1–0.3 mm thick) and viable reparative tissue responses. Those at 10 months displayed a recognizable reparative microvascular (arterial and venular) pattern with less necrosis than at 5 months. The changes were circumferential. While the cuffed aortic wall was thinner than the normal wall, there was no evidence of progressive damage to the inner media and intima when comparing results from sheep at 5 months to those at 10 months.

In conclusion, the structural integrity of both the counterpulsation cuff and the inner wall of the ascending aorta enclosed by the cuff remained intact for 10 months. Intermittent ongoing focal areas of damage and repair in the outer media were related to the device. Infection was an important complication leading to aortic disruption in one case. The anatomical intimacy between aorta and pulmonary artery in the sheep is closer than that observed in humans, and the aorta is more friable. Also, in this sheep study the cuff was inflated to transmural pressure at least twice that considered for humans.

PROSPECTIVE OBSERVATIONAL STUDY

Following preclinical studies and the intra-operative clinical study, a prospective observational study of the C-Pulse System in NYHA Class III to IV end-stage heart failure patients was undertaken. Endpoints were safety, quality of life and cardiac performance. Five patients aged 54–73 years underwent implantation.

There were no hospital deaths. All patients were discharged to rehabilitation and/or home. All patients were able to tolerate the device being turned off for short periods.

There was a mean improvement of one NYHA class at one month. The cardiac index was increased and systolic pulmonary artery pressure reduced. One patient died of progressive multi-organ failure at 3 months, and two required device removal at 5 & 7 weeks respectively due to mediastinitis – one subsequently died from persistent intrathoracic infection. One patient was successfully transplanted at one month and one was symptomatically and hemodynamically improved on the device at 6 months follow-up. This latter patient developed an exit-site infection with Pseudomonas and died at 7 months of sepsis-related multi-organ failure.

In this first human long-term experience, the C-Pulse System was safely implanted and was able to be turned off for brief periods[25]. The C-Pulse System provided important relief of heart failure symptoms and improved cardiac performance. Early infection is likely related to the implant procedure. The device, training, implant procedure and peri-operative care procedures have been modified to reduce infection risk. An expanded feasibility study is warranted.

US IDE FEASIBILITY STUDY (G070096)

The IDE Feasibility Study was intended to examine the effect of C-Pulse® System on long-term heart failure and to look for trends in performance indicators. The objectives of the Feasibility Study were as follows:

- Demonstrate feasibility of device/procedure
    - Assess learning curve
    - Refine technology and implant technique
- Provide reasonable assurance of safety
    - Learn how to mitigate risk
- Explore preliminary efficacy signals
- Support design of subsequent pivotal trial

The study was not powered to detect statistical significance. As such, clinical judgment and assessment of the totality of the data are required to evaluate device safety and potential efficacy from data collected during this study. This clinical judgment was provided by the independent DSMB.

[25] [Hayward 2010]

The DSMB reviewed the entire dataset prior to submission to FDA in November 2011. The DSMB recommendations were:

- Implement dressing change procedures and processes to reduce the infection rate.
- Ask patients if they are on a transplant list prior to enrollment to differentiate between patients that had plans for transplant vs. patients without plans for transplant that received one.
- Provide the feasibility data to the FDA as soon as possible in order to start the pivotal trial and enroll patients under a controlled study.

The aforementioned objectives were met in several ways. The technology was refined, such that a minimally invasive approach to implantation was developed and successfully implemented during the trial. Other technology refinements (e.g., enhancements to Driver hardware and software) were also made. The feasibility of device explantation for "weaning" to native function, device explantation for transplant and device explantation for placement of left ventricular assist devices were demonstrated successfully in the trial. Subjects were supported on the device for a total of 5,439 days, with a mean of 272 days, median of 230 days and a range of 60 to 644 days.

Risk mitigation strategies were developed, including a revised infection control guideline, new PIL stabilization accessory and lead management strategy to be implemented in the pivotal trial. The primary safety endpoint demonstrated that the device related events were substantially lower in some categories (e.g. neurological dysfunction, bleeding) compared to other heart assist devices. The exit site infections were the primary SAE reported. The exit site infections were treated and managed in an outpatient setting. Despite the infections, the subjects continued therapy to the next stage of their heart failure cascade whether transplant, LVAD or recovery.

The primary efficacy endpoint of NYHA demonstrated 12 out of 15 subjects had at least a one Class improvement. In addition, the primary efficacy endpoint of MLWHF demonstrated 13 out of 15 subjects had at least a seven point decrease (improvement) in MLWHF. The 6MHW demonstrated trends toward efficacy. The Peak VO_2 testing did not show a trend toward a positive response but did not demonstrate a negative response. Other observations support the potential efficacy of the C-Pulse® System. For example, inotropes were weaned in all subjects whom had inotropes prior to implant. Diuretic doses were able to be decreased in some subjects. The LVEF, Septal E/E, mitral regurgitation, wedge pressure, LVEDD, LVEDV and CI tended to demonstrate improvement supporting the benefit of LV unloading with the C-Pulse. The initial North American experience demonstrated that the C-Pulse System met the intended use for the device with trends toward efficacy and reasonable assurance of safety with a minimal adverse event profile. Subjects enrolled and implanted with the C-Pulse System were able to be discharged, lived through the post-op period experiencing an improved quality of live than prior to implant. The therapy is treating patients with severe-to-moderate heart failure at a stage in the cascade of the failure in a way that benefits subjects at home providing an increased quality of life compared to alternative therapies. One distinct advantage of the C-Pulse System is the absence of a blood contacting surface, limiting the risk of thrombosis/thromboembolism or the risk of bleeding seen with devices requiring anticoagulant therapies. The preliminary risk/benefit profile of the C-Pulse, supported by this feasibility study, made it a potentially attractive option for the intended patient population (ACC/AHA Stage C, NYHA Class III to ambulatory Class IV patients) and warranted a pivotal trial.

APPENDIX C: LABELING AND OPERATOR MANUAL

The Instructions for Use are provided within each product package and are included under separate cover.

APPENDIX D: SAMPLE HIPAA DISCLOSURE

Authorization for the Use and Disclosure of Protected Health Information (HIPAA)

C-Pulse® System US IDE Study

Sponsor:

Principal Investigator:

Phone Number:

This section is asking you to authorize the use and disclosure of your health information for the C-Pulse® System IDE Study. To do that you need to know:

- The kind of health information about you that the study will collect and use; this information includes:
  - medical chart review
  - imaging from x-rays, CT Scans and echocardiography
  - and laboratory test results;
- The reasons that we are doing this study, which have been described to you earlier, can be found in the Informed Consent section "Why Is This Study Being Done?"
  - Dr. <*insert site PI, or whoever may replace this doctor*> and the research staff are responsible for collecting this information here at <*insert institution name*>.
  - This clinical site will send your information on a form to the sponsor, which maintains of the database for the study.
  - Investigators for study, including representatives from the sponsor, will use your information to better understand how the C–Pulse® System improves or does not improve life for heart failure patients, but they will not use your name or social security number.
  - The investigator and sponsor who make sure that your rights and safety are protected and that study findings are accurate may also need to see information about you in your records.
- This authorization will end at the end of this study when all the information has been evaluated.
- You can stop the use of your information in this research study by sending a written request to Dr. (*insert name of PI*). If you decide to withdraw your authorization:
  - No more information will be collected from you or your records for the research study from the time the written request is received;
  - The study will only use the information it has already collected from you before you sent the written request.

