PRO 02291–I

C–Pulse® Implantable Counterpulsation Pump (ICP)

A Heart Assist Device

March 4, 2015

Investigational Plan

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Confidential

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INTRODUCTION

PURPOSE

Sunshine Heart Inc. is sponsoring a prospective, multi–center trial to assess the safety and provide indications for performance of the Sunshine Heart C-Pulse® System ("C-Pulse®").

The purpose of the study is to determine whether use of C-Pulse® as treatment for patients in moderate to severe heart failure (HF) is associated with reasonable assurance of safety and performance, such that the C-Pulse® merits Food and Drug Administration (FDA) approval for continuation into a pivotal study to examine the safety and efficacy of C-Pulse® for US market approval.

STUDY SIZE AND DURATION

This clinical study is expected to commence September 2008. The duration of the study is expected to be 120 months. The primary study population will include 20 patients enrolled and implanted with C-Pulse® in up to 7 centers in the United States (US) and potentially some Outside the United States (OUS) centers. This expansion protocol will allow 40 patients to be enrolled and implanted in up to 9 centers. The first 40 patients that meet all eligibility criteria will proceed to implantation. Up to approximately 60 patients will be enrolled and consented for performing screening and testing required to confirm eligibility, such as Computed Tomography (CT) scan. 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 screening timeframe of 30 days prior to implant.

Only the patients who meet the eligibility criteria will proceed to implantation. All patients who do not meet the eligibility requirements will be promptly study exited. Study exit of these patients must be documented on the Study Exit form. The period of follow–up will be 6 months to assess the safety and performance before initiating the pivotal randomized clinical trial. All patients will continue to be followed annually during long term follow–up to a minimum of 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 prepared by the Data and Safety Monitoring Board (DSMB) following enrollment of the first five (5) patients and at least twice per year thereafter. The recommendation(s) from the DSMB may be circulated to each of the Investigation Review Boards (IRB) 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 [(New York Heart Association (NYHA) Class III] 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]. However, 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. However, 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). However, 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 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.

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

[1] [Abraham 2002]

[2] [Demers 2003]

[3] [Rose 2002]

[4] [Reinlib 2003, Birks 2006]

augment native heart function rather than to replace it. Whilst LVADs unload the heart, it is evident that they do not necessarily increase coronary artery blood flow[5].

Counterpulsation has 2 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].

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

[5] [Ootaki 2005]

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

[7] [Cohen 1995]

[8] [Cochran 2002]

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, ambulatory, disconnectable, and not 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 or IV heart failure. It is important to point out that a counterpulsation device is aimed 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.

Sunshine Heart, Inc. has proposed C-Pulse®, a novel ambulatory, non–obligatory, non–blood contacting extra–ascending aortic counterpulsation system. 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® 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. 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 insert, and can be turned on and off as required; all natural blood pathways are maintained – there

[9] [Jeevananddam 2001]

[10] [Tranini 2002]

is no exposure of foreign material to the bloodstream. See Appendix E for a summary of experience to date with C–Pulse®.

C-PULSE DEVICE DESCRIPTION

THE SUNSHINE HEART C–PULSE® ICP SYSTEM

The C-Pulse® ICP utilizes an "extra–aortic" inflatable Cuff which is surgically implanted around the ascending aorta, thus a) avoiding blood contact, and b) allowing the device to be both ambulatory and non–obligatory, for long–term cardiac assistance. Furthermore, counterpulsation on the ascending aorta is more efficient than the descending aorta position because 1) the blood displacement is "unidirectional," and 2) diastolic and pre-systolic pulse wave propagations versus cardiac systole are better matched[11] [12]. In addition, the ascending aorta is of a predictable helical shape[13] [14], has a large capacitance, no branches and presents a minimal risk of disease[15]. The implanted Cuff is inflated by the external battery powered pneumatic Driver and timing is coordinated to the R wave of the ECG. A standard implantable cardiac pacemaker lead is used with the system. A separate, exchangeable, wire–wound percutaneous interface lead (PIL) is implanted to connect the gas line of the Cuff and the ECG Sense Lead to the Driver.

The C-Pulse® ICP has been designed to have a simple, highly reliable implantable component (the Cuff) and external wearable components (the Drive Unit and Battery Carrier) which are connected by means of a Percutaneous Interface Lead (PIL). A standard epicardial pacemaker lead serves as the ECG Sense Lead. The Driver is programmable by a physician using a Programmer via infra–red (IR) connectivity.

The modular design of the C-Pulse® is shown in Figure 1. For the IDE study, the patient will be provided with two (2) each of the Drive Unit and Battery Carrier. The Percutaneous Lead is designed to facilitate simple surgical replacement of this component, in the case of untreatable skin infections at the exit site or damage to the patient connector.

Figure 1 IDE C-Pulse System

[11] [Furman 1971]

[12] [Davies 2005]

[13] [Misfeld 2004]

[14] [Peters 2006]

[15] [Takasu 1992]

Key components of the C-Pulse system are outlined in Table 1~~Table 1~~.

Table 1 C-Pulse® System Components

SHC implantable Cuff:

- Simple, less invasive surgery
- No cardiopulmonary bypass
- 3 sizes to fit ascending aorta outside diameter 29–40 millimeter (mm)
- Non–blood contacting

SHC Percutaneous Interface Lead:

- 5 mm outside diameter
- Silicone with ECG wire re-enforcements
- Transmits air/ECG/heart sounds
- Patient connector (with water–tight cap)
- Lead is exchangeable
- Home care package including supplies for dressing changes

SHC wearable/portable Drive Unit and Battery Carrier:

- Detachable, approx. 2.5 kilogram (kg) (total weight, split between Driver and Battery Carrier)
- Ergonomic design
  - □ wear in a vest or carry in a bag
  - □ simple patient interface – on/off button and battery indicator
  - □ visual and audible alarms
- 4 hour battery life; single battery – recharge separately or in Battery Carrier
- 1.4 meter (m) Driver cable with Isolation Module
- Physician programmer
  - □ Infra–red functionality
  - □ Intuitive interface for setting counterpulsation functions
  - □ Discrete “verification” button on Driver to accept Programmer changes

SYSTEM FEATURES

C–Pulse® Allows Ambulation

It is vital for a device intended to restore a heart failure patient quality of life that the device can allow the patient to ambulate and to be discharged home. The C-Pulse® Driver and Battery Carrier can be worn on a belt as a harness – the Battery Carrier and Driver are of approximately equal weights which allows even and ergonomic distribution of weight. A single long-life battery is used and is easily exchanged and re–charged. The Driver and Battery Carrier can be alternatively placed into one small carry–bag, for carrying over the shoulder. The Driver has a 1.4m cable that allows the Driver to be comfortably used in bed or when the patient is showering, and which can be coiled up and stored on the Driver. To avoid twisting in the line, the cable can be disconnected to coil it appropriately.

Non–blood contacting

The non–blood contacting feature of the C-Pulse® 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 for C-Pulse® use.

Non–obligatory

The non–blood contacting feature of C-Pulse® also allows the device to be intermittently turned off as tolerated. This allows the patient freedom for personal hygiene and convenience. The non-obligatory feature of C-Pulse® is essential in improving the patient's quality of life and safety, however, the Device is expected to be used greater than 80% of the time during the trial period. During the trial period, patient must not disconnect for longer than 15 minute intervals for a maximum of 4 hours daily (80% usage). The Driver records usage.

INDICATIONS FOR USE AND INTENDED USE

The C-Pulse® System is indicated for use in patients with moderate to severe heart failure [American College of Cardiology/American Heart Association (ACC/AHA) Stage C; NYHA Class III/IV], who are refractory to optimal medical therapy. The C-Pulse® System is intended to relieve the symptoms of heart failure, improve quality of life and cardiac function. The C-Pulse® System is also indicated for use in patients who are non responders to CRT pacemaker therapy. 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 and 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 marked on the Cuff and the Cuff is wrapped 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. Interrupted 'mattress' sutures are recommended, placed with the Cuff 'open' and using the circumferential marks as guidance, and such that the inflation chamber of the Cuff is always visualized. A bipolar ECG Sense Lead is placed on the heart and the gas line of the Cuff and ECG Sense Lead are attached to the intra–corporeal "Y– connector" end of the Percutaneous Lead. The Percutaneous Lead is then tunneled out over the abdomen, the extra–corporeal end of the Lead having a Patient Connector permanently attached. Alternatively, the Percutaneous Lead may be tunneled retrograde and secondarily attached to the gas line and sense lead. The Percutaneous 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 designed to assess the safety and potential benefit of the C-Pulse® System before initiating a wider randomized clinical trial to demonstrate safety and effectiveness. The effect of the C-Pulse® system in relieving heart failure symptoms in patients with ACC/AHA Stage C, NYHA Class III-ambulatory Class IV heart failure will be documented with this study.

This Feasibility Study is multi-center study which is being expanded to include up to 9 centers in the US and potentially some OUS centers. The study population will be expanded to include 40 patients enrolled and implanted with the C-Pulse® System. The period of follow-up for the initial 20 patients will be 6 months to assess the safety and performance before initiating the pivotal clinical trial. It is desired that the system be used all the time. However, the System should not be "Off" for greater than one hour at any one time for a maximum of four hours total per day during the study period. For the extent of the trial period (6 months), C-Pulse ®should be used at least 20 hours per day (i.e. device must be used greater than 80% of the time). The patient must limit the duration of disconnection to 15 minute intervals for a maximum of 4 hours total during the trial period to ensure the device is used for 80% of the time. The Driver logs patient usage automatically and stores into the system files.

Patients will be followed for up to 10 years or until the study is closed.

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

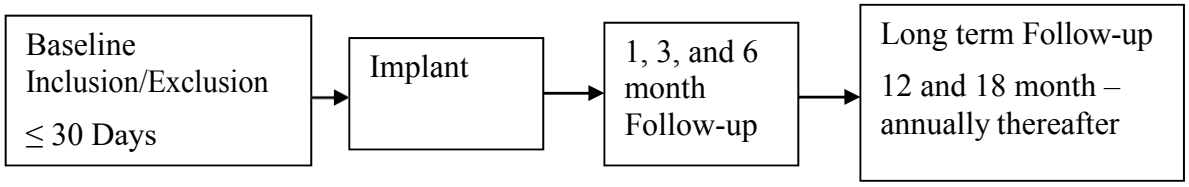

Figure 1A. Study Design

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. Data collection will be noted prior to implantation of the device and at one, three, and six months following implant and then long term at 12 and 18 months followed by annually post–implant for five years. Adverse events will be collected throughout the study until study closure and will be adjudicated by the Clinical Event Committee (CEC).

Progress reports of the clinical outcomes will be reviewed by the DSMB after enrollment of five (5) patients and twice per year thereafter, unless slow enrollment does not warrant this meeting frequency.

Progression to the Pivotal study will be based on the assessment for safety of the device and indicators of performance. Baseline and follow–up data will be used to assess any significant difference in quality of life and functional variables pre and post implant and to assess the effect of counterpulsation.

Following successful completion of this Feasibility Study, a pivotal study will be conducted to examine the safety and efficacy of the C-Pulse® system in patients in moderate to severe heart failure. The pivotal trial is expected to measure the same variables as the Feasibility Study.

The total duration of the Feasibility Study is expected to be approximately 120 months or until the study is closed.

OBJECTIVES

Primary Objectives

Following are the primary objectives for this study. The primary objective of the C-Pulse feasibility study is to assess safety, while at the same time obtain performance data for evidence of efficacy to assist planning for a pivotal study. Refer to the section on Statistical Methods and Data Analysis for a detailed discussion of the definitions and methodology.

The Clinical Investigation shall:

1. Assess the risks with regard to the performance of the device as defined by the serious adverse event rates, under normal conditions of use.
2. Assess the potential benefits of C-Pulse as defined by improvements in Peak VO_2, hemodynamic measures, quality of life and HF symptoms.

Secondary Objectives

Secondary objectives are intended to provide additional information on patient response and device performance and to allow planning for the pivotal study. The secondary objectives are as follows:

1. Further assess the potential risks with regard to the performance of the device as defined by the device failure rate, adverse event rates, adverse event attribution, re-hospitalization rates, duration of support, and length of time to hospital discharge.
2. Further assess the potential benefits of C-Pulse as defined by improvements in quality of life, fatigue impact scales, hemodynamics, average distance walked in the 6 minute hall walk test, and blood tests.
3. Assess the device usage.

Together the primary and secondary objectives will:

1. Allow refinement of clinical and physiological criteria for patient selection and refinement of protocols for the operative procedure and concomitant medical therapy and rehabilitation post-operatively – the results of the Feasibility Study will allow effective planning of a larger study to examine device efficacy
2. Develop predictors for adverse events and measures for minimizing the frequency and/or severity of such events
3. Determine the parameters of implantation, patient recovery, hospitalization, rehabilitation and home discharge
4. Determine the means to design a successful pivotal trial in regards to the anticipated randomization, feasibility of blinding, core lab procedures and data collection

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. Patient has ACC/AHA Stage C heart failure and remains in NYHA Class III - ambulatory Class IV despite optimal **medical** therapy. Patients must have stable, evidence–based optimal medical therapy for heart failure as defined below:
   - ACE inhibitor or ARB (Angiotensin Receptor Blocks) at least 30 days preceding implant or nitrate/hydralazine at the investigators discretion
   - Beta–blocker for at least 90 days and stable for 30 days preceding implant

     Note: Stable is defined as no more than a 50% reduction or 100% increase in the medications listed above. Transition within a therapeutic class is allowed if the dose is equivalent.
2. Patient has left ventricular ejection fraction (LVEF) ≤ 35%
3. Patient has had Cardiac Resynchronization Therapy (CRT) for at least 90 days prior to enrollment or is not indicated for a CRT device
4. Patient has had an implanted cardio–defibrillator (ICD) at least 30 days prior to enrollment or is not indicated for ICD implantation.
5. Patient is at least 18 years of age and not older than 75 years
6. Patient six minute hall walk assessment between 100–350 meters
7. Patient understands the nature of the procedure, is willing to comply with associated follow–up evaluations, and provide written informed consent prior to the procedure

Exclusion Criteria

Candidates must be excluded from the study if any of the following are met:

1. Patient has any evidence of:

- Ascending aortic calcification on posterior–anterior or lateral chest x–ray at initial screening

  OR

- Atherosclerotic ascending aortic disease, specifically intimal thickening greater than 3mm or mobile atheroma (moderate) or mural calcification (severe) as detected by CT scan or echocardiography (Echo) [16]

[16] [Davila–Roman 1999]

2. Patient has ascending aorto-coronary artery bypass grafts, history of aortic dissection, Marfans disease or other connective tissue disorder or has had an aortic root replacement
3. Patient aorta not conforming to specified dimensional constraints defined by CT scan, most specifically mid ascending aortic outside diameter less than 29mm or greater than 40mm
4. Patient has severe mitral valve incompetence, grade 4+
5. Patient has moderate to severe aortic valve incompetence, grade 2–4+
6. Patient has systolic blood pressure less than 90 or greater than 140 mmHg
7. Patient has a Serum Sodium less than 130 mEq/L
8. Patient has an Estimated Glomerular Filtration Rate (GFR) less than 40 ml/min/1.73m^2
9. Patient has any two of three of Bilirubin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) greater than three times upper limit of normal for each institution
10. Patient has a serum Albumin less than 3.0 g/dL
11. Patient has Body Mass Index (BMI) less than 18 or greater than 40 kg/m^2
12. Men with Peak Oxygen Uptake (VO_2) of greater than 18 ml/kg/min or less than 10 ml/kg/min

    OR

    Women with Peak VO_2 of greater than 16 ml/kg/min or less than 9 ml/kg/min
13. Patient has any active infection
14. Patient has had a myocardial infarction (MI), stroke, transient ischemic attack (TIA), cardiac or other major surgery, in the 90 days prior to study enrollment
15. Patient has severe Chronic Obstructive Pulmonary Disease (COPD) as evidenced by Forces Expiratory Volume (FEV1) less than or equal to 0.9 L/min
16. Patient requires a concomitant surgical procedure [i.e. coronary artery bypass graft (CABG), Valve repair]
17. Patient is supported with a left ventricular assist device or intra–aortic balloon pump
18. Severe Right Heart Dysfunction with systemic venous congestion evidenced by clinical signs/symptoms such as Central Venous Pressure (CVP) ≥ 20 mmHg, Cardiac Index (CI) < 2.0 l/min./m^2, elevated liver function tests beyond three time the upper limit of normal and presence of ascites
19. Patient has reversible causes of heart failure that may be remedied by conventional surgery or other intervention
20. Patient is pregnant; Note: Negative pregnancy test required in all women of child bearing potential

21. Patient has any other condition that, in the opinion of the investigators, would disqualify the patient for inclusion in the study, limits survival to less than one year, or not permit valid consideration
22. Patient is currently enrolled or has participated in the last 30 days in another therapeutic or interventional clinical study that is likely to confound study results or affect study outcome
23. Patient has symptomatic Carotid artery disease or asymptomatic disease with a stenosis greater than 70% as determined by Carotid Doppler Ultrasound

INVESTIGATIONAL CENTER INFORMATION

Number of Sites

It is intended that up to 9 centers in the US and potentially some OUS 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. and/or designee before commencement of the study at a clinical site.

Curriculum vitae including the investigator's current position and title 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 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

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 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® ICP System
- Standard cardiac surgery required equipment and facility
- Echocardiography equipment
- CT Scanning equipment
- Cardiopulmonary Exercise 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 investigation devices, software, and administrative forms necessary to conduct and administer the study. A limited amount of investigational product will be distributed to designated Sunshine Heart field personnel and 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 Device & Equipment Disposition Log shall be maintained at each center to track investigation product information including, but not limited to, the model, serial number of each investigational product and the date used. Completed System Implant and Implant Equipment Case Report Forms and Device & Equipment Disposition Logs 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 patients 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

Before initiation of the study, 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

Screening and Patient Informed Consent

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. A Screening Log is located within the site Regulatory Binder and should be completed for all patients screened but not enrolled for the study.

