Protocol Title	**CHAMPION-PAS**: **C**ardioMEMS **H**eart Sensor **A**llows **M**onitoring of **P**ressure to **I**mprove **O**utcomes in **N**YHA Class III heart failure patients – **P**ost **A**pproval **S**tudy
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Investigational Device	CHAMPION HF Monitoring System
Principal Investigators	Philip Adamson, MD, FACC Oklahoma Heart Hospital Oklahoma City, OK
	William T. Abraham, MD, FACP, FACC The Ohio State University Medical Center Columbus, OH
Sponsor Contacts	Susan Neville Vice President, Clinical Operations CardioMEMS, Inc. 387 Technology Circle NW, Suite 500 Atlanta, GA 30313 Phone: (678) 651-2326 Fax: (404) 393-0737
Investigational Sites	A listing of participating investigational sites is on file at CardioMEMS, Inc.

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Protocol Version: 1.1

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INVESTIGATOR ACKNOWLEDGEMENT

I have read the attached protocol and agree that it contains all the necessary details for performing the study. I agree to conduct the study according to the protocol.

I will provide copies of the protocol, the pre-clinical, and the clinical information on the Investigational Device (e.g., Investigator Brochure, Instructions for Use) that was furnished to me by the Sponsor to all members of the study team responsible to me. I will discuss this material with them to assure that they are fully informed regarding the Investigational Device and the conduct of the study.

I will not consent or enroll subjects until IRB approval is obtained. Once the protocol has been approved by the IRB/IEC, I will not modify this protocol without obtaining the prior approval of the Sponsor and of the IRB/IEC. I will submit all protocol modifications and/or any informed consent modifications to the Sponsor and the IRB /IEC, and approval will be obtained before any modifications are implemented. I will also submit all Serious Adverse Events and Protocol Violations to the IRB/IEC per their requirements.

_____ _____

Principal Investigator's Signature Date

LIST OF ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Event
CEC	Clinical Event Classification
CRF	Case Report Form
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HF	Heart Failure
HFR	Heart Failure Related
ICF	Informed Consent Form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IFU	Information For Use
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NYHA	New York Heart Association
O_2	Oxygen
PP	Protocol Population
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PTFE	Polytetrafluoroethylene
RHC	Right Heart Catheterization
RF	Radio Frequency
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
WHO	World Health Organization

1 PROTOCOL SYNOPSIS

Sponsor:	CardioMEMS® Inc., Atlanta, GA
Protocol Title:	**CHAMPION-PAS**: **C**ardioMEMS **H**eart Sensor **A**llows **M**onitoring of **P**ressure to **I**mprove **O**utcomes in **N**YHA Class III heart failure patients – **P**ost **A**pproval **S**tudy
Protocol Number:	CM-10-02
Device:	**Champion HF Monitoring System** A system consisting of a pressure sensor implanted into the pulmonary artery and an external interrogation device that can communicate wirelessly with the implanted sensor and transmit episodic real-time pulmonary artery pressure waveforms and measurements to a secure website for Investigator review and patient management.
Objective:	The objective of the study is to evaluate the safety and efficacy of the Champion HF Monitoring System in subjects suffering from heart failure.
Study Population:	Male and female subjects, at least 18 years of age, diagnosed with New York Heart Association (NYHA) Class III HF.
Study Design:	This is a prospective, multi-center, open-label trial conducted in the United States (US). All subjects who sign the informed consent form and satisfy the inclusion/exclusion criteria at the Baseline Visit will be enrolled into the CHAMPION-PAS trial and will be scheduled for follow-up visits every 6 months for 2 years. Subjects deemed ineligible for the study will be documented as screen failures. Following the Baseline Visit, all eligible subjects will return for the Implant visit where the Champion Sensor will be implanted. Following the Champion Sensor implant, at the investigator's discretion, subjects may be discharged once stable or hospitalized overnight for observation and evaluation. After hospital discharge, subjects will take their HF pressure measurements on a daily basis. These measurements will be automatically transmitted to the secure Champion HF Patient Database.
Timeline:	Study visits will be scheduled at Month 1, Month 6, and every 6 months thereafter for 2 years or until study termination.
Number of Subjects:	A sample size of 600 patients will be required to provide adequate power for the safety analysis. Given a 6 month attrition rate of 9.5% in the CHAMPION trial, or a two year attrition rate of 38%, 967 subjects will be enrolled. Enrollment will be limited to 15% of the