- When you sign this document and authorize the use and disclosure of your health information for this research, the information disclosed may no longer be protected by the federal privacy regulations found at 45 CFR Part 164. But, the researchers for this study can only use or disclose your health information for purposes that are approved by an Institutional Review Board or as required by law or regulation.

STATEMENT OF CONSENT

(*NOTE: This is only a suggested signature format. Sites may use their own signature page*.)

The details of this authorization have been explained to you and you have been given the opportunity to ask any questions you wish.

If you voluntarily agree to allow the researchers to use and disclose your health information for the purpose of this study, please print and sign your name below.

_____	_____	_____
Participant Name (print)	Participant Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

_____

PI or Designee's Statement:

I have reviewed the authorization for the use and disclosure of protected health information with the patient. To the best of my knowledge, she understands the meaning of this authorization.

_____	_____	_____
PI or Designee Name (print)	PI or Designee Signature	Date

Note: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

APPENDIX E: SAMPLE INFORMED CONSENT

SAMPLE OF INFORMED CONSENT
FOR INVESTIGATIONAL RESEARCH STUDY

PROTOCOL TITLE: **C-Pulse® System US IDE Study**

PROTOCOL NUMBER: **PRO 03970**

INSTITUTION: [Institution]

INVESTIGATOR: [Investigator]

Introduction

Your physician has recommended that you consider participation in an investigational research study in which you may undergo a surgical procedure to receive the C- Pulse® System, a heart assist device to treat your heart failure. The C-Pulse device works to assist the heart to pump blood, rather than "replacing" the heart function, and can be safely turned on or off as required.

Currently, heart transplantation is the only widely accepted treatment option for patients with heart failure resistant to standard medications. Mechanical heart assist devices, pumps that do all the work of the heart to pump blood around the body, are used in some patients as a bridge-to-transplant, and in other patients who are not suitable for heart transplant, as a long-term implant (otherwise known as "destination therapy"). Such blood-contacting heart pumps require extensive surgery to implant, and cannot be turned off without the risk of permanent injury to the patient or death.

Purpose

The purpose of this consent form is to provide you with information to decide whether to participate in this study. Before you consent, study procedures will be explained to you, as well as the possible risks and benefits associated with the study. You are being asked to take part in a clinical research study. If you sign this form, you agree to participate in this study.

The purpose of this research study is to evaluate a new heart assistance device, known as the C-Pulse System, to assist your failing heart. The C-Pulse System is an investigational device and is not approved by the Food and Drug Administration (FDA) in the United States. The C-Pulse device is being studied to evaluate its safety and ability to provide your body with improved blood flow. This means that the sponsor is conducting this study in order to verify that the new C-Pulse device can safely and effectively improve heart function in people with ongoing heart

failure and who are resistant to medications. If you agree and you are suitable for the study, your surgeon may perform an operation on you to connect the cuff of the device to the aorta (largest artery in your body that comes from your heart and supplies your body with blood), thread a lead from the outside of your heart and tunnel it through your skin over your abdomen and to the outside Driver unit that controls the operation of the system and is placed in a carry bag that you will wear.

There will be up to 388 patients enrolled and randomized in this study in the United States and up to 40 centers in the US and potentially some Canadian centers. Your part in the study and follow-up visits are expected to last up to five years.

It is important that you read and understand this consent form. It may contain words that you do not understand. Please ask your doctor to explain any words or information that you do not understand. Do not sign this consent form unless you have received answers to all of your questions.

Device Description

The C-Pulse System is a new heart-assist device that allows you to remain active and does NOT contact the blood; therefore, you will not need blood thinning medications. The C-Pulse device works to assist the heart to pump blood, rather than "replacing" the heart function, and can be safely turned on or off as required.

The C-Pulse Cuff is positioned around the ascending aorta, the main artery coming out of the heart that delivers blood to the body. The Cuff deflates just before the heart pumps blood, reducing the workload of the heart (Fig 1A), and the Cuff is timed to re-inflate in between heart beats, once the heart has finished ejecting blood and the aortic valve closes. During this latter period, as the heart is re-filling, the Cuff inflation acts like a second heart beat, producing a second surge of blood flow to the heart muscle and around the body (Fig 1B). Reducing the load on the heart and increasing the blood flow to the heart muscle are very important in assisting the heart to pump blood around the body. Keeping the device out of the bloodstream limits the difficulty of implantation of the device and allows the device to be turned on and off for short periods of time.

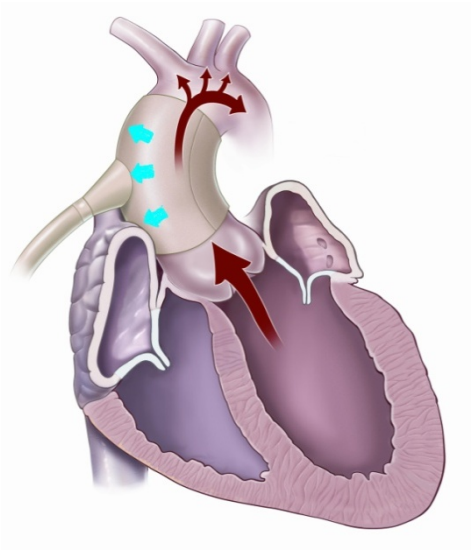

Figure 1A. C-Pulse Cuff deflates as the heart ejects blood, unloading the heart

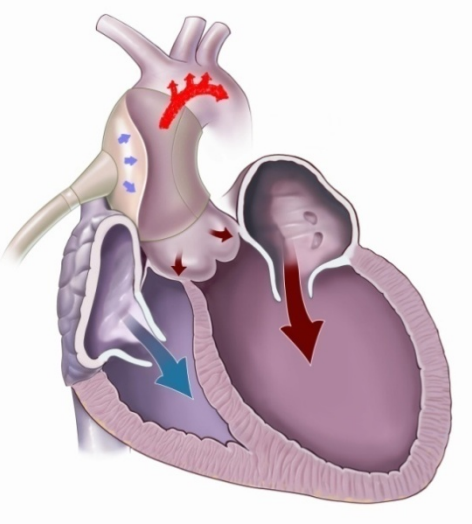

Figure 1B. C-Pulse Cuff inflates as the heart refills with blood, giving a secondary pulse of blood to the body and heart muscle

The C-Pulse device is intended as a permanent implant and for the duration of the study to be used continuously. It is considered safe to turn the device off for short periods (up to 15 minutes) to sponge bathe or shower, though you may experience return of symptoms of heart failure such as shortness of breath or dizziness during the period the device is off.