Patients will undergo a pre–implant baseline assessment to ensure they meet the inclusion and exclusion criteria no more than **30 Days** prior to the implant date. Patient informed consent must be signed prior to conducting any screening or baseline testing procedure performed for study purposes. **When a patient signs an informed consent for the study, he/she is considered enrolled in the study and will be assigned a study identification number by the center.** 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 timeframe of 30 days prior to implant. Upon completion of screening, all patients that do not satisfy the eligibility criteria will be promptly study exited without proceeding to implantation. Study Exit of these patients must be documented on the Study Exit Form. Any patient whom undergoes anesthesia for the purpose of C-Pulse implantation but does not receive the device will be monitored for adverse events as

defined by the protocol for 30 days or discharge whichever occurs first. Any Sunshine Heart field personnel or designee present for the implant procedure should review the informed consent prior to the procedure to ensure compliance.

In accordance with the ethical principles that have their origin in the Declaration of Helsinki, each patient 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 H for the sample Consent Form). 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 10 years.

Patient Withdrawal or Loss to Follow–Up

In the event a patient 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/Death Form must be completed and the patient will no longer be followed in the clinical study.

In the event the patient becomes lost to follow-up, the investigational site should make two documented attempts to contact the patient. A Study Exit/Death Form must be completed and the patient 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 all imaging and functional test must be collected no more than **30** days prior to the implant date.

Follow–up data will be collected at the time of implant, hospital discharge, at planned follow–ups (1-month, 3-month, 6-month, 12-month, 18-month and annually from the implant date thereafter), and “unscheduled” follow–ups (device testing, patient symptoms requiring re-hospitalization, etc.). All adverse events will be collected throughout the study until closure.

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.

The table below outlines the data collection with the appropriate time windows.

Table 2. Follow–up Windows

Evaluation	Time Window
Pre–Implant Evaluation	No more than 30 days prior to implant
Implant	Day 0 – Implant
Pre-Discharge	Within 36 hours prior to discharge
1–month follow–up	Days 30 ± 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 ± 60 Post-Implant
18-month follow-up	Day 540 ± 60 Post-Implant
Annually Post-Implant	Years 2, 3, 4, 5, 6, 7, 8, 9 and 10 Post Implant (± 60 days of anniversary)

Testing should be conducted at the investigational site. The data collection criteria are summarized in Table 3.

Table 3. Data Collection Summary

Follow-up Requirements Baseline to 6 months Post Implant						
	Pre-Implant	**Implant**	**Pre-Discharge[7]**	**1 mo**	**3 mo**	**6 mo**
A. PATIENT ELIGIBILITY	X					
B. GENERAL						
Demographic Data	X					
Medical History	X					
General Physical Examination	X	X	X	X	X	X
Concurrent Medications	X	X	X	X	X	X
Pregnancy test (if applicable)	X					
C. VITAL PARAMETERS						
Weight	X		X	X	X	X
Heart rate (ECG pre-implant)	X		X	X	X	X
Blood pressure	X		X	X	X	X
Respiratory rate	X		X	X	X	X
D. CARDIOPULMONARY						
CT aorta	X					X
CXR	X				X	X
ECHO	X	X[2]		X	X	X
Right heart catheterization (CVP, PAP, CI, PCWP,SVR, PVR)	X					X
Peak O2 uptake	X					X
E. QUALITY OF LIFE						
NYHA Classification	X			X	X	X
MLHF Score/ KCCQ	X			X	X	X
Fatigue Impact Scales	X		X	X	X	X
Six Minute Walk	X			X	X	X
F. HEMATOLOGY						
Hemoglobin	X		X	X	X	X
Hematocrit	X		X	X	X	X
Plasma free hemoglobin	X		X	X	X	X
Platelet count	X		X	X	X	X
White cell count	X		X	X	X	X
APTT	X		X	X	X	X
INR	X		X	X	X	X
Fibrinogen	X		X	X	X	X
G. BIOCHEMISTRY						
Serum sodium	X		X	X	X	X
Serum potassium	X		X	X	X	X
Serum creatinine/ GFR[3]	X		X	X	X	X
BUN	X		X	X	X	X
Serum albumin	X		X	X	X	X
Serum bilirubin	X		X	X	X	X
Serum ALT	X		X	X	X	X

Follow-up Requirements Baseline to 6 months Post Implant						
	Pre-Implant	**Implant**	**Pre-Discharge[7]**	**1 mo**	**3 mo**	**6 mo**
Serum AST	X		X	X	X	X
Serum BNP	X					X
H. NEUROLOGICAL ASSESSMENT						
Neurological testing (NIHSS)[4]	X		X	X	X	X
Modified Rankin [4]	X		X	X	X	X
Head CT [5]	X					
Neurological Consultation	X		X[6]			
I. IMPLANT DETAILS		X				
J. DEVICE LOG		X		X	X	X
K. DISCHARGE CHECKLIST			X			

1 Annually post-implant
2 Epi-aortic Echo at implant
3 Estimated GFR at Baseline and within one week post CT to evaluate contrast induced nephropathy.
4 Post Neurological Dysfunction AE – 30, 60 and 90 days post event
5 At Baseline only or as clinically indicated with any Neurological Dysfunction AE – Head CT should be completed only after clearance for implantation
6 Required at 5-7 days post ICU discharge or at hospital discharge whichever occurs first and at the time of any suspected Neuro Dysfunction AE
7 At Discharge - within 36 hours prior and as close to discharge as possible (see Appendix M)

Long-term Post Implant Follow-Up Requirements			
	12 month	18 month	Annually Year 2-10
A. PATIENT ELIGIBILITY			
B. GENERAL			
General Physical Examination	X	X	X
Concurrent Medications	X	X	X
Pregnancy test (if applicable)			
C. VITAL PARAMETERS			
Weight	X	X	X
Heart rate (ECG pre-implant)	X	X	X
Blood pressure	X	X	X
Respiratory rate	X	X	X
D. CARDIOPULMONARY			
ECHO	X	X	X
E. QUALITY OF LIFE			
NYHA Classification	X	X	X
MLHF Score/ KCCQ	X	X	X
Fatigue Impact Scales	X	X	X
Six Minute Walk	X	X	X
F. HEMATOLOGY			
Hemoglobin	X	X	X
Hematocrit	X	X	X
Plasma free hemoglobin	X	X	X

Long-term Post Implant Follow-Up Requirements			
	12 month	18 month	Annually Year 2-10
Platelet count	X	X	X
White cell count	X	X	X
APTT	X	X	X
INR	X	X	X
Fibrinogen	X	X	X
G. BIOCHEMISTRY			
Serum sodium	X	X	X
Serum potassium	X	X	X
Serum creatinine/ GFR[3]	X	X	X
BUN	X	X	X
Serum albumin	X	X	X
Serum bilirubin	X	X	X
Serum ALT	X	X	X
Serum AST	X	X	X
J. DEVICE LOG	X	X	X
K. DISCHARGE CHECKLIST[7]			

Summary of Required Testing

Testing information will be recorded on the appropriate eCRF (Appendix K). Required testing includes:

Device Performance Parameters – (at all follow–up visits)

Device performance parameters shall be retrieved after optimization following implantation on Day 0, at all follow–up periods and whenever there is an unscheduled visit accompanied by a change to any device parameters. Parameters to be recorded include:

- Counterpulsation mode
- Counterpulsation volume
- Inflation slew rate
- Deflation slew rate
- Inflation hold pressure
- Device usage log (patient should use device for a minimum of approximately 20 hours per day)
- Other Events (i.e. alarms and/or events logged into the driver system file)
- Heart rate
- Non-invasive sitting blood pressure must be recorded at the time of the device check.

Data will be downloaded from the driver. Data will be recorded on the Follow-up eCRFs and stored electronically.

Echocardiographic Testing - (Baseline, 1, 3, 6, 12, 18 month, and annual follow–up visits)

A transthoracic echocardiography test will be performed at Baseline and at the 1, 3, 6, 12, 18 month and annual follow-up visits. A recording of the echocardiogram must be collected and sent to the Echo Core Lab for analysis. The Echocardiography measurements will include:

- Left ventricular end-diastolic and end-systolic dimensions (diameters, areas and volumes)
- Assessment of mitral, tricuspid and aortic valve function (regurgitation and gradient)
- Right ventricular systolic pressure (with estimation of CVP)
- Ejection Fraction and Myocardial Mass
- LV diastolic function

Data will be recorded on the Baseline and Follow-up eCRF.

Epi-Aortic Surface Echo - (collected at implant)

A surface ultrasound interrogation will be performed on the ascending aorta to confirm the absence of significant aortic disease. Confirmation of the absence will be recorded on the Implant eCRF.

Right Heart Catheterization - (Baseline and 6 month follow–up visits)

A right heart catheterization will be performed at Baseline and 6 month visit. The right heart catheterization should be performed using the thermal dilution method if possible with access via the subclavian or internal jugular (i.e. swan ganz). Data required from the procedure include: central venous pressure (CVP), systolic/diastolic/mean pulmonary artery pressure (PAP), Cardiac Index (CI), pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (PAP), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR).

Data will be completed on the Baseline and Follow-up eCRFs – Appendix K.

CT Scan - (Baseline and 6 month follow–up visits)

An ECG gated 1–2 mm slice thoracic CT scan is required at Baseline, and at the 6 month visit. A recording of the CT Scan must be collected and sent to the CT Scan Core Lab for analysis of the Baseline and 6 month assessment. A contrast study should be completed for Baseline testing. A minimum contrast injection rate of 4 cc/sec is recommended.

(Note: Protection of renal function is important. Please minimize the volume of contrast, ensure prehydration and use acetylcysteine.)

A contrast study is not required for follow–up tests unless there is a concern there is extravasation of blood from the aorta.

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 intima for the degree of atherosclerotic ascending aortic disease, specifically: Nil, Mild (intimal thickening less than or equal to 3 mm), Moderate (intimal thickening greater than 3mm or mobile atheroma) or Severe (mural calcification)[17]. The CT Scan Core Lab will assess the outcome of the test for acceptability. Data will be completed on the Baseline and Follow-up eCRFs.

NOTE: Contrast-induced nephropathy must be evaluated within one week post-baseline CT scan. Patients with an increase in Creatinine ≥ 0.5 mg/dL or a greater than 20% reduction in GFR must be followed until resolution of the decrease in renal function. This will be tracked as an observation via the follow-up form and should not be reported as an adverse event.

Neurological Assessment - (pre-implant, pre-discharge, 1, 3 and 6 month follow-ups)

A series of tests/assessments are required to assess for the presence of neurological dysfunction. Outlined below is the required assessment tool and specific required interval for collection:

NIH Stroke Scale and Modified Rankin
NIH Stroke Scale (NIHSS) is the standardized assessment tool for screening for any unobserved neurological dysfunction. The Modified Rankin is a standardized assessment tool for scoring disability status and/or ability to function. The NIHSS and Modified Rankin are required at pre-implant, at pre-discharge, 1, 3 and 6 months post implant. In the case of a neurological dysfunction adverse event, the NIHSS and Modified Rankin are required at 30 and 60 days post event in addition to the regular follow-up schedule. Clinicians performing the NIHSS and Modified Rankin are required to be trained. Clinicians performing NIHSS must also be certified prior to performing the assessment. Access to required training and certification tools will be provided in the study activation training for the study personnel designated for collecting the NIHSS. A neurological consultation is also required if an increase of 2 or more is noted on the NIHSS.

Head CT Scan
A standard CT scan of the head is required at pre-implant as a baseline measure immediately prior to device implant (but after study enrollment). In the case of a neurological dysfunction adverse event a CT scan of the head is also required as clinically indicated at the time of the adverse event. The scheduled baseline CT scan of the head should be completed only after the scheduled CT of the aorta – if the aorta does not meet inclusion criteria then he/she is not exposed to a further CT scan.

[17] [Davila–Roman 1999]

Standard Neurologic Consultation
A neurological consultation is required within days 5-7 post ICU discharge or at hospital discharge whichever occurs first. A neurological consultation is also required if an increase of 2 or more is noted on the NIHSS and at the time of a neurological dysfunction adverse event. The neurologist must record the outcome from the consultation into the medical record per institutional requirements for source documentation and on the Neurological Exam eCRFs (see Table 4 below).

Data will be completed on the NIHSS, Neurological Exam, Baseline and Follow-up eCRF.

The table below highlights the neurological testing follow-up data collection:

Table 4. Neurological Testing Collection Schedule

Item	Pre-Implant	Post-ICU Discharge	Neuro AE [5]	Post- Neuro AE Day 30, 60, 90[5]	PID 30	PID 90	PID 180
Neurological Exam [1]	X	X	X				
Head CT[2]	X		X				
NIHSS[3]	X	X	X	X	X	X	X
Modified Rankin[4]	X	X	X	X	X	X	X

1- Performed by a neurologist after study enrolment and prior to implant. Collected on Neuro Exam eCRF.

2- After study enrolment and prior to implant. Result collected on Neurological Exam eCRF and Neuro Dysfunction eCRF.

3-Collected on the NIHSS eCRF.

4- Collected on the Modified Rankin eCRF.

5- Neuro Assessment and testing expected within 7 days post AE, between days 23-37 days post AE, between days 53-67 and between days 83-97 post AE.

Laboratory Parameters and Hemodynamics - (Baseline, Pre-Discharge, 1, 3, 6, 12, 18 month and annual follow–up visits)

A full listing of all required lab tests and hemodynamic measurements is included in Table 3 above.

Measurements must be done at Baseline, Pre-Discharge, 1, 3, 6, 12, 18 month visits and annually thereafter.

Data will be completed on the Baseline, Pre-Discharge, and Follow-up eCRFs.

Six Minute Hall Walk Test - (Baseline, 1, 3, 6, 12, 18 month, and annual follow–up visits)

The patient must perform a six–minute hall walk test (6MHW) at Baseline, and at 1, 3, 6, 12, 18 month visits and annually thereafter with the C-Pulse™. Detailed information is included in Appendix P.

A familiarization test is required, but may have been performed in the previous one–year prior to implant. Instructions for conducting a six-minute walk test are located in Appendix P.

Data will be completed on the Baseline and follow-up eCRFs.

Quality of Life Assessment - (Baseline, 1, 3, 6, 12, 18 month and annual follow–up visits)

The patient must complete the Minnesota Living with Heart Failure Questionnaire (MLWHF) and the Kansas City Questionnaire (KCCQ) at Baseline, 1, 3, 6, 12, 18 month and annual visits.

Copies of the questionnaires are included for reference in Appendix N.

Data will be completed on the Baseline and Follow-up eCRFs.

Fatigue Impact Scales - (Baseline, Pre-Discharge, 1, 3, 6, 12, 18 month and annual follow–up visits)

The patient must complete the Fatigue Impact Scale and the Daily Fatigue Impact Scale at Baseline, Pre-Discharge, 1, 3, 6, 12, 18 month and annual visits.

Data will be completed on the Fatigue Impact and Daily Fatigue Impact eCRFs.

NYHA Class Assessment - (Baseline, 1, 3, 6, 12, 18 month and annual follow–up visits)

A clinician at each site shall complete the NYHA Classification at Baseline, 1, 3 6, 12, 18 month and annual visits.

Data will be completed on the Baseline and follow-up eCRFs. Refer to Appendix O for detailed description of the assessment.

Concomitant Medications (Baseline, 1, 3, 6, 12, 18 month and annual follow–up visits)

All medications will be recorded on the Medication eCRF. Doses are required for all cardiac medications including diuretics. Heart Failure medications such as ACE inhibitors and Beta Blockers must remain stable through the six month study period. Upward titration is not permitted beyond the baseline equivalent dose.

Cardiopulmonary (CPX) Testing - (Baseline and 6 month follow–up visits)

Two CPX tests may be required pre–operatively:

1) a familiarization test to allow the patient to become familiar with walking on a treadmill and with the breathing apparatus in his/her mouth and
2) a baseline test.

During the familiarization, the patient should exercise to his/her symptomatic maximum. If the patient reaches his/her maximum, this test will be considered the baseline test.

The first test should be conducted prior to implant for baseline assessment. If a second test is required it should be conducted greater than 24 hours after the first. **Note:** If a patient has a documented CPX test within the past 6 months prior to implant, then this test will be considered the familiarization test. A baseline test will still be required prior to implant if not conducted within the past 30 days, but the familiarization can be skipped.

Follow up measurements must be taken at the 6 month visit.

Please refer to Appendix Q for additional information on the testing procedure. A blinded independent core lab will evaluate the CPX test results. A recording of the CPX must be collected and sent to the CPX Core Lab for analysis.

Data will be completed on the eCRF and via the electronic data stored on disk.

Pre-implant Preparation

When a patient signs the informed consent for the study, he/she is considered enrolled into the study. The patient informed consent must be signed prior to conducting any procedure/testing performed for study purposes. Any patient that does not meet the eligibility requirements will be promptly study exited.

Pre-Implant Baseline Testing and Data Collection Summary

The following pre–implant baseline data will be obtained 30 days prior to implant. These data will be used by the center to confirm inclusion and exclusion criteria are met. A complete reference list of tests and hemodynamics to measure is included in Table 3.

- Inclusion and Exclusion Verified
- Informed Consent Obtained
- Medical History and Physical Exam
- Echocardiogram
- Chest X–ray
- ECG
- Right Heart Catheterization
- Cardiopulmonary Exercise Testing
- Six Minute Hall Walk
- Fatigue Impact Scales
- Cardiovascular Medications Documented
- Cardiovascular Medical History Documented
- CT Scans – Aorta and Head Documentation
- Neurologic Assessment (Neurology Consult, NIHSS and Modified Rankin)
- Quality of Life Questionnaires (MLWHF and KCCQ)
- Baseline Hemodynamics
- Serum Labs
- NYHA Classification
- Medications
- All adverse events reported

Clinical Procedures – Implant through discharge

The System Implant eCRF will be used to collect implant data.