	total study population at any one site.
Number of Sites:	This is a prospective, multi-center, open-label clinical trial to be conducted at between 45 and 200 sites.
Safety Measures:	Safety will be assessed throughout the study by the frequency of Adverse Events (AEs), Adverse Device Events (ADEs), Serious Adverse Events (SAEs), Serious Adverse Device Events (SADEs), Unanticipated Adverse Device Events (UADEs), device / system-related complication rate, pressure sensor failure rate and subject survival rate. The Clinical Events Classification (CEC) Committee will evaluate all SAEs to determine whether or not the SAE is device / system-related complication or pressure sensor failure.
Efficacy Measures:	Information regarding HFR hospitalizations will be collected throughout the study and will be adjudicated by the CEC. The primary efficacy endpoint is HFR hospitalizations at 1 year. The secondary efficacy endpoint is HFR hospitalizations at 2 years.
Statistical Considerations:	**Sample Size Determination** For the freedom from device / system-related complication rate, using an exact test for one-sample binomial proportions with a two-sided alpha of 0.05, a sample size of 600 subjects will provide greater than 90% power to detect a difference as small as 6% from the null proportion rate of 80%. For the freedom from pressure sensor failure rate, using the exact test for one-sample binomial proportions with a two-sided alpha of 0.05, a sample size of 600 subjects will provide greater than 90% power to detect a difference as small as 4% from the null proportion rate of 90%. For the primary efficacy endpoint of HFR hospitalizations at 1 year, 538 patients will provide 90% power to show a difference in rates as small as 0.09 between treatment and historical control using a one-sided, one-sample Poisson test with an alpha of 0.05. Given a 6 month attrition rate of 9.5% in the CHAMPION trial, or a two year attrition rate of 38%, 967 subjects will be enrolled. **Safety** The primary safety hypotheses are that the freedom from device / system-related complication rate will be at least 80% at 24 months and that the freedom from pressure sensor failure rate will be at least 90% at 24 months. Adverse Events (AEs), Adverse Device Events (ADEs), Serious Adverse Events (SAEs), Serious Adverse Device Events (SADEs) Unanticipated Adverse Device Events (UADEs), and device / system-related complications will be summarized by system organ class using absolute and relative frequencies. The laboratory results, physical examination, and medication data

	will be tabulated across study period assessments. All safety analyses will be performed on the safety population. **Efficacy** The primary efficacy evaluation will be HFR hospitalizations collected throughout the study and adjudicated by the CEC. The primary efficacy evaluation will compare the annualized HFR hospitalization rate at 1 year compared to the patients' historical control HFR hospitalization rate in the year prior to enrollment in CHAMPION PAS. Secondary efficacy analysis will compare the annualized HFR hospitalization rate at 2 years compared to the patients' historical control HFR hospitalization rate in the year prior to enrollment in CHAMPION PAS. The efficacy population consists of all subjects who received a sensor implant regardless of study completion status.
Version:	1.1
Date:	1 August 2011

2 BACKGROUND AND RATIONALE

2.1 INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by a complex therapeutic regimen, frequent hospitalization, poor quality of life, multiple comorbidities, and high mortality. Coronary artery disease, hypertension, and dilated cardiomyopathy are the most common causes of HF, although other cardiovascular diseases such as valvular heart disease, can contribute to the disease. In fact, nearly any form of heart disease may ultimately lead to HF. The resulting cardiac dysfunction impairs the ability of the ventricle to fill or eject blood that leads to neurohormonal and circulatory abnormalities.

Affected individuals have a variety of symptoms such as dyspnea, fatigue, limited exercise tolerance, fluid retention, pulmonary congestion and peripheral edema. All patients suffer impairment in functional capacity and quality of life. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema and report few symptoms of dyspnea or fatigue. In addition, since not all patients have volume overload at the time of initial or subsequent evaluation, the term "heart failure" is now preferred over the older term "congestive heart failure" (Hunt, et al., 2009).

The incidence of HF is on the rise, affecting more than 5 million people in the US alone. HF is a major public health problem with severe effects on the morbidity and mortality of patients. It is one of the most common reasons for hospitalization for people over 70 years of age. Despite current guideline-recommended therapies, rates of heart failure hospitalization have improved little over the past three decades. Between 1996 and 2006, hospital discharges for heart failure rose from 877,000 to 1,106,000, along with an increasing prevalence of heart failure. Among

Medicare beneficiaries, 27% of heart failure patients discharged are re-hospitalized within 30 days.

Patients who deteriorate to the point of requiring hospitalization have a worsening prognosis. Setoguchi demonstrated that regardless of age or underlying chronic kidney disease, the number of hospitalizations for worsening heart failure was inversely correlated with median survival (Setoguchi S. N., 2009). Eighty percent of males and 70% of females under age 65 diagnosed with heart failure are expected to die within 8 years. One in five HF patients die within 1 year of diagnosis and only 15% survive more than 10 years (American Heart Association Heart and Stroke Statistics, 2010).