The implanted C-Pulse Cuff is intended to have an operational life of at least five years. The Driver is designed to detect any Cuff failure and alarm and stop pumping. The Cuff and the line that goes from the Cuff out of your body at the abdomen where it connects to the Driver are expected to be able to be replaced if this is needed.

Previous Clinical Study

A smaller study enrolled twenty-one patients who were implanted with the C-Pulse System with the intent to follow the patients for up to five years. There are five patients still in this smaller study. Two patients are using C-Pulse therapy and three patients are not using C-Pulse therapy but have the Cuff still implanted. It is common for patients in a study not to participate for the entire study. The reasons for patients not completing five years of follow up may be due to heart failure symptoms improving so they came off the device, not wanting to stay on the therapy, going on to other therapies such as a Left Ventricular Assist Device (LVAD), heart transplant, other medical conditions that arise (e.g. cancer) or death. This smaller study showed that these twenty-one patients were on the C-Pulse for a total of 13,633 days, with an average of 649 days.

The status of these twenty-one patients over the six years since the first patient was implanted with the C-Pulse System is presented in Table 1.

Table 1: Patient Status Over-Time

Patient Status Over-Time	6 mths	12 mths	2 yrs	3 yrs	4 yrs	5 yrs
Still in the Study	16	13	6	6	4	1
Went to LVAD	1	1	1	NA	NA	NA
Received a Heart Transplant	1	1	2	NA	NA	NA
Device Related Death	1	0	2	NA	1	NA
Non-Device Related Death	2	0	1	NA	NA	NA

NA – no reported events during this time.

The study also demonstrated signs of benefit for the patients on therapy. These improvements were as follows:

- The majority of patients improved a minimum of at least one heart failure classification (New York Heart Association Classification)
- An improved quality of life (MLHFQ Score – Figure 2)
- An improvement in the 6 Minute Walk Test (Figure 3)

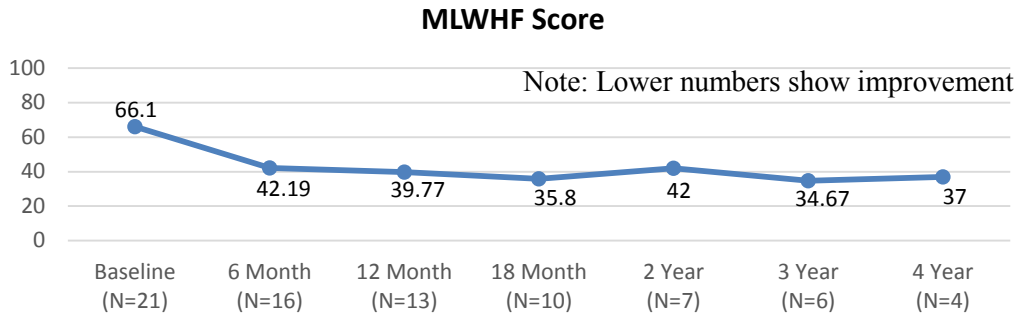

Figure 2. Minnesota Living With Heart Failure Score (MLWHF)

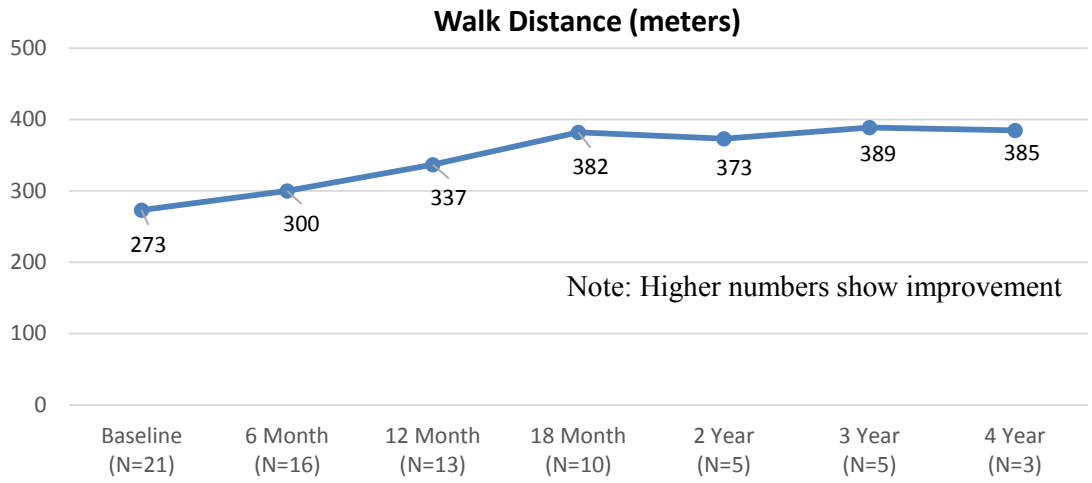

Figure 3. Six Minute Walk Distance

Infection of the exit site (where the lead comes out of the body), chest wound (after surgery) and the internal implanted components were the most serious adverse events. The exit site infections were the most frequent adverse event reported. These infections need to be managed by you and your doctor. If the infection reaches your Cuff, the Cuff must be removed. There were four deaths associated with infections that reached the Cuff and the Cuff was not removed. There was a fifth patient, at approximately 4 ½ years post implant, with an infection at the aorta. During surgery to remove the cuff the aorta tore and required repair. The patient recovered and was discharged from the hospital. If the infection stays in the Cuff area it can affect the aorta and cause a tear in the aorta that can result in death.

In one patient there was an infection of the chest wound from placing the cuff. The chest area, near the cuff, remained infected for four months. During a surgical procedure to address the infection at the cuff, the aorta tore and the patient died due to bleeding from the tear. Three patients had exit site infections that continued for months and the infection moved from the exit site to the cuff. For two of these patients, infection at the cuff resulted in a tear and bleeding from the aorta which resulted in death, at approximately two and four years after implant. For the third patient, at approximately one year after implant there was an infection at the cuff resulting in a tear and slight bleeding from the aorta which ultimately stopped. The patient was taken off their medications and subsequently died.

Your doctor can tell you about the risk of infection and how he would manage an infection.

Screening Evaluation, Tests, and Procedures

You are being asked to participate in some screening tests and procedures to determine if you are eligible for the COUNTER HF study. If you meet criteria based upon these tests, you may be eligible to participate in the study. If you do not meet these criteria, you will not qualify to participate in the study. Once you sign this consent form you will begin your screening tests and procedures.

If, after discussing the screening test procedures with your doctor, you agree to participate in the screening, your doctor will need to get information from you to determine if you have any medical condition that could exclude you from the study, increase your risks of surgery or interfere with the therapy. Your evaluation may include the following;

- Medical history
- General physical exam
- Recording of weight, heart rate/rhythm, blood pressure and temperature
- Documentation of heart failure medications

You will be asked to have a chest x-ray to determine the condition of your aorta (the largest artery in your body that comes from your heart and supplies your body with blood) and lungs to see if you have any hardened areas in your aorta or any lung problems that may be a risk to you if you receive the C-Pulse Cuff. If your chest x-ray indicates you have hardened areas in your aorta or your lungs are not clear, you will not need to go on with any further screening tests and procedures as you will not be able to participate in the study.