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. Premed given per 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

Have the patient try on the Vest and bag to determine the best exit site. The goal is to minimize trauma to the exit site and to maximize patient comfort. 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

Administer prophylactic antisepsis coverage. Recommended prophylaxis:

- Vancomycin 15mg/kg IV one hour pre-op given over 30 minutes and with minimum 5 minute 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 Q12–24 hr post-operatively for 48 hrs, guided by serum Vancomycin trough levels.
- Keflex 1g IV one hour pre–op then Q8–12hr for 48 hrs
- Rifampicin 600 mg PO 2hrs pre–op then daily for 2 days – stop if liver function tests become deranged greater than two times baseline
- Nasal Bactroban application day prior to surgery

Note: Record all drugs and doses on the Medication eCRF.

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

Observe Operating Room precautions – particularly, limit the number of people in the room, and traffic in and out of the room.

Baseline Procedures

Baseline investigational procedures as above should have been completed and data collected into the System Implant and Medication eCRFs.

Implant Procedure

Note: Refer to the Instructions for Use (IFU) for the C-Pulse® Cuff, Percutaneous Interface Lead and C-Pulse® System, which outline device preparation, implantation, and operation. The IFUs may be found in Appendix F.

Procedure Summary

1. Establish intra-venous and intra-arterial lines (if not already established above). Insert central venous sheath and position right heart catheter (may be done following general anesthesia), and connect surface ECG.
2. Induce general anesthesia: intubate with endotracheal tube and ventilate per routine. Blood gases, Hb, and Hct are monitored during surgery per routine.
3. Recommended three–step approach to skin preparation:
    a. antiseptic scrub (Septisol or Chlorhexidine)
    b. alcohol, which is then allowed to dry
    c. Betadine gel, which is allowed to dry.

    Note: combination alcohol/Betadine preparation may be used
4. Drape patient with steri-drapes (e.g. Ioban), over exposed prepared skin.
5. Perform chest incision.
6. Incise pericardium up onto ascending aorta, mobilize ascending aorta from pulmonary artery.
7. Using umbilical tape, measure mid-ascending aortic circumference and record on System Implant eCRF.
8. Use CT scan to select Cuff size per mid–ascending aortic outside diameter.
9. Delay opening sterile packaging for the C-Pulse® Cuff, ECG lead and PIL until they are ready to be implanted. See IFU for details regarding opening and implanting the C–Pulse® Cuff and PIL, including Warnings and Precautions.
10. Evacuate air from C-Pulse Cuff and mark circumferential lines for suturing.
11. Massage antibiotic solution* into the flocking anchors and into the wrap. (*Gentamicin and normal saline 160g/L, or Vancomycin and normal saline 2g/L)
12. Implant device about the aorta and secure according to the IFU.
13. Open ECG lead sterile packaging when required.

14. Attach a bipolar epicardial ECG sensing lead to the RV or LV per IFU.
15. Create exit site by excising skin button that is approximately 80% of the tube outside diameter.
16. Secure Cuff and Lead and attach to intracorporeal aspect of PIL per IFU and track out under the costal margin through a curvilinear pathway, either superior or inferior to the umbilicus as it suits best, to the desired pre–determined exit site. A separate small incision may be needed to allow further tunneling of the Lead and gas-line to the intended exit site. The PIL may alternatively be tunneled from "out–to–in" and connected to the Cuff gas-line and ECG lead secondarily.
17. The PIL at the exit site should be oriented horizontally or slightly downward to allow good natural drainage of the exit site.
18. The flocking of the PIL should be positioned to be subcutaneous, approximately 2 cm from the exit site.
19. Verify device function:
    a. Test for adequate sensing of the R wave by the Driver with respect to beginning of LV systole per IFU.
    b. Optimize inflation/deflation and displacement volume. Gas inflation hold pressure should not exceed 50mmHg above the mean arterial pressure. See IFU C–Pulse® System (LBL 01918).
20. Fill chest with saline, massage any trapped air from under the Cuff, and observe to ensure no air-leaks are visible.
21. Inflate lungs fully to check percutaneous lines – gas–line and ECG lead may be immobilized at 1–2 other locations e.g. right anterior mediastinum, sub–costal incision.
22. Check for hemostasis, irrigate with antibiotic solution.
23. Insert mediastinal and any other drains as required, and close all wounds.
24. Apply occlusive surgical dressings to all wounds and to immobilize the percutaneous tube.

Post–Implant Considerations (prior to discharge)

1. Patient taken to ICU – driver may be disconnected for transport.
2. Ensure both Drivers are configured with the same settings and verify function of both as above.
3. Extubate patient, when appropriate – move to the telemetry ward when appropriate.
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. Recommended atrial arrhythmia treatment for new atrial fibrillation with rate greater than 110 beats per min: IV or oral amioderone loading and oral amioderone maintenance.

6. Heart rates should be maintained below 120 bpm and MAP below 100 mmHg to allow optimal counterpulsation and minimize alarms from the Driver.
7. Commence over–night naso-gastric feeding post-operatively if diet not re–established at day 2 or if serum Albumin below 3.3 g/dL.
8. 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.
9. Active deep vein thrombosis management includes TED stockings, subcutaneous Clexane or similar and bed leg exercises.
10. Early mobilization and graduated physiotherapy is to be conducted as tolerated from day 1, but the driver should not be used in a wearable configuration in the first week or until the chest incision is stable and comfortable. Use of the driver with the vest should be gradually built up and used with assistance from physiotherapy or other hospital staff.
11. The C–Pulse® can be de–activated intermittently for patients that are considered symptomatically stable per physician discretion (e.g. acceptable degree of shortness of breath and absence of dizziness), initially for short intervals (less than 5 minutes) once or twice a day, and this may be built up after 7–10 days post–operatively such that de-activation periods provide an opportunity for the patient to be free of the Driver for 15 minute intervals during the day or night. The Driver should not be 'Off' for greater than 30 minutes at any one time and not be 'Off' for a maximum of four hours total per day. **For the extent of the trial, the device should be used at least 20 hours per day (i.e. device must be used greater than 80% of the time).**
12. Heart failure medications should be re–started cautiously and drug doses titrated to clinical effect. It is recommended that the following regime be used as a guideline for post–operative medications:
    - Dopamine or Dobutamine for first 1–7 days, weaned down
    - Diuretics at pre–op dose or higher (including IV infusion as required) from day 1: Diuretics may be weaned as indicated later in the post–operative period
    - ACE inhibitors from day 2–3 – aim to titrate to then maintain at pre-op dose for duration of the study follow-up
    - Beta blocker from day 5–7, as tolerated – aim to titrate to then maintain at pre-op dose for duration of the study follow-up
13. Strict hygiene/hand washing must be practiced for all staff handling patient and lines. Remove all indwelling catheters as soon as possible. Change other lines regularly (at least every 4–7 days) as per hospital policy.
14. The exit–site dressing should be changed as frequently as required post–operatively while ensuring that the percutaneous lead is immobilized – this may be up to 2–3 times per day in the first 1–2 weeks. If wounds are healing well and there is no discharge, then go to daily or second-daily dry dressings. Exit-site dressings must be limited to the least number of clinical personnel, and preferably done by the patient or care-giver as much as possible

after the early post-operative phase, to limit exposure to micro-organisms and to limit cross-contamination.

15. Antibiotics IV peri-operatively as described above. Ongoing oral broad spectrum/gram negative cover is recommended for 10 days or until chest drains are removed and the exit–site has dried sufficient for once daily dressing only.
16. 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.
17. Maintain a routine dressing change and observe for signs of infection (refer to Appendix U for detailed infection control procedures):
    - Always wash hands and apply alcohol hand rub and use sterile gloves when handling the exit site.
    - Exit site should be examined and managed once per day (or more frequently if there is excessive moisture) by one person, specifically the wound should not be disturbed or inspected at any other time.
    - Irrigate wound site gently with Chlorhexidine solution and use sterile gauze to lift off any debris. Dry with clean sterile gauze. Keep the exit site dry between dressings. Use 2–3 small square gauzes or similar (e.g. Softwik), alternately split, to securely surround the percutaneous lead, and secure with tape or similar.
    - Wound deterioration is usually caused by excess moisture. Increase dressings per day until this resolves – also consider oral broad spectrum antibiotic or similar.
    - If wounds not responding to increased dressings, change wound irrigation solution (examples include 2% Chlorhexidine gluconate in normal saline, or Vancomycin in normal saline 2g/L)
    - Swabs for culture should only be taken of copious or purulent discharge. Blood cultures should be done if the patient is to be treated with antibiotics or if there is evidence of sepsis.
18. Showering: If the patient is symptomatically stable while disconnected from the device, then the interface can be capped off, allowing the patient to shower. Leave the dressing intact during showering – cover the exit site and capped off connector with a 4x4 gauze sealed with an occlusive adhesive plastic dressing such as Tegaderm. It is recommended that the patient be sitting on a stool or chair initially to avoid the risk of vasodilation hypotension. The dressing should be changed, per above, following showering.
19. Instruct patient to avoid sleeping on abdomen to avoid gas tube complications.
20. Educate patient and care–giver on how to operate the drivers, per the Patient Handbook. Training of the patient and/or caregiver will be documented.

Hospital Discharge

Preparation

Educate patient and care–giver on how to operate 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 M for discharge checklist.

Discharge Criteria

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

- Healing wounds, and with no signs of infection or sepsis
- Oxygen saturation greater than or equal to age–predicted O_2 saturation on room air
- Sinus rhythm or atrial arrhythmia with ventricular rates < 120 bpm
- 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 Drivers, changing and recharging batteries, and to understand and respond to the Driver alerts and alarms
- Home assessment visit prior to discharge may be completed to assess environmental conditions
- All scheduled follow-up 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

Readmission

Should the patient be re-hospitalized at any time post index hospitalization, the Unscheduled Follow-up Form should be completed. While hospitalized, the Follow-up Forms will continue to capture data and adverse events should be documented on the adverse event forms should they occur. When the patient is discharged again, the patient should be assessed per the discharge criteria to ensure they continue to meet the criteria.

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 patients 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 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 (component or system replacement). In the event that the C-Pulse® System requires modification (e.g. Cuff or PIL) a System Modification Form should be completed along with an adverse event form. Modifications should be done only in communication with Sunshine Heart Service personnel, unless the modification is a medical emergency. In which case, Sunshine Heart personnel should be notified as soon as possible. In addition, the System Modification Form should be completed documenting the removal of the existing device or component. The C-Pulse® component(s) should be processed according to the Explant Handling Instructions and returned to Sunshine Heart 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 patient will remain unchanged (i.e. the patient should continue to be seen for follow–up and associated forms should be completed based on the original follow–up schedule). All adverse events should be reported and classified by the investigator. Additionally the CEC will provide further classification of adverse events.

Adverse Event Reporting

Overview

Information on adverse events (AE) will be collected throughout the study. Upon identification, the investigator completes the adverse event information via the Adverse Event eCRF. Sunshine Heart 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, seriousness of the event, the relationship of the event to the implant procedure, device, concomitant medications, patient management, other actions taken as a result of the event, and the outcome of the event.

Adverse Event Definitions

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.

Major Bleeding

An episode of internal or external bleeding that results in death, the need for re-operation or hospitalization; or necessitates 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 contrast or by trans-esophageal echocardiography.

Device Malfunction

Device malfunction denotes a failure of one or more of the components of the MCSD system which either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. The manufacturer must confirm device failure. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure.

Device failure should be classified according to which components fails as follows:

1) **Pump** failure (implanted components of pump and any motor or other pump actuating mechanism that is housed with the implanted components). In the special situation of **pump thrombosis,** thrombus is documented to be present within the device or its conduits that result in or could potentially induce circulatory failure.

2) **Non-pump** failure (e.g., external pneumatic drive unit, electric power supply unit, batteries, controller, interconnect cable, compliance chamber).

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 90 mm Hg diastolic (pulsatile pump) or 110 mm Hg 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.) 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

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

Infection of the implanted C-Pulse Cuff 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 and Modified Rankin (for patients > 5 years old) must be re-administered at 30, 60 and 90 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.

NOTE: Contrast-induced nephropathy must be evaluated within one week post-baseline CT scan. Patients with an increase in Creatinine ≥ 0.5 mg/dL or a greater than 20% reduction in GFR must be followed until resolution of the decrease in renal function. This will be tracked as an observation via the follow-up form and should not be reported as an adverse event.

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.

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

- Relatedness (i.e. device, procedure, concomitant medication, or patient management);
- Timing (i.e. pre–implant, implant or post–implant);
- Serious events (i.e., result in death, are life-threatening, require surgical intervention, result in permanent disability, require hospitalization or hospitalization is unduly prolonged).
- 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, or operation (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 implantation 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 of managing the co–morbidities of heart failure.

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.

Unavoidable Events

The events listed in Table 5 are considered minor and if the onset occurs within the timeframe specified, are not subject to adverse event reporting.

Table 5. 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)]

Patient Deaths

All patient deaths must be documented on the Study Exit/Death Form. If the patient dies during the study, notify the Sunshine Heart 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 patient 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 beneath the C-Pulse® Cuff should be collected for analysis. Please call Sunshine Heart Clinical Support for more instruction. For patients 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 clinical support personnel according to a standardized device retrieval protocol.

A death summary and an autopsy report are required, please send upon completion to Sunshine Heart to provide to the adjudication committee.

Explant Handling and Final Device Disposition

Promptly call Sunshine Heart Clinical Support for instruction regarding Explant Handling. Cultures should be taken from the device implantation site along with visual analysis and photographs when possible. Explanted products should be returned to Sunshine Heart for analysis.

Complete the Study Exit/Death Form. Report all associated adverse events. Update the Device & Equipment Disposition Log with all products. If the device is not returned to Sunshine Heart, justification must be provided in the log.

Patient Withdrawal and Study Exit

A Study Exit/Death Form shall be completed if patient 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 patient withdrawal/study exit.

If the patient fails to comply with follow–up visits, the study center must make repeated attempts to contact the patient. Each attempt to contact the patient must be documented in the patient's records and on the Study Exit/Death form.

If the patient 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 Study Exit/Death form.

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

STATISTICAL METHODS AND DATA ANALYSIS

This feasibility study intends to examine the effect of C-Pulse® on long-term heart failure, and to look for trends in performance indicators. This study is not powered to detect statistical significance. As such, clinical judgment is required to assess device safety and potential efficacy from data collected during this study. This clinical judgment will be provided by the DSMB.

Justification of Methodology

This study is designed as an open-label single-arm study to develop a further understanding of the C-Pulse®. It will provide safety and efficacy information for patients in whom C-Pulse® is implanted and maintain counterpulsation for six months or longer.

At six months post-procedure, the patients will provide an adverse event profile related to surgical placement of the C-Pulse® and six months employment of C-Pulse® counterpulsation. After six months of the study there will be additional information related to the adverse event profile. The patients will provide an adverse event profile for patients in whom C-Pulse® is placed and maintain counterpulsation for greater than six months.

Similarly, these patients will provide an efficacy profile. At six months post-procedure, the patients will provide information on how well a patient improves since baseline through six months of counterpulsation. After six months these patients provide additional efficacy information related to how well a patient improves since baseline through greater than six months of counterpulsation.

Primary Safety Measures

The safety of the C- Pulse® will be evaluated by reviewing a composite of the device-related adverse events through six months, as classified by the CEC. The composite device-related adverse event rate will be the percent of patients who experience at least one of the following adverse events as adjudicated by the CEC as device-related out of the total number of patients:

- Death
- Neurological Dysfunction
- Aortic Disruption
- Myocardial Infarction
- Major Infection
- Any other device-related adverse event (as adjudicated by the CEC)

The definitions for these adverse events are provided in the Adverse Event Definitions section.

Performance Requirements

Safety will be represented in the composite device-related adverse event rate which will be reported with its 95% two-sided exact confidence interval. The composite device-related adverse event rate will be assumed to follow the Binomial Distribution. The DSMB will decide the clinical acceptability of this observed event rate in assessing trial success. Additionally each event will be presented with its respective rate and confidence interval. Death will be separated into deaths that occur before 30-days post-procedure and those that occur between 30-days post-procedure and 6 months.

Efficacy measurements

The efficacy of C-Pulse® will be evaluated by assessing the change of the efficacy variables from baseline to 6 months post-implant. The following measurements will be taken at baseline and 6-months.

- Peak VO_2
- Quality of Life as measured by the Minnesota Living with Heart Failure (MLWHF)
- HF Symptoms as measured by NYHA
- Six Minute Hall Walk Test

Performance Requirement

Trial success will be evaluated by analyzing each patient's response to the four efficacy variables. A responder analysis will for each patient will performed assessing the response to each of the four efficacy variables. Each efficacy variable will be assessed for clinical improvement ("responder"), decline ("non-responder") or no change ("indeterminant").

Clinical improvement will be defined for each efficacy variable as:

- 1.2 ml/kg/min improvement in peak VO_2
- 7 point improvement in MLWHF score
- 1 class improvement in NYHA
- 50 meter improvement in the Six Minute Hall Walk

Clinical decline will be defined for each efficacy variable as:

- 1.2 ml/kg/min decrease in peak VO_2
- 7 point decrease in MLWHF score
- 1 class decrease in NYHA
- 50 meter decrease in the Six Minute Hall Walk

A patient that shows no improvement or decline in a particular endpoint will be labeled as "indeterminate" for that endpoint.

The overall percentage of responders, non-responders and indeterminates for each efficacy variable along with the respective 95% two-sided exact confidence interval will be presented. Additionally the point estimate for the average change and its respective standard deviation will be presented for peak VO_2, MLWHF, and the Six Minute Hall Walk. The improvement in NYHA will be presented by a cross-tabulation summary. The DSMB will decide the clinical acceptability of this responder analysis in assessing trial success.

Secondary Objectives

The secondary objectives are descriptive in nature and will be evaluated in order to gain additional information regarding the C-Pulse® system. There are no specified performance criteria for these objectives. For continuous measures the mean, standard deviation, minimum and maximum values will be presented. For categorical variables the frequency and percent will be presented.