More than half of the annual direct cost of heart failure in the U.S. is attributable to hospitalization costs. The estimated average cost of the final two years of life for advanced heart failure patients exceeds $156,000, with more than 75% of this attributed to hospitalizations for worsening heart failure during the last six months of life. The disease is also costly, due in large part to the frequency of acute heart failure episodes, which require emergency treatment and hospitalization. The estimated direct and indirect cost of heart failure in the US for 2010 is expected to be $39.2 billion (American Heart Association Heart and Stroke Statistics, 2010). Improvements in out-patient management of patients with chronic heart failure are needed to address the growing burden of decompensation requiring hospitalization.

Although HF is progressive, current therapy may provide short term clinical stability; improve myocardial dysfunction and remodeling, which may prolong survival in patients with mild to moderate LV dysfunction. Therapy with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, and cardiac resynchronization therapy (CRT) can lead to slowing or partial reversal of remodeling (HFSA, et al., 2010).

The treatment goals of HF include reduction of the heart's workload, control of excess salt intake and water retention, and improvement of heart function. Pharmacological therapy is the cornerstone of the treatment of HF patients. Diuretics are used to relieve both pulmonary congestion and peripheral edema. ACE inhibitors, ARBs, and beta blockers have been proven effective in prolonging life and reducing morbidity in large, randomized trials. Thus, almost all patients are taking a complex medication regimen of up to 10-12 different medications, which is often challenging to the physician and the patient. The long-term strategy is to establish a regimen that offers the subject the greatest chance of survival with an enhanced quality of life.

2.2 RATIONALE

Given the complex and changing picture of HF and the accumulation of evidence-based HF therapy, it is not possible for a clinician to rely solely on personal experience and observation to guide therapeutic decisions. After establishing neurohormonal and device therapies according to published guidelines, treatment strategies for patients with chronic heart failure rely on accurate clinical assessment of intravascular volume by a physical examination and diagnostic assessment. It is well established that significant changes in volume or ventricular performance often cause cardiac decompensation, leading to severe symptoms, and many times to hospitalization. Strategies to prevent these events include frequent physical examinations and close monitoring of the patient's clinical status, either through telephone contacts or recording of daily weights, in order to optimize volume control by adjustment of HF medications (Adamson, et al., 2003). However, these strategies are frequently unsuccessful in preventing the cost and morbidity of repeated hospitalizations (Chaudhry, et al., 2010). Published guidelines have

recommended titrating medications to "optimal" doses based on the results of randomized clinical trials but these optimal doses are rarely achieved in clinical practice. Further, titrating to a published dose does not permit tailoring the optimal dose for an individual patient. Finally, many patients cannot report symptoms or record weights in a reliable manner. These limitations have prompted intensive research into other treatment strategies that could provide accurate and reliable patient assessments of critical hemodynamic parameters.

Ambulatory pressure monitoring from implanted devices demonstrates that patients at high risk for heart failure decompensation leading to hospitalization are consistently characterized by high filling pressures coupled with small persistent increases in pressures over time. Many times the high filling pressures are not evidenced by physical examination alone. This supports the concept that cardiac filling pressures and their change over time are important determinants of heart failure outcomes, especially when focusing on hospitalization for decompensation. Therefore, a growing body of data acquired from several hemodynamic monitoring systems supports the hypothesis that clinical management of patients with chronic heart failure based on frequent filling pressure assessment may be superior to traditional methods.

Right heart catheterization (RHC) is a direct and very effective means for measuring intracardiac pressures to gain insight into the patient's hemodynamic status. A catheter is inserted through a large vein in the neck or groin and advanced into the pulmonary artery. These pressures are used to carefully monitor a patient's condition and provide information to titrate medications for appropriate volume control. Additionally, invasive hemodynamic information may detect subclinical deteriorations in patient clinical status that might prompt early treatment. However, RHC is not without risk. Bruising and/or bleeding at the insertion site, cardiac arrhythmias, trauma to the vein, and lung puncture if the neck or chest veins are used, and, rarely, death are the main risks associated with the procedure. Finally, it is a one-time measurement and is therefore not useful for long term measurements in the outpatient setting.

The Champion HF Monitoring System provided a method for measuring pulmonary artery pressure using a wireless pressure sensor implanted into the pulmonary artery, an external interrogation device, and a patient database. Previous studies support the theory that changes in intra-cardiac pressure may be indicative of disease fluctuation or progression and could be used to guide earlier intervention in HF patients. The goal of this trial was to determine if the Champion HF Monitoring System when combined with a comprehensive, protocol driven system for titration and optimization of drugs, could reduce HF related (HFR) hospitalizations in patients with heart failure.