If the chest x-ray indicates you have no hardened areas in your aorta and your lungs are clear, your doctor will ask you to have a more extensive procedure to determine the condition of your aorta called a computed tomography (CT) scan or CAT scan. This test is used to show by imaging in detail, sections of your aorta to determine if disease is present. This scan will be performed in the hospital or out-patient image center. You will be asked to lie on a narrow table that slides into the center of the scanner while x-ray beams rotate around your chest. You may be asked to hold your breath during image capture. You may need some medication to help you relax. If the CT scan indicates you have aortic disease, it may be a risk to you if you receive the C-Pulse Cuff, therefore, you will not need to go on with any further testing and will not participate in the study.

Once the condition of your aorta has been determined to be suitable for the study by chest x-ray and the CT scan; you may have more tests to determine if you are eligible for the study. If at any time during the testing you are not eligible for the study, your doctor will stop any further testing and you will not participate in the study. The following is a remaining list of procedures that you will be tested for to determine if you are eligible for the study.

- Transthoracic echocardiogram, (ECHO of your chest and heart) a painless procedure where gel is placed on a transducer which then goes on your chest to measure your heart chambers and function including the valves of your heart.
- Complete two questionnaires relating to your quality of life (MLHFQ Score and KCCQ)
- Complete two assessments (NYHA Classification, Six Minute Walk - to measure how far you can walk in 6 minutes)
- Pregnancy test (if applicable)
- Blood tests

Study Procedures

After discussing the study with your doctor, if you meet all screening criteria for the study and you decide to participate in the study, you will be randomized into the study and you will have a 50% chance "like the flip of a coin" to either undergo surgery to implant the C-Pulse System or to remain with your current optimal medical management. You will not be able to receive the C-Pulse System if you are randomized to the option of current optimal medical management.

If you are randomized to receive the C-Pulse System you will be expected to stay on the device. The following are a list of procedures you can expect during and after the surgery:

<u>During the implant procedure (2 hours)</u>
During surgery, your chest will be surgically opened and a cuff that has been correctly sized to your aorta will be wrapped around your aorta and activated to help assist the heart in pumping blood.

The ascending aorta (the main blood vessel which carries blood ejected from the heart) is freed up.

The pre-shaped inflatable C-Pulse Cuff is wrapped around the aorta and a lead to sense the ECG (the electrical signals of the heart) is attached to your heart. The gas line and sensing lead are connected to a single tube that is tunneled under the skin and brought out through the skin over the abdomen. This tube has a connector that allows it to be connected to a Driver (Fig 1)
The Driver is activated during surgery to ensure the device performs as expected. Monitoring of arterial blood pressure will also happen.

Fig 2: C-Pulse device with wearable driver unit

After the procedure and before you leave the hospital:
All patients who receive the device will have it turned ON for the duration of the study.

Following the surgery, the expected stay in Intensive Care is 2-3 days to ensure the device is functioning in time with the heart and there are no heart rhythm disturbances and that the blood pressures are stable. The stay in the hospital may be up to 14 days and discharge from the hospital will be judged on your medical condition, your ability to walk without aid for short distances and you and your care-giver being able to handle the Driver and look after the exit site dressings. You will continue to take heart failure medication under the guidance of the investigators and your cardiologist. Rehabilitation following surgery is important to ensure a good recovery and this will also involve a program of physical and nutritional guidance.

In order to study the device therapy the C-Pulse System needs to remain "On". Your doctor and medical team will teach you how to disconnect from your device for short periods of time for personal hygiene. You will need to discuss this with your doctor.

You will not leave the hospital until your doctor has decided that you are ready.

You will be given instructions to be sure that you understand the complete device information and personal care that you need to do at home.

If you have the C-Pulse System implanted or if you do not, all patients will have the visits and tests explained below. If you do not have the device implanted, the device checks and exit site pictures will not be completed.

6 Week Follow-up Visits
- General physical examination
- Documentation of heart failure medications
- Recording of weight, heart rate, blood pressure
- A picture of your exit site will be taken and placed in your study records
- The C-Pulse System will be checked

3 Month Follow-up Visits
- General physical examination (including blood tests)
- Documentation of heart failure medications
- Recording of weight, heart rate, blood pressure
- ECHO of your heart
- Complete NYHA Classification and Six Minute Walk-assessment (to measure how far you can walk in 6 minutes)
- Complete 2 questionnaires relating to your quality of life
- Blood tests
- A picture of your exit site will be taken and placed in your study records
- The C-Pulse System will be checked

6 and 18 Month Follow-up Visits
- General physical examination (including blood tests)
- Documentation of heart failure medications
- Recording of weight, heart rate, blood pressure
- Complete NYHA Classification and Six Minute Walk-assessment (to measure how far you can walk in 6 minutes)

- Complete 2 questionnaires relating to your quality of life
- Blood tests
- A picture of your exit site will be taken and placed in your study records
- The C-Pulse System will be checked

Annual Follow-up Visits

- General physical examination (including blood tests)
- Documentation of heart failure medications
- Recording of weight, heart rate, blood pressure
- CT scan of your chest (for implanted patients at 12 months only).
- ECHO of your heart
- Chest X-Ray
- Complete NYHA Classification and Six Minute Walk-assessment to measure how far you can walk in 6 minutes
- Complete 2 questionnaires relating to your quality of life
- Blood tests
- A picture of your exit site will be taken and placed in your study records
- The device data will be saved and adjustment will be made if needed
- Device usage will be evaluated

After five years of annual visits, your participation in the study will be completed.

Risks

Screening Tests and Procedures

There are some risks in going through the screening tests and procedures. These risks are described below:

- Possible infection at the needle puncture site from blood tests
- Exposure to x-ray

Study Risks

There are several risks associated with participating in this study listed below.

Risks in this study may come from the surgical procedure itself, implantation procedure or the investigational device. Your study doctor will discuss them with you.

General Anesthetic

- Drug reactions
- Low blood pressure
- Difficulty with maintaining adequate oxygen to the body

Surgical procedure / Implantation or During Therapy:

- Bleeding, possibly requiring blood transfusions, surgical or medical interventions
- Infection possibly requiring surgical or medical intervention (e.g. intravenous medication, antibiotics)
- Stroke or other neurologic event
- Memory and thinking problems

- Decrease or loss of kidney function, possibly requiring use of a machine to filter your blood
- Irregular heartbeats
- Fluid buildup around the heart
- Damage to the aortic wall that may cause the layers of the aorta to separate
- Device malfunction such as damage to the cuff, misplacement of the lead on the heart
- Blood disorders
- Abnormal liver function; digestion complications; fever or chills, organ failure or dysfunction
- High blood pressure
- Heart attack
- Separation of your incision
- Lack of sufficient oxygen to limbs or organs to support normal organ function
- Partial or full blockage of your veins or arteries
- Breathing problems
- Death

C-Pulse® System Heart Assist Device:

- Infection – infection from the line that is tunneled through your skin to the outside of your body may occur that could spread to the cuff
- Aortic disruption – infection of the aorta under the cuff may cause a split in the aortic wall that may cause the layers of the aorta to separate
- Worsening of heart failure symptoms – you may experience symptoms of heart failure, such as shortness of breath or dizziness
- Lack of effect – the device may not provide relief from your heart failure symptoms if they are severe
- Device failure – failure of the device to provide adequate support to relieve the symptoms of heart failure
    - Persistent leaking balloon may cause surgical emphysema (injury to the air sacs in the lung) or pneumothorax (abnormal collection of air in between the lung and chest wall)
    - Leakage of non-sterile air may cause pneumothorax or chest infection
    - Air emboli in the aorta
    - Needle puncture in the cuff
    - Failure of the electronic system to detect any system failure such as current leakage, voltages, power supply or over inflation of the cuff
- Emboli – due to the repeated inflations of the cuff, small particles in your blood may come loose from the aortic wall causing a stroke
- Death

There may be additional risks which are unknown. Your doctor has been chosen to participate as an investigator in this study because he or she has the skills and knowledge to perform the study procedures and this should minimize your risk.