Endpoints consistent with the primary safety and efficacy objectives will be evaluated at all additional time points.

1. The adverse event rate will be presented at 3, 6, 12 and 18 months post-procedure, and annually for years 2-5 post-procedure.

2. The change from baseline to follow-up will be evaluated for peak VO_2, Six Minute Hall Walk, MLWHF, Fatigue Impact Scales and heart failure symptoms from NYHA.

The device failure rate will be quantified. Failure will be defined as both failure of the device, and failure of the device to be programmed to the treatment.

Additionally, the adverse event rate for each of the adverse events described in the Adverse Event Definitions section – pages 36-40 – will be provided. Exact 95% two-sided confidence intervals with an underlying Binomial Distribution will be provided for each event. Adverse events will also be tabulated by attribution (seriousness, device-relatedness, and procedure-relatedness) according to the CEC.

The following additional efficacy measures will be analyzed at each time point to evaluate the efficacy of the C- Pulse® System. For these measures the averages and the average change from baseline to each follow-up period will be presented along with the trend over time:

- Hemodynamic measures are from right heart catheterization (RHC): Cardiac Index (CI), Pulmonary Artery Pressure (PAP), Pulmonary Capillary Wedge Pressure (PCWP), and Cardiac Output (CO).
- Quality of Life
    - Kansas City Questionnaire.
- Blood tests (e.g. Serum sodium, serum creatinine, serum bilirubin, hemoglobin, ALT and AST).
- Concomitant cardiovascular medications

The following measures will also be summarized:

- Re-hospitalization (HF-related and all-cause)
- Duration of support/survival duration.
- Length of time to ICU and hospital discharge
- Device evaluation – Device log and C-Pulse® User log will be evaluated and summarized. Average daily device use will be provided for each time period.

Sample Size Determination

This is a single-arm study designed to determine the safety of the C-Pulse® as well as give an insight into the efficacy of counterpulsation.

Because estimates from this study will be used to power the pivotal study, this study must be able to provide such estimates. A sample size of 20 implanted patients is considered clinically sufficient to give indications of both safety and potential efficacy. With this sample size, we feel we can decide whether to proceed to a pivotal study, determine endpoints for such a study, and design the study to answer the proposed hypotheses. Up to approximately 10 additional subjects may be enrolled to account for subjects who do not meet inclusion/exclusion criteria involving non-standard clinical practices.

Subjects for Analysis

Patients will be included in two analyses. The primary analysis will be an "as- treated" analysis, wherein only subjects in whom the device is placed are analyzed. The secondary analysis will be an "intention to treat" analysis, wherein all followed-up subjects will be analyzed.

RISK ANALYSIS

SHC has evaluated the potential risks and benefits (listed below) associated with the C-Pulse® and its appropriateness for therapy for symptomatic Stage C HF patients with NYHA Class III–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

Implantation is an invasive procedure requiring a median sternotomy 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
- Arterial Non–CNS Thromboembolism
- Wound Dehiscence
- Death

There may be other unforeseen risks.

Risk Related to the Investigational Device

The C-Pulse ICP 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/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®, 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 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 Dacron 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.[18,19,20] 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.

The C-Pulse Cuff has a maximum target volume setting of 20–30cc, 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 proven by FDA, 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

[18] [Furman 1970]

[19] [Gitter 1998]

[20] [Davies 2002]

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 most aortas, 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.[21] 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, whilst 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 atheromatous 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 counterpulsation.

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.

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 is not indicated in Class IVb heart failure patients; those that are not ambulatory, are inotrope dependent 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.

[21] [Legget 2005]

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 to 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 Dacron, 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 Dacron has proven long-term use clinically as both a peri-vascular wrap and as a graft replacement, and has only 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. Surgeons are required to undergo multiple implantations of the cuff on a mock inflated ascending aorta prior to their first implantation, and there is an intra-operative check-list to reduce the chance of making an inadvertent needle-hole, and to check for and discover any such hole and thus replace the cuff.

The Driver is designed to detect air leaks and trigger an alarm and to stop. 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 device 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.

Emboli arising from ascending aorta and risk of neurological damage

The device does not contact blood thus in normal use there is no foreign surfaces in contact with the blood. Thromboembolism may result from ascending aortic disease or left ventricular mural thrombus. There is a risk such emboli may cause cerebral ischemia. If there is a breach of the intimal lining caused by the cuff then mural thrombus may develop and embolize.

Significant contraindications for implanting the C-Pulse include pre-existing ascending aortic atheroma, particularly intimal thickening greater than 3mm or any mural thrombus or mobile atheroma or calcific or aneurysmal disease of the ascending aorta. Patient eligibility in this regard may be determined accurately by CT scan and/or echocardiography: CT specificity (as compared to epi-aortic scanning at surgery) has been reported at 98%. [22]

The incidence of atherosclerosis increases with age, the presence of coronary artery disease, and distance from the aortic valve. The ascending aorta is one of the areas least affected by atherosclerosis because there are no branches to create turbulence and the flow is vortical in nature given the natural shape of the ascending aorta.[23]

In the pilot intra-operative clinical study to confirm safety and performance of a gas-driven C-Pulse Cuff in patients with normal ventricles undergoing OPCAB[24], the Cuff fit all patients and counterpulsation was effective with approximately 50–70% compression of the aortic lumen. No patient that consented for the study was later excluded for aortic disease, and no complications arose. The right common carotid artery was monitored over 20 minutes intervals with the device both on and off – there was no significant difference in the rate of high intensity transient signals (HITS) detected and there were no post-operative neurological events.

The frequency of HITS has been studied in relation to various types of prosthetic aortic heart valves and LVADs. Most studies have measured HITS in the middle cerebral artery. Mechanical valves appear to have higher HITS rates[25], but most appear to be harmless epiphenomena[26]. Thrombo-embolic events are prevalent in LVAD patients, and there may be a significant relationship between HITS and thrombo-embolic events; this may be

[22] [Davila–Roman 1999]

[23] [Leuprecht 2002]

[24] [Leggett 2005]

[25] [Laas 2003]

[26] [Nadareishvili 2002]

influenced in part by increased hemostatic activity despite aggressive anticoagulant therapy and in part by the type of LVAD in situ.[27,28,29]

Aortic Rupture

There are several examples of extra-aortic banding or counterpulsating, using different materials, and in different species. In humans, Dacron wraps have been used to support primary ascending aortic aneurysm repair as described in a number of clinical series, with 10 year follow-up.[30,31,32] Note that patients requiring an aorto-coronary graft had it placed via a hole cut in the Dacron 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.[33]

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 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 no 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 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

[27] [Nabavi 2003]

[28] [Kofidis 2002]

[29] [Wilhelm 1999]

[30] [Barnett MG 1995]

[31] [Carel 1991]

[32] [Rubiscsek 1994]

[33] [Bauer 2003]

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 ionotropic support, those who are severely cachetic 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 specific guidelines are given to care-givers and patients for managing this wound site long-term. The percutaneous lead has been specifically designed to reduce the risk of infection – the outside diameter is approximately 5 mm, the material is Silicone, and the tubing is soft and flexible. Flockings exist subcutaneously to anchor the Lead in a manner similar to Tenkhoff and Hickman catheters.[34] There is no device 'pocket' created.

The Cuff and ECG lead can be terminated subcutaneously and sealed if the Percutaneous 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® through careful design and pre-clinical testing. Preclinical testing includes bench and animal testing to verify performance, software validation testing, destructive analysis and shock tests, and packaging qualifications.

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.

[34] [Ash 1990]

Prior to implant patients should go through a complete cardiac evaluation. After implantation, patients 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® to hospitals equipped with redundant systems and staffed by qualified, trained personnel.

C-Pulse® Potential Benefits

Anticipated benefits of the C-Pulse® 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) .[35] 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 1.4M people in the USA in Class III and IV 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 2~~Figure 2~~ highlights the trend of heart failure, and the relationship of severity of heart failure with repeat hospitalization and with mortality.

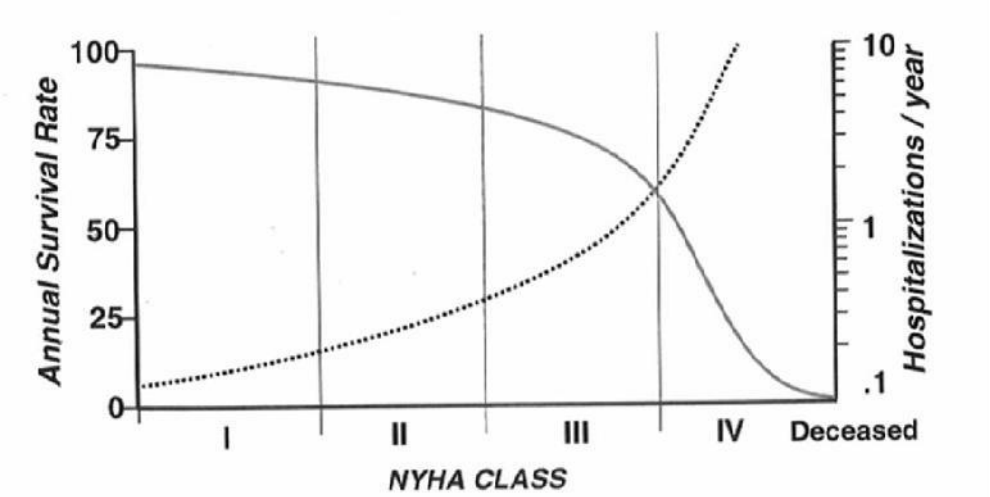

Figure 2. Annual survival rate and frequency of hospitalizations versus NYHA Classification

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® i.e. NYHA Class III–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.

[35] [Warner–Stevens]

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–IV. Basic safety has been demonstrated on a very sick group of patients (NYHA Class III–IV) in a Pilot Study in Australia and New Zealand. Significantly, there was no surgical-related mortality and while there were very good indicators for device performance in relation to heart failure symptoms and cardiac function, there was an incidence of early infection. The method of training, the Cuff itself, the percutaneous line, and the inclusion and exclusion criteria have all been modified to reduce this infection risk. Furthermore, the need for a back-up ECG sense lead in a subcutaneous pocket has been eliminated.

The focus of the IDE Feasibility Clinical Investigation will be on safety but also on examining the dose–effect of counterpulsation, much like a Phase II drug trial. Measurements including Peak VO_2, Quality of Life scores, LV function and blood tests will be made to allow planning for a pivotal study design. Assessment will be made of all adverse events.

Study Design – Control Groups

The IDE Study will be conducted in two phases: Feasibility is an open-label, single arm study to determine the safety of the device as well as examine the effect of different levels of counterpulsation. For the Pivotal trial, an expanded randomized double-blind crossover study is anticipated.

The template of the double-blind, randomized control trial has emerged as the gold standard for evaluating new pharmacological therapies. Multiple large, randomized, placebo-controlled trials established angiotension-converting enzyme inhibitors as the cornerstone of therapy[36], and more lately beta-adrenergic blocking agents have shown longer-term improved hemodynamics and survival in recent large trials of mild-moderate heart failure[37]. Chronic use of intravenous inotropic drugs has not provided sustained hemodynamic improvements and mortality is increased. End points of survival, clinical status, cardiovascular function and cost-effectiveness can be evaluated using this template without either physician or patient knowing who has received the new therapy being tested.

The inability to provide comparable placebo therapy (e.g. sham operations), strong patient preferences regarding invasive procedures, and the front-loaded risk of LVAD studies have complicated the evaluation of new mechanical circulatory support devices for advanced heart failure using a randomized control trial template. The impact of the device is more transparent than that of a drug, in part because the most obvious risks are front-loaded compared with those from new drugs. The combination of debilitating disease and unblinded therapy raises ethical issues – patients consenting to new trials are likely to be already biased toward the procedure and thus may perceive randomization to the control arm as a loss of hope, with potentially deleterious impacts on individual outcomes.[38] Furthermore, patient preference for specific therapies perceived to be life–saving may limit enrollment into the randomization process.

Resynchronization therapy has, because of the nature of the device, allowed use of a randomized, double-blinded trial structure to evaluate its safety and efficacy. The device requires surgery for implantation, thus exposing front–loaded risk to all patients, but it can be tuned to optimize bi-ventricular timing or used in a simple pacing mode.

C-Pulse acts to a) increase coronary blood flow, b) reduce ventricular afterload to reduce the workload of the left ventricle, and c) increase cardiac output. C-Pulse® offers the unique situation whereby the level of counterpulsation can be adjusted without the patient being cognizant of how much benefit he/she is receiving from the device. Cohen et al showed in a limited study of 20 patients a significantly higher velocity time integral across the LV outflow tract resulted when counterpulsated at 1:1 versus at 1:8. They did not show any difference with varying the balloon volume from 40 to 32 cc.[39]

[36] [Davis 1979]

[37] [Packer 2001]

[38] [Neaton 2007]

[39] [Cohen 1995]

Trial End–Points

The End Points for a Clinical Trial are chosen according to the severity of disease in the population selected. The target population for this trial has been defined widely to include patients with the best natural history compatible with the degree of certainty that the device will provide an improvement. This will help maximize the generalization of the results. The primary endpoint should be clinically relevant and sensitive to the hypothesized effect of the treatment. End-points should be obtainable in all patients and be inexpensive to measure. Endpoints may include clinical outcomes such as death or morbid events such as repeat hospitalizations, or measures of quality of life such as NYHA Class or QOL scores. Surrogate measures of heart failure for heart assist devices have not been established but may strengthen a trial by showing correlation with clinically relevant findings. Composite endpoints may include clinical outcomes and surrogates, but should avoid combining safety and efficacy outcomes; composite structure has the advantage of reducing sample size, though selection of composites requires that the treatment has similar affect for all endpoints selected.

The C-Pulse® is targeted at Class III–IV patients, where mortality is difficult to predict, but the quality of life of patients is poor enough to consider the need for an implantable heart assist device. The primary endpoint in this Feasibility study is safety, and will be assessed by showing the device is not associated with an unacceptable mortality or morbidity profile in the selected patient population, as judged by the DSMB. Performance variables will allow statistical planning of the Pivotal study and selection of appropriate endpoints and study design.

Studies regarding NYHA Class III and IV patients also are useful to identify boundaries of expected changes in endpoints.

Summary

The objective of the feasibility clinical investigation shall be related to establishing or verifying the safety, and identify trends of efficacy and performance of the device, when used for its intended purpose and according to the documented instructions. The study may be expanded to a pivotal randomized double-blinded trial after taking into account the serious adverse event profile and anticipated levels of performance and efficacy as compared to other circulatory support devices.

The primary objective of the feasibility study is to demonstrate reasonable safety in patients in Class III–IV heart failure. Placing C-Pulse® in suitable patients in ACC/AHA Stage C; NYHA Class III–IV HF with the objective of improving the patient's quality of life and cardiac performance is justifiable based on the results of testing of the C-Pulse® device to date, and on the efficacy of clinical performance and safety data of similar devices, such as biventricular pacemakers, other forms of chronic counterpulsation, and LVADs.

STUDY OVERSIGHT AND INTEGRITY

DESIGNATION OF SPONSOR, DATA MANAGER, AND AUDITOR

Role	Organization	Address	Contact Numbers
Sponsor	Sunshine Heart, Inc.	12988 Valley View Rd Eden Prairie Minnesota 55344	Primary Contact: Aleela Baune 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 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 patients' files as per the informed consent at the investigator's site when so requested.

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: patient accrual at each center, total number of patient 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 patient records, study management documents, device tracking and Patient 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 regulatory requirements have been satisfied per the Investigational Plan (IP) and/or by a decision of the business leaders for Sunshine Heart. 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 patient enrollment, recent monitoring visit, etc.)

NAME AND ADDRESS OF STUDY MONITORS

Sunshine Heart 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 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.

STUDY SAFETY

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 device-relatedness, seriousness, and procedure-relatedness. The committee will consist of a minimum of three physicians including a chairperson appointed by Sunshine Heart 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 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, patient or physician identification.

Data and Safety and Monitoring Board (DSMB)

A DSMB will convene, composed of a least one heart failure cardiologist, cardiac surgeon, medical doctor of associated disciplines and a biostatistician who are not directly involved in the trial. The DSMB will review the study data after enrollment of the first five patients. Enrollment of further patients will occur as the DSMB reviews the data. The DSMB will provide a report following the review and may recommend to Sunshine Heart to continue, modify or stop the trial based on their findings. The DSMB will provide further evaluation at least twice per year and after the first five patients are enrolled. If slow enrollment is experienced, the DSMB may meet less frequently.

Based on the data, the DSMB may recommend to Sunshine Heart to modify or stop the trial. All final decisions, however, regarding the trial modifications, rest with Sunshine Heart and the Medical Advisory Board.

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 patient training in preparation for discharge. At the end of the training course, all participants should be competent in ensuring optimum care of the patient. 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 standard operating procedures and quality system requirements. A summary of the contents and audience are included in the table below.

Training component	Audience	Format required
Surgical training	• Surgeon	• Cuff mock implant training • Observe Surgery, if possible • Mentor support at implant
Expert users training	• Cardiologists • Clinical coordinator • Surgeon	• Product overview • Protocol overview • System/Programmer training
Site Initiation /protocol training	• **All investigators** • Study coordinator • Back-up study coordinator must be trained on protocol, ICH/GCP and investigator responsibilities	• Self directed review of presentation by **ALL** Investigators and self assessment with optional independent education by Clinical trial staff **AND** • Meeting with key investigators/personnel & clinical coordinator to discuss recruitment, logistics for equipment storage, monitoring schedule
Clinical /support staff training (as appropriate)	• Emergency, • Intensive care • Coronary care • Cardiothoracic surgical ward • Cardiac ward • Operating Room • Physiotherapy • Nutrition • Occupational Therapy • Infectious Diseases • Patients Local EMT • Patients Primary Caregivers	• Product overview • Implant overview • Protocol overview • Practical “get to know” equipment session

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 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 patient in an emergency. Prior notification is required in situations where the unforeseen circumstances are beyond the control of the Investigator (e.g. inadvertent mistakes, equipment failure, patient ill and unable to perform testing, etc.).

Protocol deviations must be recorded on the Protocol Deviation eCRF. Include a description of the deviation, justification for the deviation, corrective action and whether the clinical manager was notified prior to the deviation.

Deviations will be reported to the clinical manager regardless of whether medically justifiable, pre-approved by the clinical manager or taken to protect the patient in an emergency. Protocol deviations should be reported as soon as possible upon notification 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 eCRF 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

The following will not be considered protocol deviations:

- Minor titration of cardiovascular medication regimen including:
- Any downward titration of medications less than 50% of initial dose
- Any upward titration of medication greater than 100% of initial dose
- ACE/ARB may be added after implantation if tolerated

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.
- Patient's case history records, including the signed patient 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 & Equipment Disposition Logs, containing Site delivery dates of devices, implant dates and returned to Sponsor dates, quantities and serial numbers of devices delivered at the site, quantities and serial numbers of devices returned to Sponsor, expiration dates and patient IDs of the patients 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~~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 Reports

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 patient. Except for the deviations under emergencies, prior notification must be submitted to Sunshine Heart.
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 will retain the following records:

- All correspondence which pertains 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 Reports

Report	Submit to:	Description
Unanticipated Adverse Event – Device Related	FDA, all IRBs and all Investigators	Sunshine Heart 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 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 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 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 will form a publication committee that includes participating investigators, the VP of Clinical Studies, and other Sunshine Heart 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 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 patient 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 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 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 C-Pulse® 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 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 results will be evaluated for scientific validity and the ability of Sunshine Heart 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 Xray
ECHO	Echocardiogram
eCRF	Electronic Case Report Form Template
ICU	Intensive Care Unit
IV	Intra–venous
PRBC	Packed Red Blood Cells

APPENDIX B: NATIONAL CO–PRINCIPAL INVESTIGATORS

The following physician–investigators have been designated as Principal Investigators for this study:

William T. Abraham, M.D.

Chief of Cardiovascular Medicine

Ohio State University

Division of Cardiovascular Medicine
Room 110P DHLRI
473 W. 12th Ave.
Columbus, OH 43210–1252

Patrick McCarthy, M.D.

Chief, Division of Cardiothoracic Surgery

Co–Director, Bluhm Cardiovascular Institute

Heller–Sacks Professor of Surgery

Northwestern University Feinberg School of Medicine
201 East Huron Street, Galter 11–140
Chicago, IL 60611–2968

APPENDIX C: PARTICIPATING INSTITUTIONS

Up to 9 centers in the US and potentially some OUS centers will participate in the study. The following table represents the centers proposed for investigational sites.

Site Name/Co-Principal & Principal Investigators	Investigator Contact Info
Ohio State University Medical Center Principal Investigator: Garrie Haas, MD (HFC)	Ohio State Heart Center 473 West 12th Ave, Suite 200 DHLRI Columbus, OH 43210-1252 Ph (614) 293-4967 Fax (614) 247-7789
Northwestern University Feinberg School of Medicine Principal Investigator: Edward C. McGee, Jr.MD (CTS)	Northwestern University Feinberg School of Medicine Bluhm Cardiovascular Institute 201 East Huron Street, Galter 11-120 Chicago, Illinois 60611-2968 Ph (312) 695-3121 Fax: (312) 695-1903
Penn State Hershey Medical Center Principal Investigator: Walter Pae, MD (CTS)	Penn State Milton S. Hershey Medical Center Division of Cardiology, H047 500 University Drive, Room H1511 Hershey, PA 17033-0850 Ph (717) 531-8329 Fax: (717) 531-8521
University of Alabama at Birmingham Principal Investigator: Salpy Pamboukian, MD (HFC)	Division of Cardiothoracic Surgery University of Alabama at Birmingham 760 THT, 1900 University Blvd. Birmingham, AL 35294 Ph: (205) 934-5486/ (205) 934-3368 Fax: (205) 975-2553
University of Louisville Jewish Hospital Principal Investigator: Sumanth Prabhu, MD (HFC)	University of Louisville-Jewish Hospital 201 Abraham Flexner Way, Suite 1200 Louisville, KY 40202 Ph (502) 629-2555 Fax (502)-629-2551
United Heart and Vascular Clinic Principal Investigator: Alan Bank, MD (HFC)	Allina Hospital and Clinics 2925 Chicago Ave Minneapolis, MN 55407
Saint Luke's Hospital – Mid America Heart Institute Principal Investigator: Sanjeev Aggarwal, MD (CTS)	Saint Luke's Hospital of Kansas City 4401 Wornall Road Kansas City, MO 64111
To be determined – will provide in Progress Report once IRB approval received	To be determined

APPENDIX D: IRB LIST

A list of the IRB contacts for each participating investigational center is included below.

Site Name/Principal Investigator	Institutional Review Board	IRB Chairperson
Northwestern University Feinberg School of Medicine Principal Investigator: Edward C. McGee, MD (CTS)	Northwestern University Office for the Protection of Research Subjects 750 North Lake Shore Drive, Suite 700 Chicago, Illinois 60611	Darren R. Gitelman, MD
Ohio State University Medical Center Principal Investigator: Garrie Haas, MD (HFC)	Western Institutional Board (WIRB) 3535 7th Avenue SW Olympia, WA 98502-5010	Theodore D. Schultz, J.D.
Penn State-Milton S. Hershey Medical Center Principal Investigator: Walter Pae, MD (CTS)	Penn State College of Medicine Penn State Milton S. Hershey Medical Center Human Subjects Protection Office, Institutional Review Board Room ASB 1140 600 Centerview Drive, PO Box 855 Hershey, Pennsylvania 17033-0855	Kevin Gleeson, MD
University of Louisville Jewish Hospital Principal Investigator: Sumanth Prabhu, MD (HFC)	University of Louisville MedCenter One, Suite 200 501 E. Broadway Louisville, KY 40202-1798	Laura L. Clark, MD
University of Alabama at Birmingham Principal Investigator: Salpy Pamboukian, MD (HFC)	Western Institutional Board (WIRB) 3535 7th Avenue SW Olympia, WA 98502-5010	Theodore D. Schultz, J.D.
United Heart and Vascular Clinic Principal Investigator: Alan Bank, MD (HFC)	Allina Hospital and Clinics IRB 2925 Chicago Ave Minneapolis, MN 55407	Thomas Ducker, MD
Saint Luke's Hospital – Mid America Heart Institute Principal Investigator: Sanjeev Aggarwal, MD (CTS)	Saint Luke's Hospital of Kansas City 4401 Wornall Road Kansas City, MO 64111	Alan Forker, MD

APPENDIX E: SUMMARY OF PREVIOUS STUDIES

Experience to date by Sunshine Heart 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 counterpulsation augments coronary flow and reduces left ventricular afterload.

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.

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 haemorrhages, 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 in NYHA Class III–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 was safely implanted and was able to be turned off for brief periods. C-Pulse 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.

APPENDIX F: LABELING AND OPERATOR MANUAL

Not related to this change – not resubmitted.

APPENDIX G: SAMPLE HIPAA DISCLOSURE

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

C-Pulse® Implantable Counterpulsation Pump (ICP) US Feasibility 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® Implantable Counterpulsation Pump (ICP) which is a Heart Assist Device 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
  - 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® 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 volunteer. A copy should be placed in the volunteer's medical record, if applicable.

APPENDIX H: SAMPLE INFORMED CONSENT

SAMPLE OF INFORMED CONSENT
FOR INVESTIGATIONAL RESEARCH STUDY

PROTOCOL TITLE: **C-Pulse® Implantable Counterpulsation Pump (ICP) US Feasibility Study**

PROTOCOL NUMBER:

INSTITUTION: [Institution]

INVESTIGATOR: [Investigator]

Introduction

Your physician has recommended that you consider undergoing a surgical procedure to receive the C-Pulse® 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. The C-Pulse ® device is a new heart-assist device that allows you to remain active and does NOT contact the blood, therefore, the device does not require the use of blood thinning medications.

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 understand that you are being asked to take part in a clinical research trial. 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 C-Pulse device to assist your failing heart. The C-Pulse is an experimental device and is not approved by the Federal 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 will 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 attached to a vest or carry bag that you will wear.

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.

There will be up to 40 patients enrolled and implanted in this study in the United States and up to 9 centers in the US and potentially some OUS centers. Your part in the study and follow-up visits are expected to last up to 8 years.

Device Description

The C-Pulse device 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.

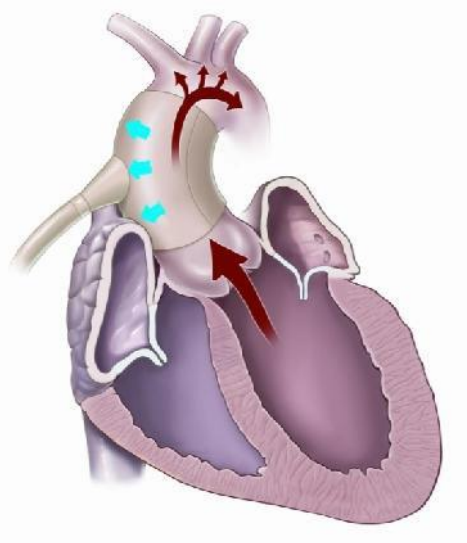

Fig 1A: C-Pulse Cuff deflates as the heart ejects blood, unloading the heart.

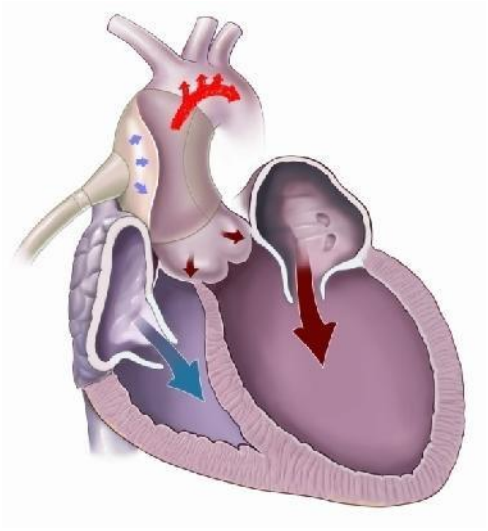

Fig 1B: C-Pulse Cuff inflates as the heart refills with blood, giving a secondary pulse of blood to the body and heart muscle.

The C-Pulse device is intended as a permanent implant and for the duration of the study to be used for at least 20 hours per day. It is considered safe to turn the device off for short periods (up to 15 minutes) 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 four years. The Driver is designed to detect any Cuff failure and alarm and stop pumping. The Cuff is expected to be able to be replaced if this is indicated.

Screening Evaluation, Tests, and Procedures

You are being asked to participate in some screening tests and procedures determine if you are eligible for the study. If you meet criteria based upon these evaluations, 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, respiratory rate
- Documentation of 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. You will also be given some medication as part of the test to make the images more clear. Your doctor will monitor your kidneys after the CT scan to check for any damage from the medication. 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 go on to obtain 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.

- CT scan of your head will follow the CT scan of your aorta. It is exactly like the CT scan of your aorta only the x-ray beams will rotate around your head.
- Right heart catheterization is the passing of a thin tube (catheter) into the right side of the heart. The procedure is done to see blood movement through the heart and to monitor your heart's function. An X-ray image will help the doctor see where the catheter is placed. The test can be done in the hospital or outpatient procedure center depending upon your hospitals requirements. The physician who will perform the catheterization will go over the risks with you before it is done.
- Transthoracic echocardiogram, (ECHO of your chest and heart) a painless procedure where gel is placed on a transducer which is 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 (MLHF Score, KCCQ) and a questionnaire about how you feel (Fatigue Impact Scales)
- A Neurological test called the National Institute of Health Stroke Score (NIHSS) and a test called the Modified Rankin will be done to assess your neurologic state
- Complete two assessments (NYHA Classification, Six Minute Walk - to measure how far you can walk in 6 minutes)
- Pregnancy test (if applicable)

- Cardiopulmonary test shows the maximum amount of oxygen your heart can provide to your muscles during constant activity. Doctors consider this a true measure of your heart's ability to keep you going. This test requires special equipment so it is usually done in a special clinic or hospital. You will be asked to blow into a tube connected to a lung doctor's machine first. They you will have small adhesive electrodes stuck to your chest and sides like for an EKG. The wires will attached to the electrodes will connect you to a heart monitor. You will stand on a treadmill or exercise bike and your blood pressure will be taken with a cuff. A padded clothespin is clamped over your nostrils so you cannot breathe except through your mouth. The treadmill starts slowly and speed will slowly increase until it is as fast as you can manage and you are not talking "comfortable". This is a test where they want to push you hard. You will be monitored during the exercise closely. The test continues until you are unable to go on.
- Blood tests

Study Procedures

If you meet all screening criteria for the study and after discussing the study with your doctor, you decide to participate in the study, you will be scheduled and prepared to undergo surgery.

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, a sternotomy (your breast bone will be cut open) will be performed 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.

During the surgery, examination of your heart and aorta with an ultrasound probe
Monitoring of arterial blood pressure

Fig 2: C-Pulse device with wearable driver unit.

<u>After the procedure and before you leave the hospital:</u>

All patients in the study will receive the device and it will be 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 on the ward is 7-14 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. Your will continue to take anti-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.

Your doctor and medical team may teach you to disconnect from your device for short periods of time (no more than 15 minutes at a time). You will need to discuss this with your doctor.

You will not leave the hospital until your doctor has decided that you are ready. Before you leave, your doctor will do the following:

- Echocardiogram, (ECHO of your chest and heart) a painless procedure where jell is placed on a transducer which is then goes on your chest to measure your heart chambers and function including the valves of your heart.
- A neurological consultation from a specialist that will assess your brain and reaction functions.

Be sure that you understand the complete device information and personal care that you need to do at home.

1-Month Follow-up Visits

- General physical examination (including blood tests)
- Documentation of medications
- Recording of weight, heart rate, blood pressure, respiratory rate
- (ECHO of your chest and heart)
- Complete Six Minute Hall Walk and NYHA Classification assessment
- Complete 2 questionnaires relating to your quality of life (MLHF Score, KCCQ) and two questionnaires about how you feel (Fatigue Impact Scales)
- A Neurological test called the National Institute of Health Stroke Score (NIHSS) and Modified Rankin will be done to assess your mental state*

3-Month Follow-up Visits

- General physical examination (including blood tests)
- Documentation of medications
- Recording of weight, heart rate, blood pressure, respiratory rate
- Chest X-Ray
- (ECHO of your chest and 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 (MLHF Score, KCCQ) and two questionnaires about how you feel (Fatigue Impact Scales)
- A Neurological test (NIHSS) and Modified Rankin will be done to assess your mental state

6-Month Follow-up Visits

- General physical examination (including blood tests)
- Documentation of medications
- Recording of weight, heart rate, blood pressure, respiratory rate
- CT 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 will be asked to hold your breath during image capture. You may need some medication to help you relax
- (ECHO of your chest and heart)
- Chest X-Ray
- A very fine tube (catheter) will be inserted into one of your blood vessel, either in your groin or neck, and passed into the right chamber of your heart to assess the pressures in your heart (right heart catheterization)
- 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 (MLHF Score, KCCQ) and two questionnaires about how you feel (Fatigue Impact Scales)
- A Neurological test (NIHSS) will be done to assess your mental state
- A Neurological test called the Modified Rankin
- Walking test to measure your maximum limit for exercise (Peak O2 uptake)

Long term Visits 12, 18 Month and Annual Visits (from implant date)

- General physical examination (including blood tests)
- Documentation of medications
- Recording of weight, heart rate, blood pressure, respiratory rate
- (ECHO of your chest and 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 (MLHF Score, KCCQ) and two questionnaires about how you feel (Fatigue Impact Scales)

*If at any time during the study you experience a neurological adverse event you will have the NIHSS and the Modified Rankin collected 30 and 60 days after your event.

After 10 years of annual visits or the study is closed, 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 and are described below:

- Drug reactions to any pre-medications you might receive before the CT scan or right heart catheterization such as drowsiness, low blood pressure, nausea or vomiting.
- For the right heart catheterization you may experience the following;
    - Bruising around the area where the catheter was inserted
    - Injury to the vein
    - Puncture to the lung if the neck or chest veins are used
    - rare complications could include cardiac arrhythmias, cardiac tamponade (pressure on your heart due to fluid build-up in the sac around your heart), low blood pressure, infection, or embolism (blocking an artery)caused by blood clots at the tip of the catheter.
    - Before the heart catheterization test, your doctor will review all the risks associated with the test
- For the pulmonary testing, you may experience the following;
    - Very dry throat as well as excessive drooling
    - fatigue
- Possible infection at the needle puncture site from the right heart catheterization or 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 (1-5%)

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

Surgical procedure:

- 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
- Death

C–Pulse® Heart Assist Device:

- 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

- Infection – infection from the line that is tunneled thru your skin to the outside of your body may occur
    - Your doctor may perform additional testing that may expose you to radiation
- Emboli – due to the repeated inflations of the cuff, small particles in your blood may come loose from the aortic wall causing a stroke
- Aortic disruption- due to the repeated inflations of 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
- 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 thru 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. The C- Pulse device is intended as a treatment option in patients who are ambulatory, 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.

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

Termination

This research project 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 decisions made in the commercial interests of 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). Nothing about you, your illness or treatment will be made public. If the results of this study are published, your identity will remain confidential.