If your doctor suspects that you have an infection from the line that is tunneled through your skin to the outside of your body, additional tests may be requested. These tests may include blood tests for infection, CT or PET scans, to determine if the tube should be removed to let the infection heal.

In the event of your death during the study, an autopsy may be requested. If an autopsy is performed, small pieces of your aorta may be collected for examination under a microscope. This may be requested regardless of whether you have had the C-Pulse System implanted for the study. If you had a device implanted, that device may be returned to the Sponsor for testing as well, if an autopsy is performed.

If you are pregnant or plan to become pregnant or are nursing a baby, you cannot enter this study. There may be a risk of severe problems. Women may participate in this study only if they are past menopause, have had surgery to make them sterile, or are using an acceptable form of birth control throughout the course of the study. If you become pregnant during the trial, you must notify your doctor immediately.

Benefits

There is no guarantee that you will benefit from taking part in this study. The main benefit from participation in the study may be some improvement in your quality of life. It is not expected that there will be a complete restoration to a quality of life that you had before heart failure.

The information from this study may also benefit future patients who are in moderate to severe heart failure.

Alternatives

The alternative to using this new device includes ongoing medication for alleviating the symptoms of heart failure. If symptoms persist, cardiac transplantation or mechanical blood pumps may be an option in some patients. Your disease process could also improve after adequate medications or pacemaker placement and can actually stabilize and remain stable for a period of time. The C- Pulse device is intended as a treatment option in patients who are able to walk, on optimal medical therapy but continue to have a poor quality of life.

Voluntary Participation

Your participation in this study is voluntary. You may choose whether you wish to be in this study and whether to remain in the study at all times after enrollment. If you withdraw from the study, you will not lose any benefits to which you are entitled. Your participation in the study may be stopped at any time by your doctor without your consent. If you withdraw or are withdrawn from the study for any reason, you may be asked to return to the clinic for a follow-up examination.

If you elect to discontinue participation in the study and were implanted with the study device, you may choose to have the entire the C-Pulse System removed or you may choose to have it remain in your body. Removal of the entire system would include a surgical procedure similar to the original implant procedure; although similar, the risks associated with the removal of the system are inherently greater. Alternatively, the Percutaneous Interface Lead (PIL), the tube that exits your abdomen, can be removed in a minor surgical procedure. Your doctor would make a small incision near the tube connector in your abdomen, disconnect the tubing, cap the interior line, remove the PIL, and close your skin. Removal of the PIL, the tube that exits your

abdomen, reduces your risk of infection by eliminating an open exit site. If you elect to discontinue participation in the study while any part of the C-Pulse system remains in your body, you will need to continue being seen regularly by your cardiologist.

You will be informed of any new information that may affect your decision to continue in the study.

Termination

This research study may stop for a variety of reasons. These may include reasons such as: unacceptable side effects, the device being shown not to be effective or not need further investigation; and business decisions made by the Sponsor.

New information arising during the study

During the study, new information about the risks and benefits of the device may become known to researchers and might alter your willingness to continue your participation in the study. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

Cost

Routine costs are those costs normally incurred as a result of medical care associated with the treatment of your heart failure condition. These costs are generally the patient's responsibility or, where appropriate, the responsibility of your insurance company. You will not incur any additional costs as a result of your participation in this Study.

Compensation

You will not receive any compensation for participating in this study.

Financial Arrangements with Sponsor

As is usually the case for clinical trials that are sponsored by a manufacturing company, <Hospital> will receive payment from the Sponsor for each patient enrolled in this study. These payments will be used to defray the costs of data collected for the study. No hospital staff member will receive private income as a result of your enrollment in this study.

Injury

In the event that physical or psychological injury occurs as a result of your participation in this research project, medical treatment will be available. This treatment, as well as other medical expenses, will be paid for by you or your health insurance in your usual manner. No compensation or reimbursement is available from_____ (name of institution) _____, or the Sponsor, Sunshine Heart, Inc.

If you are injured you should report the injury by contacting:

_____ _____

(Principal Investigator) (Telephone number)

Confidentiality

If you agree to take part in this study, your medical records will be treated confidentially except as required by law. Access to your medical records will be limited to the medical staff at the study center, some qualified representatives from the sponsor, the Institutional Review Board (IRB) reviewing the study, and the US Food and Drug Administration (FDA). Any billing or payment information related to the study, including your hospital bill (Form UB04) your physician's bill (Form CMS1500) and payments from Medicare, Medicaid or your insurance company (remittance advice or explanation of benefits) may be reviewed by Sunshine Heart, Inc. Nothing about you, your illness or treatment will be made public. If the results of this study are published, your identity will remain confidential. A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Study Questions

If you have questions about the study, you may contact

_____ _____

(Principal Investigator) (Telephone number)

Patient Rights

If you have questions regarding the conduct of this study or your rights as a research patient, you may contact:

_____ _____

Chairperson of the IRB (Telephone number)

Permission for Access to and Use of Health Information

If you decide to take part in the study, Sunshine Heart Inc. and others will see your health data. This section governs how your health data will be used and shared during and after the study. The health data that may be used and shared includes all data collected during the study and any health data in your medical records that is relevant to the study.

Providers' Disclosure of Health Information in Your Medical Records

You agree to permit [hospital and/or clinic], your doctors, and your other health care providers ("Providers") to share health data in your medical records with [investigator(s)] and [his/her/their/its] staff ("Researchers"). You agree to permit Providers to share your health data:

- With Sunshine Heart Inc. and its agents and contractors
- As required by law
- With government organizations and review boards required to watch over the safety and effectiveness of medical products and therapies and the conduct of research
- With other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research

Researchers' User and Disclosure of Your Health Information

You agree to permit the Researchers to use and share your health data

- Among themselves to conduct the study
- With other researchers in the study
- With Sunshine Heart Inc.
- With government organizations and review boards required to watch over the safety and effectiveness of medical products and therapies and the conduct of research
- With other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research

Once Providers or Researchers have shared your health data with a third party, the data may be patient to further sharing by the third party. Federal privacy laws may no longer protect it from further sharing.

While the study is in progress, you will not be allowed to see your health data that is created or collected for the study. After the study is done, you may see this data as in the [hospital/clinical trial sits]'s Notice of Information practices.

Sunshine Heart User and Disclosure of Your Health Information

This section describes what Sunshine Heart will do with the study data. This includes your health data received during the study.

Sunshine Heart Inc. will keep your health data confidential in keeping with all applicable laws. Sunshine Heart Inc. may use your health data to conduct this study. Sunshine Heart Inc. may also use your health data for other purposes, such as

- Watch over and improve the device performance
- New medical research
- Plans for making new medical products or procedures
- Other business purposes

Any reports about the study will not include your name or a description of you. Data received during the study will not be used to market to you. Your name will not be placed on any mailing lists or sold to anyone for marketing purposes.

Your Country's regulations and other laws control Sunshine Heart Inc.'s work in making new devices. These laws help make certain the safety and quality of medical devices. Sunshine Heart Inc. may share your health data with the United States Food and Drug Administration (FDA) or other US and foreign government authorities that are responsible for the safety of medical devices. Sunshine Heart Inc. may share your health data with institutional review boards and persons who watch over research and the safety and effectiveness of medical products and research. You agree to allow Sunshine Heart Inc. to use study data in these ways.

This consent does not have an ending date. But you may change your mind and take back this consent to use your health data at any time. To take back this consent, you must write to [name and contact information]. If you take back this consent, you cannot take part in the study. Even after your part in the study ends, Sunshine Heart Inc. and Researchers may continue to use and share the health data they obtained during the study as described here.

Consent

I have read the information in this consent form (or it has been read to me).

I have had an opportunity to discuss with my study doctor the purpose, methods, risks (including the added risk related to re-operation to remove the device if necessary) and potential benefits of this research as well as available alternatives, and to ask questions regarding my participation in this research. My questions have been answered to my satisfaction.

My participation in this research is voluntary. I agree to participate in this research study. By signing this consent form, I have not given up any of my legal rights.

I will be given a copy of this informed consent form.

Authorization

I have been given the information about the use and disclosure of my health information for this research study. My questions have been answered.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

_____ _____

Signature of Patient Date/Time

_____

Print Name of Patient

_____ _____

Patient's Legal Representative Signature (if applicable) Date/Time

_____

Printed Name of Patient's Legal Representative (if applicable)

_____ _____

Investigator Signature (or Designee) Date/Time

_____

Printed Name of Investigator (or Designee)

APPENDIX F: HOME DISCHARGE CHECKLIST

Discharge Check List

This checklist has been developed to be used as a guideline for the Discharge Criteria for each patient prior to going home.

	Acceptable	**Unacceptable**	**Comments**
Stable Medical Condition. *(e.g. Healing wounds, no sign if infection or sepsis)*			
Able to walk 30 meters with device without stopping due to shortness of breath, muscle fatigue, unsteady gait, pain			
Care–giver demonstrates aseptic technique in changing exit site dressing			
Patient and caregiver independently demonstrate connection and disconnection of the drivers			
Patient and caregiver independently demonstrate changing, recharging and calibrating batteries			
Patient and caregiver understand and respond to the Driver Alerts and Alarms			
All protocol required testing is completed up to point of discharge			
Patient Manual supplied to patient, with Emergency Contact details specified			

APPENDIX G: HEART FAILURE ASSESSMENTS

NYHA Classification

In 1928, the New York Heart Association published a classification of patients with cardiac disease based on clinical severity and prognosis. This classification has been updated in seven subsequent editions of Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (Little, Brown & Co.). The ninth edition, revised by the Criteria Committee of the American Heart Association, New York City Affiliate, was released March 4, 1994. These classifications are summarized below.

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina.

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.

Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina.

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

ACC/AHA Stages of Heart Failure

In 2001, the ACC/AHA published an update subdividing clinical heart failure into four ‘stages’. The stages are listed below:

Stage A. Patients at high risk for developing clinical HF (i.e. those with hypertension, diabetes, dyslipidaemia, and so on), but without detectable structural heart disease.

Stage B. Patients with detectable structural heart disease (i.e. LVH, LV Dysfunction), but no clinical signs or symptoms of HF.

Stage C. Patients with current or past clinical HF.

Stage D. Patients with end-stage refractory HF, who are candidates for extraordinary forms of therapy or for compassionate end-of-life care.

APPENDIX H: SIX MINUTE HALL WALK

The six minute walk test (6MWT) will be conducted as described by Guyatt et al.[26] and as used by other investigators in heart failure clinical trials[27] [28]. In a corridor, a course approximately 30.5 meter (100 feet) (without elevations) will be marked and a chair will be placed at each end. The corridor should be long, flat, straight and one that is seldom travelled. The turnaround points should be marked with a cone (such as an orange traffic cone or brightly colored tape). A starting line, which marks the beginning and end of lap, should be marked on the floor using brightly colored tape. In addition to the turnaround points, a 15 ft marker should be placed for timing of the first 15 ft walked for the frailty data collection.

PATIENT PREPARATION

- Comfortable clothing should be worn.
- Appropriate shoes for walking should be worn.
- Patients should use their usual walking aids during the test (cane, walker, etc.).
- The patient's usual medical regimen should be continued.
- A light meal is acceptable before early morning or early afternoon tests.
- Patients should not have exercised vigorously within 2 hours of beginning the test.

The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate.

Patients will be instructed to walk from end to end at their own pace while attempting to cover as much ground as possible in the allotted period of six minutes. A nurse coordinator will time the test, and encourage the patient every 30 seconds in a standardized fashion, while facing the patient and using one of two phrases:

“You’re doing well” or “Keep up the good work”.

Patients will be allowed to stop and rest during the test, but will be instructed to resume walking as soon as they feel they are able to do so. After six minutes, patients will be instructed to stop walking. The total distance walked will be measured to the nearest meter (and foot). Symptoms experienced by patients during the walk (e.g., angina, dyspnea, fatigue, dizziness) will be recorded.

Before the Baseline Six Minute Hall Walk test, a familiarization Six Minute Hall Walk test is required. The familiarization test should take place at least one hour before the Baseline test.

[26] [Guyatt]

[27] [Bittner 1993]

[28] [Riley 1992]

APPENDIX I: CARDIOPULMONARY EXERCISE TESTING SUBSTUDY

Cardiopulmonary exercise (CPX) testing will be performed at baseline (pre-implant) and at the 12-month follow-up visit to assess patients' exercise tolerance. CPX testing will be conducted among patients enrolled at a subset of sites. These sites will be selected based on their interest and experience in performing these CPX tests. Testing methods will be standardized between all participating sites through a manual of operations and webinar training. Each site will be required to participate in quality assurance testing before testing subjects and regularly throughout the trial. All CPX test data will be analyzed centrally through a Core Laboratory.

Exercise will be performed on a treadmill using a modified Naughton protocol or leg (cycle) ergometer using a 10 watt per minute ramped protocol. The same exercise mode will be used at baseline and follow-up within a given patient. Patients will be exercised until they have reached a symptom-limited maximal effort. Tests will be conducted in accordance with guidelines outlined by the American Cardiology of Cardiology and the American Heart Association (Gibbons 2002).