Study Questions

If you have questions about the study, you may contact:

(Principal Investigator)	(Telephone number)

Subject Rights

If you have questions regarding the conduct of this study or your rights as a research subject, 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 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 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
- 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 subject 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 will keep your health data confidential in keeping with all applicable laws. Sunshine Heart may use your health data to conduct this study. Sunshine Heart may 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's work in making new devices. These laws help make certain the safety and quality of medical devices. Sunshine Heart 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 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 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 and Researchers may continue to use and share the health data they got 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 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 Subject Date/Time

_____

Print Name of Subject

_____ _____

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

_____

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

_____ _____

Investigator Signature (or Designee) Date/Time

_____

Printed Name of Investigator (or Designee)

APPENDIX I: REQUIRED TESTS

Follow-up Requirements Baseline to 6 months Post Implant						
	Pre-Implant	**Implant**	**Pre-Discharge[7]**	**1 mo**	**3 mo**	**6 mo**
A. PATIENT ELIGIBILITY	X					
B. GENERAL						
Demographic Data	X					
Medical History	X					
General Physical Examination	X	X	X	X	X	X
Concurrent Medications	X	X	X	X	X	X
Pregnancy test (if applicable)	X					
C. VITAL PARAMETERS						
Weight	X		X	X	X	X
Heart rate (ECG pre-implant)	X		X	X	X	X
Blood pressure	X		X	X	X	X
Respiratory rate	X		X	X	X	X
D. CARDIOPULMONARY						
CT aorta	X					X
CXR	X				X	X
ECHO	X	X[2]		X	X	X
Right heart catheterization (CVP, PAP, CI, PCWP, SVR, PVR)	X					X
Peak O2 uptake	X					X
E. QUALITY OF LIFE						
NYHA Classification	X			X	X	X
MLHF Score/ KCCQ	X			X	X	X
Fatigue Impact Scales	X		X	X	X	X
Six Minute Walk	X			X	X	X
F. HEMATOLOGY						
Hemoglobin	X		X	X	X	X
Hematocrit	X		X	X	X	X
Plasma free hemoglobin	X		X	X	X	X
Platelet count	X		X	X	X	X
White cell count	X		X	X	X	X
APTT	X		X	X	X	X
INR	X		X	X	X	X
Fibrinogen	X		X	X	X	X
G. BIOCHEMISTRY						
Serum sodium	X		X	X	X	X
Serum potassium	X		X	X	X	X
Serum creatinine/ GFR[3]	X		X	X	X	X
BUN	X		X	X	X	X
Serum albumin	X		X	X	X	X
Serum bilirubin	X		X	X	X	X

Follow-up Requirements Baseline to 6 months Post Implant						
	Pre-Implant	**Implant**	**Pre-Discharge[7]**	**1 mo**	**3 mo**	**6 mo**
Serum ALT	X		X	X	X	X
Serum AST	X		X	X	X	X
Serum BNP	X					X
H. NEUROLOGICAL ASSESSMENT[6]						
Neurological testing (NIHSS)[4]	X		X	X	X	X
Modified Rankin [4]	X		X	X	X	X
Head CT [5]	X					
Neurological Consultation	X		X[6]			
I. IMPLANT DETAILS		X				
J. DEVICE LOG		X		X	X	X
K. DISCHARGE CHECKLIST			X			

1 Annually post-implant
2 Epi-aortic Echo at implant
3 Estimated GFR at Baseline and within one week post CT to evaluate contrast induced nephropathy.
4 Post Neurological Dysfunction AE – 30, 60 and 90 days post event
5 At Baseline only or as clinically indicated with any Neurological Dysfunction AE – Head CT should be completed only after clearance for implantation.
6Required at 5-7 days post ICU discharge or at hospital discharge whichever occurs first and at the time of any suspected Neuro Dysfunction AE
7 At Discharge - (see Appendix M)

Long-term Post Implant Follow-Up Requirements			
	12 month	18 month	Annually Year 2-10
A. PATIENT ELIGIBILITY			
B. GENERAL			
General Physical Examination	X	X	X
Concurrent Medications	X	X	X
Pregnancy test (if applicable)			
C. VITAL PARAMETERS			
Weight	X	X	X
Heart rate (ECG pre-implant)	X	X	X
Blood pressure	X	X	X
Respiratory rate	X	X	X
D. CARDIOPULMONARY			
ECHO	X	X	X
E. QUALITY OF LIFE			
NYHA Classification	X	X	X
MLHF Score/ KCCQ	X	X	X
Fatigue Impact Scales	X	X	X
Six Minute Walk	X	X	X
F. HEMATOLOGY			
Hemoglobin	X	X	X
Hematocrit	X	X	X

Long-term Post Implant Follow-Up Requirements			
	12 month	18 month	Annually Year 2-10
Plasma free hemoglobin	X	X	X
Platelet count	X	X	X
White cell count	X	X	X
APTT	X	X	X
INR	X	X	X
Fibrinogen	X	X	X
G. BIOCHEMISTRY			
Serum sodium	X	X	X
Serum potassium	X	X	X
Serum creatinine/ GFR[3]	X	X	X
BUN	X	X	X
Serum albumin	X	X	X
Serum bilirubin	X	X	X
Serum ALT	X	X	X
Serum AST	X	X	X
I. IMPLANT DETAILS			
J. DEVICE LOG	X	X	X
K. DISCHARGE CHECKLIST7			

1 Annually post-implant
2 Epi-aortic Echo at implant
3 Estimated GFR at Baseline only
4 Post Neurological Dysfunction AE – 30, 60 and 90 days post event
5 At Baseline only or as clinically indicated with any Neurological Dysfunction AE – Head CT should be completed only after clearance for implantation.
6 Required at 5-7 days post ICU discharge or at hospital discharge whichever occurs first and at the time of any suspected Neuro Dysfunction AE
7 At Discharge (see Appendix M)

APPENDIX J: CORE LABORATORIES

Cardiopulmonary Exercise Testing

Henry Ford Health System

Clinical Exercise Physiology Core Lab

6525 Second Ave

Detroit, MI 48202

Voice: (313) 972-1920, FAX: (313) 972-1921

cepcorelab@hfhs.org

Primary Contact: Clinton Brawner

Echocardiography

Cardiovascular Core Labs
100 Irving Street, NW
Suite EB-5123
Washington, DC 20010

Voice: (202)877-0223

Primary Contact: Neil J Weissman, MD

CT Scan

Cardiovascular Core Labs
100 Irving Street, NW
Suite EB-5123
Washington, DC 20010

Voice: (202)877 6177

Primary Contact: Wm Guy Weigold, MD

APPENDIX K: SAMPLE CASE REPORT FORMS

Not related to this change – not resubmitted

APPENDIX L: NEUROLOGICAL TESTING

NIH STROKE SCALE

The NIH Stroke Scale (NIHSS) must be administered at Pre–implant Baseline and each follow–up. Administer the stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinical thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated the patient should not be coached (i.e. repeated requests to patient to make a special effort).

Instructions	Scale Definition
1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation	0 = Alert; keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.

Instructions	Scale Definition
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11.	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)
4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or noncomprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.	0 = Normal symmetrical movement 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)
5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9".	
5a. Left Arm **5b. Right Arm**	0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls. 4 = No movement 9 = Amputation, joint fusion explain:_____
6a. Left Leg **6b. Right Leg**	0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5 second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement 9 = Amputation, joint fusion, explain:_____

Instructions	Scale Definition
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heelshin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.	0 = Absent 1 = Present in one limb 2 = Present in two limbs If present, is ataxia in Right arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain _____ Left arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain _____ Right leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain _____ Left leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain _____
7a. Right Arm: Ataxia present? **7b. Left Arm**: Ataxia present? **7c. Right Leg**: Ataxia present? **7d. Left Leg**: Ataxia present?	1 = Yes 2 = No 9 = amputation or joint fusion, explain _____
8. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.	0 = No aphasia, normal 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example in conversation about provided materials examiner can identify picture or naming card from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored "9", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.	0 = Normal 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. 9 = Intubated or other physical barrier, explain_____

Instructions	Scale Definition
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.

MODIFIED RANKIN

The Modified Ranking must be administered at Pre–implant Baseline and each follow–up. Administer the stroke scale items in the order listed. Score should reflect what the patient does, not what the clinical thinks the patient can do.

The Modified Rankin is a score that is given according to the scale provided below:

0 = No symptoms at all

1 = No significant disability despite symptoms; able to carry out all usual duties and activities

2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 = Moderate disability; requiring some help, but able to walk without assistance

4 = Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 = Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 = Dead

APPENDIX M: 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)*			
Acceptable Oxygen Saturation on room air			
Sinus Rhythm or Atrial arrhythmia with Ventricular rates < 120 bpm			
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 and recharging batteries			
Patient and caregiver understand and respond to the Driver Alerts and Alarms			
Home Assessment Visit prior to discharge			
All protocol required testing is completed up to point of discharge			
Patient Handbook supplied to patient, with Emergency Contact details specified			

APPENDIX N: QUALITY OF LIFE QUESTIONNAIRES

MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE

This questionnaire is to be completed by the patient, after receiving basic instruction from the Clinical Investigator or Research Nurse (Instructor). All attempts should be made to administer the questionnaire:

- by the same person each time, in same setting
- before any other scheduled investigations or medical reviews
- in isolation from spouse and/or other persons who might affect the answers

Furthermore, the Instructor will not paraphrase the pertinent question if asked about the question, but just reiterate the pertinent instructions and the question itself, then ask the patient to respond according to what he or she thinks is appropriate

Begin by showing the patient the questionnaire and asking that they answer a few questions.

Tell the patient to read and think about each question carefully and telling them to make sure to answer all questions. Then go through the first question with him/her to make sure the instructions are clear – indicate that over the last month only.

“If the answer is No then you circle the zero (point to zero). If the answer is Yes, then how much did it stop you living as you wanted over the last month – how much did it prevent you doing things, or how bothersome was it?

Circling 1 means little effect, and circling 5 means very much effect. The 2–4 represent a range of effect in between little and very much.

Did your heart failure prevent you from living as you wanted during the last month by:	No 0	1	Very Little 2	3	4	Very Much 5
1. causing swelling of your ankles, legs, etc.?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends and family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports, or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the food you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low in energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side–effects from medications?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self–control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

KANSAS CITY CARDIAC QUALITY OF LIFE QUESTIONNAIRE

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1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you were limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line.

	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering/Bathing	☐	☐	☐	☐	☐	☐
Walking 1 block on ground level	☐	☐	☐	☐	☐	☐
Doing yardwork, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue or ankle swelling changed?

My symptoms of **heart failure** have become:

Much Worse	Slightly worse	Not Changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles, or legs bothered you?

It has been:

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been:

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been:

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. **Heart failure** symptoms can get worse for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse (for example, weighing yourself, eating a low salt diet, etc.)?

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks how much has your **heart failure limited** your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life
☐	☐	☐	☐	☐

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
☐	☐	☐	☐	☐

How much does your **heart failure** affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line.

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Intimate relationships with loved ones	☐	☐	☐	☐	☐	☐

APPENDIX O: 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 P: SIX MINUTE HALL WALK

The six minute walk test (6MWT) will be conducted as described by Guyatt et al.[40] and as used by other investigators in heart failure clinical trials[41] [42]. In a corridor, a 30.5 meter (100 feet) course (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). A starting line, which marks the beginning and end of lap, should be marked on the floor using brightly colored tape.

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.

The six–minute walk test will be performed at baseline, 1, 3, 6, 12, 18 month, and annually thereafter through study closure.

[40] [Guyatt]

[41] [Bittner 1993]

[42] [Riley 1992]

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. If the patient had a test within 12 months of the Baseline test, that test will be considered a familiarization test. In addition, the Six Minute Hall Walk test should always be completed prior to the Cardiopulmonary testing with adequate time to rest before the CPX test (a minimum of 2 hours is recommended).

APPENDIX Q: CARDIOPULMONARY EXERCISE TESTING OVERVIEW

Cardiopulmonary exercise (CPX) testing will be performed at baseline and at the 6–month follow–up visit to assess patients' exercise tolerance.

Overview of Exercise Protocol for Cardiopulmonary Exercise Test

CPX tests will be performed at baseline and 6 months.

For all CPX tests, patients will be exercised until they have reached a symptom–limited maximal effort. Note: The patient should continue until he/she has reached a symptom–limited maximal effort or other American College of Sports Medicine (ACSM) reasons to discontinue testing occur.[43]

Exercise will be performed on a treadmill using a modified Naughton protocol. Exercise will be initiated at 1 mph (miles per hour)/0% grade and the workload will be increased every two minutes to a symptomatic maximum (up to 3 mph/17.5% grade).

Respiratory gases will be measured with a standard metabolic cart equipped with O2 and CO2 analyzers and a turbine volume transducer, which should be calibrated within 1 hour of testing. Continuous 12–lead ECG monitoring should be performed during the exercise test. The patient will then mount the treadmill and be exercised to his/her symptomatic maximum. Respiratory gas measurements will be made continuously while the patient exercises. Symptoms experienced by the patient during exercise (e.g., angina, dyspnea, fatigue, dizziness) will be recorded. Following a test, the patient should be observed for at least 15 minutes, or longer as determined by the investigator, before discharge from the laboratory.

Baseline Testing Logistics

At the beginning of the study, two CPX tests are required: 1) a "familiarization" test to allow the patient to become familiar with walking on a treadmill and with the breathing apparatus in his/her mouth, and 2) a baseline test.

During the familiarization test, the patient should exercise to his/her symptomatic maximum. If the patient reaches his/her symptomatic maximum, this test may be considered the baseline test. The CPX Core Lab will assess the outcome of the test for acceptability as a baseline.

The first test should be conducted pre-implant. If a second test is required, it should be conducted 48 hours after the first test and also pre–implant. When working the patient into the study and scheduling tests, plan for a 48 hour window between these tests.

Note: If a patient has a documented CPX test that was performed within 6 months of the implant date, this test will be considered the familiarization test. However, the patient must still perform a baseline CPX test for the study, regardless of the previous CPX test.

[43] [Pollock 2000]

Measured Exercise Variables

Minute oxygen consumption (VO_2; ml/min), minute carbon dioxide production (VCO_2; ml/min), and minute ventilation (VE; L/min) will be measured using a breath-by-breath respiratory gas analyzer. The RER will be calculated as VCO_2/VO_2. Minute oxygen consumption will be normalized for body size by dividing the patient's weight in kg (VO_2 in ml/kg/min). Peak oxygen consumption will be that oxygen consumption at peak exercise with respiratory gas exchange ratio greater than 1.0. The oxygen consumption at anaerobic threshold will be determined by the V-slope method.[44] This is the point during exercise at which the RER increases due to the generation of carbon dioxide. The anaerobic threshold divided by predicted maximum consumption for age and gender x 100 will be calculated to assess for effort. The oxygen consumption divided by the predicted maximum x 100 will be calculated to normalize for age and gender. Watts and METS at peak exercise will be a measure of maximum workload, and exercise time will also be recorded.

[44] [Wasserman 1964]

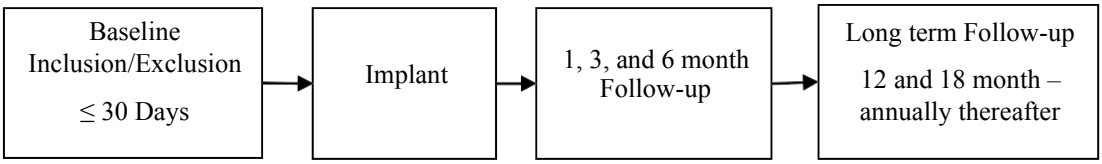
APPENDIX R: STUDY SUMMARY

TITLE	**C-Pulse® Implantable Counterpulsation Pump (ICP) US Feasibility Study** **A Heart Assist Device**
SPONSOR	**Sunshine Heart, Incorporated**
STUDY OBJECTIVES	Assess the safety and provide indications of performance of the C-Pulse® device. The study will include 20 patients enrolled at up 7 centers in the US and potentially some OUS centers. The study will be expanded to include a total of 40 patients enrolled at up to 9 centers. Patient data will be collected at baseline, 1, 3, 6, 12, 18 months and annually to 10 years.
BACKGROUND	The current need is for a heart assist device or a method that is effective enough to make its application appealing as a long-term therapy to a large number of patients and physicians to treat patients in moderate to severe heart failure who are refractory to drugs. 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 device to be small, easy to insert, disconnectable, not in the bloodstream and allows for patient ambulation. 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 ACC/AHA Stage C, NHYA Class III/IV heart failure. Sunshine Heart, Inc. has proposed C-Pulse®, a novel ambulatory, non-obligatory, non-blood contacting extra-ascending aortic counterpulsation system. The C-Pulse® is designed 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. The C-Pulse® is not an alternative to the heart, it is an augmentation device, and it does not preclude the use of other heart failure therapies such as valve surgery, heart transplantation or LVADs. It is important to point out that a counterpulsation device is aimed 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 C-Pulse® counterpulsation device is considered non-obligatory and not life-supporting.
PURPOSE	The purpose of the study is to determine whether use of the C-Pulse® used as treatment for patients in moderate to severe heart failure is associated with reasonable assurance of safety and performance, such that the C-Pulse® merits FDA approval for continuation into a pivotal study to examine the safety and efficacy of the C-Pulse® for US market approval.

DEVICE DESCRIPTION	The C-Pulse® utilizes an "extra-aortic" inflatable Cuff which is surgically implanted around the ascending aorta. The C-Pulse® ICP has been designed to have a simple, highly reliable implantable component (the Cuff) and external wearable components (the Driver and Battery Carrier) which are connected by means of a Percutaneous Interface Lead. The Driver is programmable by a physician using a Programmer via infra-red (IR) connectivity.
	 
	
	The modular design of the C-Pulse® is shown the figure above. Key features are outlined in Table 1. For the IDE study, the patient will be provided with two (2) each of the Driver and Battery Carrier. The Percutaneous Interface Lead is designed to facilitate simple surgical replacement of the external component, in the case of skin infections at the exit site or damage to the patient connector.
	Table 1: C-Pulse® System Components
	SHC implantable Cuff:
	• Simple, less invasive surgery
	• No cardiopulmonary bypass
	• 3 sizes to fit ascending aorta outside diameter 29 – 40 mm
	• Non-blood contacting
	SHC Percutaneous Interface Lead:
	• 5 mm outside diameter
	• Silicone with ECG wire re-enforcements
	• Transmits air/ECG/heart sounds
	• Patient connector (with water-tight cap)
	• Lead is exchangeable
	• Home care package including supplies for dressing changes
	SHC wearable/portable Drive Unit and Battery Carrier system:
	• Detachable, approx. 2.5 kg (total weight, split between Driver and Battery Carrier) Ergonomic design
	  • wear in a vest or carry in a bag
	  • simple patient interface – on/off button and battery indicator
	  • visual and audible alarms
	• 4 hours battery life; single battery – recharge separately or in Battery Carrier
	• 1.4m Driver cable with Isolation Module
	• Physician programmer
	  • Infra-red functionality
	  • Intuitive interface for setting counterpulsation functions
	  • Discrete "verification" button on Driver to accept Programmer changes

SYSTEM DEFINITION	**Investigational Device:**
	• C-Pulse® Cuff
	  • Small Cuff
	  • Medium Cuff
	  • Large Cuff
	• Percutaneous Interface Lead
	• External Driver and Battery Carrier
	
	Accessories:
	• Battery Charger
	• Programmer
	• Vest
	• Carry bag
	• Home Care Kit (includes Percutaneous Lead Management Kit)
	• Epicardial bipolar IS-1 pacemaker lead; Capsure Epi 35 cm, (Medtronic, Inc., Minneapolis)

PRIMARY OBJECTIVES	The primary objective of the C-Pulse feasibility study is to assess safety, while at the same time obtain performance data for evidence of efficacy to assist planning for a pivotal study. Refer to the section on Statistical Methods and Data Analysis for a detailed discussion of the definitions and methodology. The Clinical Investigation shall: 1. Assess the risks with regard to the performance of the device as defined by the serious adverse event rates, under normal conditions of use. 2. Assess the potential benefits of C-Pulse as defined by improvements in Peak VO2, hemodynamic measures, quality of life and HF symptoms.
SECONDARY OBJECTIVES	Secondary objectives are intended to provide additional information on patient response and device performance and to allow planning for the pivotal study. The secondary objectives are as follows: 1. Further assess the potential risks with regard to the performance of the device as defined by the device failure rate, adverse event rates, adverse event attribution, re-hospitalization rates, duration of support, and length of time to hospital discharge. 2. Further assess the potential benefits of C-Pulse as defined by improvements in quality of life, fatigue impact scales, hemodynamics, average distance walked in the 6 minute hall walk test, and blood tests. 3. Assess the device usage

STUDY DESIGN	The study is designed to assess the safety and potential benefit of the C- Pulse™ System before initiating a wider randomized clinical trial to demonstrate efficacy. The effect of the C- Pulse™ system in relieving heart failure symptoms in patients with ACC/AHA Stage C; NYHA Class III – ambulatory Class IV heart failure will be documented with this study. This Feasibility Study is multi-center study in up to 7 centers in the US and potentially some OUS centers. The primary study population will include 20 subjects enrolled and implanted with the C-Pulse® System. The study will be expanded to include a total of 40 patients in up to 9 centers. The period of follow-up will be 6 months to assess the safety and performance before initiating the pivotal clinical trial. Patients will be followed for up to 5 years.  Figure 1. Study Design 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. Data collection will be noted prior to implantation of the device and at one, three, and six months following implant and then annually post-implant for five years. Adverse events will be collected throughout the study until study closure and will be adjudicated by the CEC. Progress reports of the clinical outcomes will be prepared by the DSMB after enrollment of five (5) patients and twice per year thereafter, unless slow enrollment does not warrant this meeting frequency. Progression to the Pivotal study will be based on the assessment for safety of the device and indicators of performance. Baseline and follow–up data will be used to assess any significant difference in quality of life and functional variables pre and post implant and to assess the effect of counterpulsation. Following successful completion of this Feasibility Study, a pivotal study will be conducted to examine the safety and efficacy of the C-Pulse® system in patients in moderate to severe heart failure. The pivotal trial is expected to measure the same variables as the Feasibility Study.
SUBJECTS- **CENTERS-** **DURATION-**	Up to 40 eligible patients will be implanted with the C- Pulse® Up to 9 US Centers The total duration of the Feasibility Study is expected to be approximately - 120 months.

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. Patient has ACC/AHA Stage C heart failure and remains in NYHA Class III - ambulatory Class IV despite optimal medical therapy. Patients must have stable, evidence–based optimal medical therapy for heart failure as defined below: a. ACE inhibitor or ARB (Angiotensin Receptor Blocks) at least 30 days preceding implant or nitrate/hydralazine at the investigators discretion b. Beta–blocker for at least 90 days and stable for 30 days preceding implant Note: Stable is defined as no more than a 50% reduction or 100% increase in the medications listed above. Transition within a therapeutic class is allowed if the dose is equivalent 2. Patient has left ventricular ejection fraction ≤ 35% 3. Patient has had Cardiac Resynchronization Therapy (CRT) for at least 90 days prior to enrollment or is not indicated for a CRT device 4. Patient has had an implanted cardio–defibrillator (ICD) at least 30 days prior to enrollment or is not indicated for ICD implantation 5. Patient is at least 18 years of age and not older than 75 years 6. Patient six minute hall walk assessment between 100–350 meters 7. Patient understands the nature of the procedure, is willing to comply with associated follow–up evaluations, and provide written informed consent prior to the procedure
EXCLUSION CRITERIA	Candidates must be excluded from the study if any of the following are met: 1. Patient has any evidence of : a ascending aortic calcification on posterior–anterior or lateral chest x–ray at initial screening OR b. Atherosclerotic ascending aortic disease, specifically intimal thickening greater than 3mm or mobile atheroma (moderate) or mural calcification (severe) as detected by CT scan or echocardiography [45] (Echo) 2. Patient has ascending aorto-coronary artery bypass grafts, history of aortic dissection, Marfans disease or other connective tissue disorder or has had an aortic root replacement 3. Patient aorta not conforming to specified dimensional constraints defined by CT scan, most specifically mid ascending aortic outside diameter less than 29mm or greater than 40mm 4. Patient has severe mitral valve incompetence, grade 4 + 5. Patient has moderate to severe aortic valve incompetence, grade 2–4+ 6. Patient has systolic blood pressure less than 90 or greater than 140 mmHg 7. Patient has a Serum Sodium less than 130 mEq/L 8. Patient has a Estimated GFR less than 40 ml/min/1.73 m^2 9. Patient has any two of three of Bilirubin, AST, ALT greater than 3 times upper limit of normal for each institution

[45] [Davila–Roman 1999]

EXCLUSION CRITERIA **(continued)**	10. Patient has a serum Albumin less than 3.0 g/dL 11. Patient has BMI less than 18 or greater than 40 kg/m2 12. Men with Peak VO_2 of greater than 18ml/kg/min or less than 10 ml/kg/min 13. Women with Peak VO_2 of greater than 16 or less than 9 ml/kg/min 14. Patient has any active infection 15. Patient has had a myocardial infarction, stroke, transient ischemic attack, cardiac or other major surgery, in the 3 months prior to study enrollment. 16. Patient has severe COPD as evidenced by FEV1 less than or equal to 0.9 L/min 17. Patient requires a concomitant surgical procedure (i.e. CABG, Valve repair) 18. Patient is supported with a left ventricular assist device or intra–aortic balloon pump. 19. Severe right heart dysfunction with systemic venous congestion evidenced by clinical signs/symptoms such as CVP ≥ 20 mmHg , Cardiac Index < 2.0 l/min/m^2, elevated liver function tests beyond three times the upper limit of normal with the presence of ascites. 20. Patient has reversible causes of heart failure that may be remedied by conventional surgery or other intervention 21. Patient is pregnant. Note: Negative pregnancy test required in all women of child bearing potential. 22. Patient has any other condition that, in the opinion of the investigators, would disqualify the patient for inclusion in the study, limits survival to less than one year, or not permit valid consideration 23. Patient is currently enrolled or has participated in the last 30 days in another therapeutic or interventional clinical study that is likely to confound study results or affect study outcome 24. Patient has symptomatic Carotid artery disease or asymptomatic disease with a stenosis greater than 70% as determined by Carotid Doppler Ultrasound.

Data Collection Summary

Follow-up Requirements Baseline to 6 months Post Implant						
	Pre-Implant	**Implant**	**Pre-Discharge[7]**	**1 mo**	**3 mo**	**6 mo**
A. PATIENT ELIGIBILITY	X					
B. GENERAL						
Demographic Data	X					
Medical History	X					
General Physical Examination	X	X	X	X	X	X
Concurrent Medications	X	X	X	X	X	X
Pregnancy test (if applicable)	X					
C. VITAL PARAMETERS						
Weight	X		X	X	X	X
Heart rate (ECG pre-implant)	X		X	X	X	X
Blood pressure	X		X	X	X	X

Follow-up Requirements Baseline to 6 months Post Implant						
	Pre-Implant	**Implant**	**Pre-Discharge[7]**	**1 mo**	**3 mo**	**6 mo**
Respiratory rate	X		X	X	X	X
D. CARDIOPULMONARY						
CT aorta	X					X
CXR	X				X	X
ECHO	X	X[2]		X	X	X
Right heart catheterization (CVP, PAP, CI, PCWP, SVR, PVR)	X					X
Peak O2 uptake	X					X
E. QUALITY OF LIFE						
NYHA Classification	X			X	X	X
MLHF Score/ KCCQ	X			X	X	X
Fatigue Impact Scales	X		X	X	X	X
Six Minute Walk	X			X	X	X
F. HEMATOLOGY						
Hemoglobin	X		X	X	X	X
Hematocrit	X		X	X	X	X
Plasma free hemoglobin	X		X	X	X	X
Platelet count	X		X	X	X	X
White cell count	X		X	X	X	X
APTT	X		X	X	X	X
INR	X		X	X	X	X
Fibrinogen	X		X	X	X	X
G. BIOCHEMISTRY						
Serum sodium	X		X	X	X	X
Serum potassium	X		X	X	X	X
Serum creatinine/ GFR[3]	X		X	X	X	X
BUN	X		X	X	X	X
Serum albumin	X		X	X	X	X
Serum bilirubin	X		X	X	X	X
Serum ALT	X		X	X	X	X
Serum AST	X		X	X	X	X
Serum BNP	X					X
H. NEUROLOGICAL ASSESSMENT[6]						
Neurological testing (NIHSS)[4]	X		X	X	X	X
Modified Rankin [4]	X		X	X	X	X
Head CT [5]	X					
Neurological Consultation	X		X[6]			
I. IMPLANT DETAILS		X				
J. DEVICE LOG		X		X	X	X
K. DISCHARGE CHECKLIST			X			

1 Annually post-implant
2 Epi-aortic Echo at implant
3 Estimated GFR at Baseline and within one week post CT to evaluate contrast induced nephropathy.
4 Post Neurological Dysfunction AE – 30, 60 and 90 days post event
5 At Baseline only or as clinically indicated with any Neurological Dysfunction AE – Head CT should be completed only after clearance for implantation.
6Required at 5-7 days post ICU discharge or at hospital discharge whichever occurs first and at the time of any suspected Neuro Dysfunction AE
7 At Discharge – within 36 hours prior to discharge and as close to discharge as possible (see Appendix M)

Long-term Post Implant Follow-Up Requirements			
	12 month	18 month	Annually Year 2-10
A. PATIENT ELIGIBILITY			
B. GENERAL			
General Physical Examination	X	X	X
Concurrent Medications	X	X	X
Pregnancy test (if applicable)			
C. VITAL PARAMETERS			
Weight	X	X	X
Heart rate (ECG pre-implant)	X	X	X
Blood pressure	X	X	X
Respiratory rate	X	X	X
D. CARDIOPULMONARY			
ECHO	X	X	X
E. QUALITY OF LIFE			
NYHA Classification	X	X	X
MLHF Score/ KCCQ	X	X	X
Fatigue Impact Scales	X	X	X
Six Minute Walk	X	X	X
F. HEMATOLOGY			
Hemoglobin	X	X	X
Hematocrit	X	X	X
Plasma free hemoglobin	X	X	X
Platelet count	X	X	X
White cell count	X	X	X
APTT	X	X	X
INR	X	X	X
Fibrinogen	X	X	X
G. BIOCHEMISTRY			
Serum sodium	X	X	X
Serum potassium	X	X	X
Serum creatinine/ GFR[3]	X	X	X
BUN	X	X	X
Serum albumin	X	X	X
Serum bilirubin	X	X	X
Serum ALT	X	X	X
Serum AST	X	X	X
I. IMPLANT DETAILS			
J. DEVICE LOG	X	X	X
K. DISCHARGE CHECKLIST[7]			

APPENDIX S: BIBLIOGRAPHY

Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, and Messenger J for the MIRACLE Study Group. Cardiac Resynchronization in Chronic Heart Failure. N Engl J Med 2002;346:1845–1853

Ash, SR. Chronic peritoneal dialysis catheters: effects of catheter design, materials and location. Seminars in Dialysis 1990;3:39–46. 3.

Barnett MG, Fiore AC, Vaca KJ, Milligan TW, Barner HB. Tailoring aortoplasty for repair of fusiform ascending aortic aneurysms. Ann Thorac Surg 1995;59:497–501

Bauer M, Grauhan O, Hetzer R.Dislocated wrap after previous reduction aortoplasty causes erosion of the ascending aorta. Ann Thorac Surg. 2003;75:583-4

Bittner V, Weiner DH, Yusuf S, et al. "Prediction Of Mortality And Morbidity With A 6–Minute Walk Test In Patients With Left Ventricular Dysfunction". JAMA 1993; 270:1702–1707

Carel T, von Segesser L, Jenni R, et al. Dealing with dilated ascending aorta during aortic valve replacement: advantages of a conservative surgical approach. Eur J Cardiothorac Surg 1991;5:137–43

Cheung AT, Savino JS, Weiss SJ. Beat–to–beat augmentation of left ventricular function by intraaortic counterpulsation. Anesthesiology 1996;84:545–54.

Cochran RP, Starkey TD, Panos AL, et al. Ambulatory intraaortic balloon pump use as bridge to heart transplant. Ann Thorac Surg 2002;74:746–52.

Cohen M, Patel JJ, Dohad S, McBride R, Venkatesulu S, Boston BA, Chandrasekaran K. Pilot prospective evaluation of counterpulsation with different intra–aortic balloon volumes on cardiac performance in humans.Cathet Cardiovasc Diagn. 1995;36:82–7

Davies AN, Peters WS, Su T, Sullivan CE, Perkidides T, Milsom FP, White G. Extra–ascending aortic versus intra–descending aortic balloon counterpulsation – effect on coronary artery blood flow. Heart, Lung & Circulation 2004. In press

Davis R, Ribner HS, Keung E, Sonnenblick EH, LeJemtel TH. Treatment of chronic congestive heart failure with captopril, an oral inhibitor of angiotensin-converting enzyme. N Engl J Med 1979;301:117-21

Davila–Roman V, Murphy S, Nickerson N, et al. Atherosclerosis of the ascending aorta is an independent predictor of long–term neurologic events and mortality. J Am Coll Cardiol 1999;33:1308–16.

Demers P, Moffatt S, Oyer PE, Hunt SA, Reitz BA, Robbins RC. Long–term results of heart transplantation in patients older than 60 years. J Thorac Cardiovasc Surg. 2003;126:224–

Furman S, Whitman R, Stewart J et al . Proximity to aortic valve and unidirectionality as prime factors in counterpulsation effectiveness. Trans Am Soc Artif Int Organs 1971; 17:153–159

Gitter R, Cate CM, Smart K, Jett GK.Influence of ascending versus descending balloon counterpulsation on bypass graft blood flow. Ann Thorac Surg. 1998;65:365-70.

Guyatt GH, Sullivan MJ, Thompson PH, et al. The 6–Minute Walk: A New Measure Of Exercise

Jeevanandam V, Jayakar D, Anderson AS, Martin S, Piccione W Jr, Heroux AL, Wynne J, Stephenson LW, Hsu J, Freed PS, Kantrowitz A. Circulatory assistance with a permanent implantable IABP: initial human experience. Circulation 2002;24(12 Suppl 1):I183–8

Kofidis T, Fischer S, Leyh R, Mair H, Deckert M, Haberl R, Haverich A, Reichart B. Clinical relevance of intracranial high intensity transient signals in patients following prosthetic aortic valve replacement. Eur J Cardiothorac Surg 2002 Jan;21(1):22–6

Laas J, Kseibi S, Perthel M, Klingbeil A, El–Ayoubi L, Alken A Impact of high intensity transient signals on the choice of mechanical aortic valve substitutes..Eur J Cardiothorac Surg 2003 Jan;23(1):93–6

Legget ME, Peters WS, Milsom FP, Clark JS, West TM, French RL, Merry AF. Extra–aortic balloon counterpulsation – an intra–operative feasibility study. Circulation 2005;112[suppl I]:I–26−I–31

Leuprecht A, Perktold K, Kozerke S, Boesiger P. Combined CFD and MRI study of blood flow in a human ascending aorta model. Biorheology 2002;39:425–429

Misfeld M, Scharfschwerdt M, Sievers HH.A novel, form-stable, anatomically curved vascular prosthesis for replacement of the thoracic aorta. Ann Thorac Surg. 2004;78:1060-3

Nabavi DG, Stockmann J, Schmid C, Schneider M, Hammel D, Scheld HH, Ringelstein EB.Doppler microembolic load predicts risk of thromboembolic complications in Novacor patients. J Thorac Cardiovasc Surg 2003;126:160–7

Nadareishvili ZG, Beletsky V, Black SE, Fremes SE, Freedman M, Kurzman D, Leach L, Norris JW. Is cerebral microembolism in mechanical prosthetic heart valves clinically relevant? J Neuroimaging 2002 Oct;12(4):310–5

Neaton JD, Normand SL, Gelijns A, Starling RC, Mann DL, Konstam MA.Designs for mechanical circulatory support device studies. J Card Fail. 2007;13:63-74.