Respiratory gases will be measured continuously during all exercise tests using the metabolic cart currently available at each site. Data will be exported from the cart software and sent to the Core Lab for analysis consistent with guidelines outlined by the American Heart Association (Balady 2010).

Key CPX variables to be reported include:

- Peak oxygen consumption (VO_2) in mL/min and mL/kg/min
- Percent of age-predicted maximum VO2
- VO2 at ventilatory derived anaerobic threshold
- Change in minute ventilation (VE) to change in carbon dioxide (VCO2) slope (VE/VCO2 slope)
- Peak respiratory exchange ratio (RER)
- Total exercise time
- Heart rate and blood pressure and rest and peak exercise

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APPENDIX K: INFECTION CONTROL GUIDELINES

Infection control encompasses many factors including nutrition, management of conditions such as diabetes, prophylactic treatments and exit site care.

Prior to surgery it is recommended that the nutritional status of the patient be assessed and addressed if the status is marginal. In addition, controlling blood sugar levels in the diabetic patients is also important.

Pre-Operative Recommendations:

- Nutritional status of the patient should be assessed prior to surgery. If nutritional status of the patient is marginal, attempts should be made to improve the patient's nutritional status prior to surgery.
- Diabetic patient's glucose levels should be normalized on a stabile regimen prior to surgery.

Percutaneous Interface Lead (PIL) exit site should be pre-selected and marked prior to surgery:

- Pre-select an exit site for the Percutaneous Interface Lead that will facilitate PIL immobilization as well as patient selection for clothing, daily routine, etc. This should preferably be done while the patient is standing. Pre-selection of the PIL exit site will help to facilitate effective PIL immobilization after implant. Pre-selection at the very least should take into account patient body habitus, patient's dominant hand, as well as input from the patient concerning daily routine and fit of clothing.

Prep for surgery:

- Pre–operative scrub with antiseptic (Septisol or Chlorhexidine) on the night prior to surgery then again the morning of the surgery, and clip the surgical area prior to transport to the operating room.

Antibiotic prophylaxis recommendations:

Administer prophylactic antisepsis coverage. Recommended prophylaxis:

- Nasal Mupirocin Ointment application day prior to surgery
- Vancomycin 15mg/kg IV ending within 30 minutes of skin incision with interval blood pressure monitoring or arterial line monitoring – note that Vancomycin can cause hypotension in this patient population and should not be given unsupervised pre-operatively on the ward. Follow-up doses every12–24 hr post-operatively for 48 hrs, guided by serum Vancomycin trough levels.
- Cephalexin 1g IV one hour pre–op then every 8–12hr for 48 hrs
- Rifampicin 600 mg by mouth 2hrs pre–op then daily for 2 days – stop if liver function tests become abnormal greater than two times baseline.

Peri-operative recommendations:

- Observe Operating Room precautions – particularly, limit the number of people in the room, and traffic in and out of the room.
- Recommended approach to skin preparation:
    - antiseptic scrub (Septisol or Chlorhexidine)
- Drape patient with steri–drapes (e.g. Ioban), over exposed prepared skin.
- Delay opening of the C-Pulse devices until necessary.
- Massage flocking and wrap with antibiotic soaked gauze (e.g. standard mix doxycycline) prior to implantation. Keep the C-Pulse devices and driveline covered with antibiotic gauze while on OR prep table.
- The PIL should be inserted in such a manner that the flocking is not visible at the end of surgery.
- After implantation and before leaving the OR, close the exit site for good apposition and leave sutures in place for 7-10 days. Place a suture-tie on the PIL adjacent but separate (1-2 cm) from the exit site and leave in place for 4-6 weeks. Secure the Percutaneous Interface Lead (PIL) Patient Connector and the Driver Lead connector with two points of anchor using two separate adhesive catheter securement devices. Strict immobilization of the PIL at the skin exit site is crucial to getting effective flocking anchoring by fibrosis formation and preventing infection at the PIL exit site.

Post-Implantation Recommendations:

- Chest and other drains should be removed as soon as practical, at the discretion of the surgeon, and typically with**in 48 hours, depending o**n drainage.
- Monitor patient's nutritional status and intervene early if their status becomes marginal.
- An Insulin infusion should be established in patients with diabetes or other glucose intolerance until a regular diet and normal diabetic therapy can be re-introduced. Early mobilization and graduated physical therapy should be conducted as tolerated from post-operative day 1. The Carry Bag Waist Strap and Driver Lead coiling Velcro strap should be used when ambulating. Ambulation should be started gradually and used with assistance from physical therapy or other hospital staff.
    - The C-Pulse Driver Lead should be attached to the patient's clothing or secured with the coiling strap to establish a 3rd level of stress relief for the driveline while the patient is out of bed.
- PIL dressing changes should be performed strictly following dressing change protocol and should be limited to as few people as possible. Ongoing oral broad spectrum/gram negative antibiotics are recommended for or until chest drains are removed and the exit-site has dried sufficient for once daily dressing only.
- Provide ongoing education to patient and caregivers on general hygiene e.g. regular hand washing and importance of PIL immobilization and care to avoid pulling, pushing or torque at the PIL exit site.

- Schedule removal of the skin suture tie at the PIL exit site according to the physician orders.

Exit Site Care:

PIL Exit Site Dressing Change Key Points

- Exit site dressing and lead stabilization should occur in the OR prior to the patient transferring from the OR table.
- First 72 hours post implant - dressing should remain untouched as long as it remains dry.
- If the dressing becomes soiled, it should be changed immediately
- As post-operative drainage decreases, exit site dressing changes can be decreased to once daily or once every other day.
- Strict immobilization of the PIL site should be observed at all times. The PIL patient connector and driver lead connector should be stabilized using two adhesive catheter securement devices - one for the PIL patient connector and one for the driver lead.
- The Driver should remain in the Carry Bag at all times when being used by the patient, Careful attention should be made to prevent the Driver from falling or being dropped.
- Limitation of personnel around patient should be exercised while performing PIL exit site dressing changes to limit contamination of PIL exit site.
- Patient and/or Caregiver should be taught strict dressing change procedure and allowed to take over dressing changes as soon as they are competent.

Dressing Change Procedure

The following procedure is to be followed for all PIL exit site dressing changes.

Equipment needed:

- Driveline Management Kit
- One adhesive catheter securement device (in addition to that supplied in the driveline management kit).

OR:

- Masks (2)
- Disposable sterile drape or towel (1)
- Clean gloves (1 pair)
- Sterile gloves (1 pair plus one unopened pair for backup)
- 2 Chlorhexidine surgical prep swab sticks (2% Chlorhexidine) or 2% Chlorhexidine Solution
- 4X4 drain sponge (1 packet of 2 sponges)

- 4X4 gauze pad (1 packet of 2 pads)
- Clear occlusive Dressing (i.e. Tegaderm)
- 2 adhesive catheter securement devices (i.e. a catheter anchor for the PIL patient connector and the Driver Lead)

Procedure Using Driveline Management Kit:

1. Wash hands and arms thoroughly with water and antibacterial soap. Dry using a clean disposable towel.
2. Place a mask over the nose and mouth of everyone in the room, including the patient if possible.
3. Put on clean gloves.
4. Open the dressing kit using sterile technique.
5. Remove open the sterile towel to create a sterile field.
6. Open and drop the chlorhexadine swab sticks into the driveline management kit container. Open and drop the 4X4 gauze pad and drain sponge on the sterile field.
7. Remove and discard old dressing.
8. Examine the site for problems with PIL integrity and signs of infection (e.g. purulent drainage, redness or tenderness to palpation).
9. If signs of infection are present, culture exit site drainage using a sterile culturette.
10. Examine the adhesive catheter securement devices. Remove if adhesive is coming loose or if PIL immobilization requires revision. Be sure to allow as little movement as possible of the PIL at the exit site.
11. Remove dirty gloves and don sterile gloves. This must be done observing strict sterile technique.

    *Note: It may be helpful to have another set of sterile gloves immediately available in the event contamination occurs.
12. Clean the PIL exit site and the percutaneous lead with the Chlorahexadine swab sticks.
    a. Follow a circular pathway from the catheter outward. Use gentle pressure moving from the exit site outward.
    b. Discard each swab once lifted from the patient's skin.
13. Allow solution to air dry for at least 2 minutes. DO NOT DRY THE SITE WITH A 4x4.
14. Take a picture and upload it to the electronic data capture system
15. Apply the 4x4 drain sponge and the SorbaView Shield Dressing
16. If not using Centurion supplies, apply a large clear occlusive dressing, or tape reinforcement to entire site covering the drain sponge and PIL.

17. Ensure that the PIL is immobilized without twisting or tension by the two separate adhesive catheter securement devices at two separate locations, one at the PIL patient connector and one at the driver lead connector. If either anchor is compromised replace it immediately.

Procedure Without Driveline Management Kit:

1. Wash hands and arms thoroughly with water and antibacterial soap. Dry using a clean disposable towel.
2. Place a mask over the nose and mouth of everyone in the room, including the patient if possible.
3. Put on clean gloves.
4. Open the disposable sterile towel to create a sterile field.
5. Open the 4x4 gauze pads and 4x4 drain sponges and drop them on the sterile field.
6. Pour the Chlorhexidine cleansing solution (2%) onto the gauze pad or drop the chlorhexadine swab sticks onto the sterile field.
7. Remove and discard old dressing.
8. Examine the site for problems with PIL integrity and signs of infection (e.g. purulent drainage, redness or tenderness to palpation).
9. If signs of infection are present, culture exit site drainage using sterile culturette.
10. Examine the adhesive catheter securement devices. Remove if adhesive is coming loose or if PIL immobilization requires revision. Be sure to allow as little movement as possible of the PIL at the exit site.
11. Remove dirty gloves and don sterile gloves. This must be done observing strict sterile technique.

    *Note: It may be helpful to have another set of sterile gloves immediately available in the event contamination occurs.
12. Clean the PIL exit site and the percutaneous lead with the Chlorhexidine soaked gauze or swabs.
    a. Follow a circular pathway from the catheter outward.
    a. Discard each gauze pad or swab once lifted from the patient's skin.
    b. If using Chlorhexidine solution on 4x4 gauze pads allow one pad to remain wrapped around PIL for 2 minutes then remove and discard
13. Allow solution to air dry for at least 2 minutes. DO NOT DRY THE SITE WITH A 4x4.
14. Take a picture and upload it to the electronic data capture system
15. Apply a 4X4 drain sponge around the PIL.
16. Apply large clear occlusive dressing (i.e. Tegaderm) or tape reinforcement to entire site covering the drain sponge and PIL.

17. Ensure that PIL is held immobile without twisting or tension by the adhesive catheter securement devices at two separate locations, one at the PIL patient connector and one at the driver lead connector. If either anchor is compromised replace it immediately.

Additional Comments:

- No ointment or cream should be use at any time on the percutaneous lead of the C-Pulse unless directed to do so by the surgeon (no other physician).
- Inspect the Driver Carry Bag to be sure the integrity of the Velcro strap used to coil the Driver Lead.
- Take digital photos of the exit site to document the condition for future reference.

Infection Advisory Committee Recommendations:

Due to the possible interaction of site infection leading to "Deep" infection or tissue swelling around the intrathoracic gas line and /or ascending aorta an infection procedure monitoring process is recommended. The following process is recommended to reduce risk of injury to the patient.

Infection Monitoring Process:

In the presence of clinical signs (pain, redness, discharge, loss of driveline fixation) and /or microbiological evidence (positive wound culture) of infection (intermittent or chronic) over a 3 month period despite treatment.

Decision Process:

Are there clinical signs or microbiological evidence of infection over a 3 month period despite treatment?

- No: Continue therapy
- Yes: Perform CT or PET scan
  - If scan is positive (i.e. shows evidence of DEEP infection or soft tissue swelling around the intrathoracic gas line and/or ascending aorta or presence of intrathoracic gas), then REMOVE PIL AND CUFF.
  - If scan is negative (i.e. shows no evidence of DEEP infection), REMOVE PIL only.
  - If at the time of surgery there is clinical evidence of DEEP infection (i.e. pus or fluid around the 'Y'- connector, positive gram stain, and infected tissue) then REMOVE the CUFF also.
- If at the time of CT/PET scan or surgery there is no evidence of DEEP infection, then REPEAT SCAN at 3 months post-op and monitor for clinical signs of infection, if none found then REPEAT SCAN annually.
- NOTE: if wound culture is positive for MRSA, MSSA or Pseudomonas, monitor more frequently with FOLLOW-UP CT-SCAN at 3 months.

Aortic Tissue Sampling Guideline

In the event of a heart transplant, LVAD placement or patient death in the control group, it is requested that a single tissue sample of the ascending aorta should be collected for analysis.

In the event of a heart transplant, LVAD placement or patient death in the treatment group, it is recommended that the C-Pulse system be removed. To ensure evaluation of the system and patient interaction the following process provides guidance on removal of the C-Pulse implanted components at the time of explant, the observations to be recorded and for device return for analysis.

- If possible, return the devices intact and connected. In the event of device dissection, attempt to maintain the connections intact.
- For the Cuff, balloon integrity should be maintained unless histopathological analysis requires dissection.
- Depending upon the event (a heart transplant, LVAD or patient death) the following three tissue samples of the aorta should be collected for analysis from patients implanted with the C-Pulse system:
  - under the cuff/balloon
  - proximal to the C-Pulse Cuff
  - distal to the C-Pulse Cuff
  - For control arm patient one tissue sample for the ascending aorta should be collected for analysis
- The aorta samples should be sent to the local pathology lab for hematoxylin and eosin stain histological studies and slides retained for Sunshine Heart. Microbial analysis should be undertaken at the time of explant.
- Cultures should be obtained at the skin exit site, at the y-connector of the PIL and at the balloon cuff and processed at the local laboratory for assessment of organisms.