Ootaki Y, Kamohara K, Akiyama M, Zahr F, Kopcak MW, Dessoffy R, Fukamachi K. Phasic coronary blood flow pattern during a continuous flow left ventricular assist support. EJCS 2005;28:711—716

Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344:1651-8

Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. J Card Fail. 2001 Jun;7(2):176–82.

Peters WS, Milsom FP. Relationship between ascending aortic anatomy and blood flow. Cardiac Society Australia/New Zealand, Canberra, Aug 2006: Heart, Lung & Circulation

Pollock ML, Franklin BA, Balady GJ, et al. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. Circulation. 2000;101:828-33.

Reichert CL, Koolen JJ, Visser CA. Transesophageal echocardiographic evaluation of left ventricular function during intraaortic balloon pump counterpulsation. J Am Soc Echocardiogr 1993;6:490–5.

Riley M, McParland J, Stanford CF, Nicholls DP. "Oxygen Consumption During Corridor Walk Testing In Chronic Cardiac Failure". Eur Heart J. 1992; 13:789–793.

Rose EA, Gelijns AC, Moskowitz AJ, et al. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long–term mechanical left ventricular assistance for end–stage heart failure. N Engl J Med 2001; 345: 1435–43.

Rubiscsek F, Thubrikar MJ. Conservative operation in the management of annular dilatation and ascending aortc aneurysm. Ann Thorac Surg 1994;57:1672–4

Takasu J, Takanashi K, Naito S, et al. Evaluation of morphological changes of the atherosclerotic aorta by enhanced computed tomography. Atherosclerosis. Dec 1992;97(2–3):107–121.

Trainini J, Cabrera Fischer EI, Barisani J, et al. Dynamic aortomyoplasty in treating end–stage heart failure. J Heart Lung Transplant 2002; 21:1068–73.

Wasserman K, MvIlroy MB. "Detecting The Threshold Of Anaerobic Metabolism In Cardiac Patients During Exercise". Am J Cardiol. 1964; 14:844–852.

Wilhelm CR, Ristich J, Knepper LE, Holubkov R, Wisniewski SR, Kormos RL, Wagner WR.Measurement of hemostatic indexes in conjunction with transcranial doppler sonography in patients with ventricular assist devices. Stroke. 1999 Dec;30(12):2554–61

APPENDIX T: CLINICAL STUDY AGREEMENT TEMPLATE

Not related to this change – not resubmitted

APPENDIX U: INFECTION CONTROL GUIDELINES

Overview

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-select an exit site for the Percutaneous Interface Lead that will facilitate the patient selection for clothing, daily routine, etc.

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

Antibiotic prophylaxis recommendations:

Administer prophylactic antisepsis coverage. Recommended prophylaxis:

- Nasal Bactroban application day prior to surgery
- Vancomycin 15mg/kg IV one hour pre–op given over 30 minutes and with minimum 5 minute 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 Q12–24 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 PO 2hrs pre–op then daily for 2 days – stop if liver function tests become deranged 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.
- Recommend 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 until necessary. Massage with antibiotic prior to implantation.
- 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 within 48 hours, depending on 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 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 to treat percutaneous line gently and to avoid undue 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 unchanged as long as it remains dry.be changed as frequently as required post–operatively whilst ensuring that the percutaneous lead is immobilized.– this may be up to 2–3 times per day in the first 1–2 weeks if it is oozing. If wounds are healing well and there is no discharge, then go to daily or second-daily dry dressings.
- 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 chlorohexadine 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 or patient death 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. 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.

APPENDIX V: INVESTIGATIONAL PLAN REVISIONS

The protocol amendments are listed below along with the justifications for change and the associated dates of the protocol revisions. Version 1 (PRO 02291-A) was sent to IRBs for study preparation.

Version 1	**Justification for Change**	**Page(s)**
Initial Version– Date 7 June 2007	Submission for IDE	All

Version 2 (PRO 02291-B) was created in response to FDA questions and incorporates the changes below. It was not delivered to IRBs for preparation of study documents.

Version 1	**Version 2**	**Justification for Change**	**Page(s)**
Randomized study design, 24 pts., blinded study.	Non-randomized study design, 20 pts. Removed all references to old design and corrected study design.	To address FDA concern.	7, 15-16, 21-27, 54-55, 108-9
Previous study population and eligibility criteria.	Updated eligibility criteria and associated references.	To address FDA concern.	15, 17-19
NA	Added additional screening process.	To address FDA concern.	20-21
NA	Clarification and addition of required testing with associated data collection intervals.	To address FDA concern.	23-27,29, 93
NA	Clarification and addition of infection control guidelines.	To address FDA concern.	31-32, 119-121
NA	Adverse events – clarified use of the *Intermacs* registry definitions. Rearranged AE section for clarification.	To address FDA concern.	34-41
Previous study design.	Replaced Stat Section with updated analysis.	To address FDA concern.	42-44
HF Composite	Removed the HF Composite due to removing randomization and to us individual assessment analysis in the feasibility.	To address FDA concern.	54
DSMB and CEC paragraphs.	Relocated these paragraphs into the study safety section.	Clarification.	59-60
Device usage statements	Clarified the usage to be greater than 80% of the time.	To address FDA concern.	13,31
NA	Added Core Lab information sheet.	To address FDA concern.	94
Study Summary	Updated with all relevant main protocol changes.	Clarification.	108-114
NA	Typos corrected.	Administrative	Throughout.

Version 3 (PRO 02291-C) was created in response to FDA questions and incorporates the changes below.

Version 2	**Version 3**	**Justification for Change**	**Page(s)**
Device usage statements	Deactivation time for the device limited to 15 minute intervals with a maximum acceptable 30 minute interval.	To address FDA concern.	13, 15, 32, 84
Previous study population and eligibility criteria.	Updated eligibility criteria with expanded definition of right heart failure. Modified Peak VO_2 to be better suited for inclusion of women.	To address FDA concern.	18
NA	Expanded the neurological assessment data collection.	To address FDA concern.	26-27, 85
NA	Added Fatigue Impact Scales to the data collection and to case report forms.	To address FDA concern.	23, 27, 45, 83, 85, 86, Appendix K
NA	Adverse events – clarified unanticipated device effect (UADE) definition.	Clarification	41
NA	Typos and grammar correction. Updated names of CRF titles.	Administrative	Throughout
NA	Changes listed above incorporated into Study Summary.	Administrative	Appendix R

Version 4 (PRO 02291-D) was created in response to FDA questions and incorporates the changes below.

Version 3	**Version 4**	**Justification for Change**	**Page(s)**
Investigator Signature Page	Deleted this page. All Principle and Sub Investigators sign the Clinical Study Agreement that includes language requiring them to follow the protocol and GCP, etc.	Clarification	Formerly pg. 6
Eligibility Criteria	Changed Albumin Exclusion level from 3.5 to 3.0 g/dL and changed upper BMI limit from 38 to 40. Clarified the clinical study exclusion to include studies that would confound the results of the C-Pulse study.	Investigator input from our last Investigator Meeting – the feedback indicated that the patient population for Class III would include patients with lower Albumin and larger BMI.	18
Investigational Center Information Section	Added that sites will send in lab normals for our clinical study files to help ensure all labs are collected within comparable normal limits.	Clarification	22

Version 3	Version 4	Justification for Change	Page(s)
Data Collection Summary Section	Expanded CT Scan language to include suggestions for minimizing renal insult due to the use of contrast. Included requirement to perform Head CT only after the patient is determined eligible for implantation.	To address FDA concern.	23
Data Collection Overview Section	Expanded Neurological Assessment to include the Modified Rankin. Refine the section for clarity of neuro assessment requirements.	To address FDA concern.	23
Data Collection Overview Section	Added Six Minute Hall Walk at 1 month timeframe to correspond with the NYHA and QoL assessments.	Additional data for 1 month interval.	23
Hospital Discharge Section	Additional language added for clarification of data collection if readmitted and for discharge.	Clarification	36
AE Section	Added definition of serious. Removed reference to children under 6 months from Neuro AE. Added Modified Rankin for data collection following Neuro AE.	Clarification	37
Explant Handling Section	Added additional instruction.	Clarification	44
Statistical Methods Section	Changed Peak VO_2 and Six Minute Hall Walk values to 1.2 ml/kg/min and 50 m, respectively.	To address FDA concern.	46
Sample Informed Consent	Changes listed above incorporated into the sample informed consent as appropriate.	Administrative	82
Appendices	Added the KCCQ, Modified Rankin and ACC/AHA Stages.	Administrative	100, 105, 110
Appendix C	Updated Investigator for UAB .	Administrative	74
Appendix K	Refined Sample Case Report Forms to incorporated changes listed above.	Administrative	99
Appendix R	Changes listed above incorporated into Study Summary.	Administrative	114
NA	Typos and grammar correction.	Administrative	Throughout

Version 5 (PRO 02291-E) was created in response to FDA questions and incorporates the changes below. This was sent to sites for IRB submission along with the Conditional FDA approval letter dated 10 Sept 2008.

Version 4	**Version 5**	**Justification for Change**	**Page(s)**
NA	Addition of data requirement to monitor contrast induced nephropathy.	FDA Request #1 - Conditional Letter from 10 Sept 2008	24, 27, 41, Appendix H – Informed Consent
Indications for Use	Removed sentence stating "The C–Pulse® System is a therapy indicated for patients who can tolerate intermittent use."	FDA Request #2 - Conditional Letter from 10 Sept 2008	12
Appendix K	Modified the Enrollment Case Report Form to include the alternative therapy a patient could receive if C-Pulse wasn't available.	FDA Request #3 – Conditional Letter from 10 Sept 2008	Appendix K – Enrollment Form
Study Size and Duration section	All subjects must be consented prior to performing any study related procedures. A subject 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 the 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 timeframe of 30 days prior to implant.	FDA Request #4a – Conditional Letter from 10 Sept 2008	6, 21
Study Size and Duration section and Appendix K	Study Exit instruction included as follows: Study Exit of these patients must be documented on the study exit form. The study exit form contains information on reason for study exit. Study Exit form modified to include details.	FDA Request #4b – Conditional Letter from 10 Sept 2008	21, 22, 30, 43 Appendix K – study exit form
Design section and Screening and Patient Informed section	Any patient whom undergoes anesthesia for the purpose of C-Pulse implantation but does not receive the device will be monitored for adverse events as defined by the protocol for 30 days or discharge whichever occurs first.	FDA Request #4c – Conditional Letter from 10 Sept 2008	14, 21
Screening and Patient Informed Consent section	A Screening Log is located in the site Regulatory Binder and must be completed for all patients screened for eligibility.	FDA Request #5 – Conditional Letter from 10 Sept 2008	21

Version 4	Version 5	Justification for Change	Page(s)
NA	Additional data collection added to assess if a patient is required to use the C-Pulse due to symptoms during the time that they could be disconnected if symptoms were not present.	FDA Request #6 – Conditional Letter from 10 Sept 2008	Appendix K – follow-up form
Data Collection Overview section and Informed Consent (Appendix	18 month follow-up visit added.	FDA Request #7 – Conditional Letter from 10 Sept 2008	14,22,24-30, 46,88,96,117,121
Secondary Objectives	Added analysis of Concomitant Medications from baseline to 6 months.	FDA Request #8 – Conditional Letter from 10 Sept 2008	46
Exclusion Criteria	Changed mild to moderate for aortic valve incompetence – Exclusion Criteria #5.	FDA Request #9 – Conditional Letter from 10 Sept 2008	18, 119, Appendix K – Enrollment Form
Follow-up Windows	6 month window extended to ±30 days; 12, 18 and annual follow-ups extended to ± 60 days.	FDA Request #10 – Conditional Letter from 10 Sept 2008	22
Neurologic Assessment	Changed the NIHSS limit: When a change of 2 or more is noted, a neuro assessment is required.	FDA Request #11 – Conditional Letter from 10 Sept 2008	27
Major Bleeding Adverse Event Definition	Reduce the transfusion limit from greater than 2 units transfusion to any transfusion triggers an event.	FDA Request #12 – Conditional Letter from 10 Sept 2008	37, Appendix K – Adverse Event form
Efficacy Performance Requirement	Defined an analysis including responders, non responders and indeterminants.	FDA Request #13 – Conditional Letter from 10 Sept 2008	45
NA	Typos and grammar correction.	Administrative	Throughout

Version 6 (PRO 02291-F) was created in response to FDA questions and incorporates the changes below. This version will be sent to sites when Final FDA approval is received.

Version 5	Version 6	Justification for Change	Page(s)
Efficacy Performance Requirement	Further revised the analysis including responders, non responders and indeterminants based on FDA feedback.	FDA Request #13 – Conditional Letter from 10 Sept 2008	45
Adverse Event Definitions	Removed reference to VAD, LVAD and blood contacting surfaces where appropriate as the C-Pulse does not have blood contacting surfaces and is more commonly a MCSD.	Feedback from the CEC members and the need to provide clarification.	38-41

Version 7 (PRO 02291-G) was created to add a seventh US site. In addition personnel and contact information was updates. During this review several clarification and typographical items were noted and corrected. This version will be sent to sites when Final FDA approval is received.

Version 6	**Version 7**	**Justification for Change**	**Page(s)**
6 US centers	Up to 7 centers in the United States (US) and potentially some Outside the United States (OUS) centers.	Reference minutes from FDA Conference Call Requesting additional site and potential use of OUS data – Call 12/09/09	6, 14, 19, 73, 82, 114, 134
Study duration\18 – 24 months	24– 30 months	Slow enrollment.	6, 15, 117
Sponsor Address CEO Name and Contact Information Sponsor Clinical Contact Name and Contact Information CRO Contact Information	Current Sponsor Address CEO Name and Contact Information Sponsor Clinical Contact Name and Contact Information CRO Contact Information	Updated based on changes which have occurred since last IP update	5, 60
--	Table 3 – Added SVR under Right heart catheterization Removed Driver NYHA Class Assessment – made heading match text	Clarifications and Typographical Errors	23, 29, 36
Appendix C – Participating Institutions	Appendix C Participating Institutions	Updated to Current PIs and contact information	73
Appendix H – Sample Informed Consent	Appendix H – Sample Informed Consent	Updated to include current information in the IP	81
Appendix I – Required Tests	Appendix I – Required Tests	Updated to include current information in IP	94
Appendix P – Six Minute Hall Walk	Appendix P – Six Minute Hall Walk	Updated to include current information in IP	110
Appendix R: Study Summary	Appendix R: Study Summary	Updated to include current information in IP	114

Version 8 (PRO 02291-H) was created as an expansion protocol to add twenty (20) additional patients and two (2) additional sites. In addition, contact information was updated and a 1 – 5 year follow-up was revised to include an ECHO. During this review several clarification and typographical items were noted and corrected. This version will be sent to sites when Final FDA approval is received.

Version 7	**Version 8**	**Justification for Change**	**Page(s)**
7 US centers	Up to 9 centers in the United States (US) and potentially some Outside the United States (OUS) centers.	Expansion protocol	6, 15, 20, 77, 87, 121, 124
20 patients implanted and 30 patients consented	40 patients implanted and 60 patients consented	Expansion protocol	6, 15, 87, 121, 124
24 – 30 months duration	36 months duration	Expansion protocol and slow enrollment	6, 16, 124
Sponsor Address CEO Name and Contact Information Sponsor Clinical Contact Information	Current Sponsor Address and contact information CEO Address and Contact Information	Updated based on changes which have occurred since last IP update	5, 63
No ECHO after 6 mth follow-up	ECHO added to 12, 18 months and 2, 3, 4, and 5 year follow-u ps	Updated to include Corelab ECHOs at all follow-ups	26, 28, 101, 128
Table 1 "3 sizes to fit ascending aorta outside diameter 28–40 millimeter (mm)"	"3 sizes to fit ascending aorta outside diameter 29–40 millimeter (mm)"	Typographical Error, changed to align with Inclusion/Exclusion Criteria	12, 123
Figure 1A Study Design	Removed Number of Implants	Clarification for the purpose of the Figure to describe the process	15, 124
Hospital Discharge Criteria	"ventricular rates <10bpm" changed to read "ventricular rates <120bpm"	Typographical Correction	109
Appendix C – Participating Institutions	Appendix C Participating Institutions	Updated to Current PIs and contact information	77
Appendix D – IRB List	Appendix D - IRB List	Updated to Current IRB List	78

Version 9 (PRO 02291-I) was created to extend the follow up period from 5 to 10 years to accommodate follow up beyond 5 years. Appendix U of Version 9 was updated to reflect current infection control guidelines.

Version 8	**Version 9**	**Justification for Change**	**Page(s)**
--	Adjust formatting, correct spelling and other grammatical edits	Adjust pagination and correct spelling and other minor edits.	8 -9, 11, 13 - 15, 17 - 19, 21, 23, 25 – 27, 30 – 33, 35 - 45, 48, 53 – 60, 62 -64, 66, 70 -71, 74-76 Appendix D – Page 80 Appendix E – Page 81 - 83 Appendix H – Page 87 - 88, 90 - 92, 96, 99 Appendix N – Page 114, 116 Appendix Q – Page 122 - 123 Appendix R – Page 124 - 125, 128 Appendix V – Page 150
Trial Contact Information	Address and contact information	Update the Manufacturer address and study contact information	7, 65
5 year follow up	10 year follow up	Accommodate follow up of patients with full or partial C-Pulse system beyond 5 years	8, 17 -18, 25 -26, 28 - 29 Appendix I – Page 103 - 104, Appendix R – Page 123, 126, 130
Appendix H	10 year follow up Additional surveillance imaging for suspected infection	Per guidance from Infection Advisory Committee	Appendix H – Page 88, 94, 96
Appendix U	Appendix U with revised infection control guidelines	Update infection control guidelines to align with current practice	Appendix U – Page 136 - 144