Through the use of the Champion HF Monitoring System, the CHAMPION trial demonstrated a 28% reduction in heart failure hospitalizations for treatment patients at 6 months and a 37% reduction in heart failure hospitalizations over study duration. Once inserted, the Champion HF Monitoring System can provide non-invasive diagnostic information as often as the physician desires, by placing an antenna over the patient's chest, back, or side. This procedure can be easily performed in the physician's office or clinic. Patients can also perform pressure measurements themselves at home. The home pressure measurements are then transmitted to a secure website via modem. The physician can access the secure website, viewing the home measurements therefore allowing the physician to manage the patient remotely. In addition, the

Sensor can be used when the subject is hospitalized to reduce the need for invasive Swan-Ganz monitoring or RHC.

2.3 DEVICE: CHAMPION HF MONITORING SYSTEM

The Champion™ HF Monitoring System (System) provides Pulmonary Artery (PA) hemodynamic data using a wireless Sensor. PA hemodynamic monitoring is used in the management of heart failure (HF). Changes in PA pressure can be used along with heart failure signs and symptoms to adjust medications. The system utilizes radiofrequency (RF) energy to power the Sensor and to measure PA pressure. The system consists of 3 components:

1. Wireless Implantable Hemodynamic Sensor/Monitor (Sensor) which is implanted into the distal PA - Model # PA-6030
2. External Patient Measurement System (Patient Measurement System)
    - Home use standard telephone line - Model # i2-6020 and i2-6020-E
    - Home use GSM cell mobile - Model # i2-6020-G and i2-6020-EG
    - Hospital use - Model # i2-6025
3. Patient Data Management System (Patient Database) – Version # 1.3

The system provides the physician with the patient's PA pressure waveform including systolic, diastolic, and mean pressures as well as heart rate. The sensor is permanently implanted into the distal PA using transcatheter techniques in the catheterization laboratory where it is calibrated to the mean PA pressure using a Swan-Ganz catheter. Daily PA hemodynamic measurements are taken by the patient in a supine position at home. The patient measurement system consists of a padded antenna and electronics unit that guides the patient through the short reading process. The data can be recorded from the home, hospital, physician's office, or clinic. The hemodynamic data, including a detailed 18 second continuous waveform, is transmitted to a secure website that serves as the patient database so that PA monitoring is available to the physician or nurse at any time via the internet.

2.4 CLINICAL STUDIES OF THE HF MONITORING SYSTEM

CardioMEMS has been using the wireless sensing technology found in the CHAMPION HF Monitoring System for approximately 7 years to measure pressure inside the human body using radio frequency energy with its first use taking place in subjects undergoing endovascular repair of an abdominal aortic aneurysm in June 2004.

CardioMEMS is currently performing clinical studies of the sensor in the heart failure application in Chile, Germany, Brazil, and the United States. There are 604 subjects who have been implanted with the device, with the first implant performed on 02 FEB 2006. Subjects continue to be evaluated for safety.

<u>CHAMPION Study Results</u>

<u>Safety</u>

- At 6 months follow-up as well as for the full study duration, the absence of device or system related complications among the treatment and control groups was significant

($p<0.0001$), indicating device usage during the study was very safe and continued after the primary endpoint time interval of 6 months.

- At 6 months follow-up as well as for the full study duration, there were no sensor failures ($p<0.0001$).

- The treatment group rate of HFR hospitalizations was significantly reduced in comparison to the control group (0.31 vs. 0.44, $p<0.0001$).

- For the full study duration (mean follow-up 15 months), the rate of HFR hospitalizations for the treatment group was significantly lower than the rate for the control group (0.44 vs. 0.72, $p<0.0001$) demonstrating continued efficacy after the primary endpoint time interval

- Over the first 6 months, there were 336 serious adverse events in 121 (44.8%) patients in the treatment group vs. 385 serious adverse events in 155 (55.4%) patients in the control group. SAEs were hospitalizations or deaths due to HF or other common comorbidities seen in this population. After 6 months, there were 345 Serious Adverse Events (SAE) in the treatment group, compared to 423 events in the control group. Over the entire study duration, the cumulative totals were 681 SAE in the treatment arm and 808 SAE in the control arm. The lower SAE event rate in the treatment arm was predominantly due to the reduced number of HFR hospitalizations.

- The overall risk of major bleeding within 30 days of implant was 0.9% (5/550). For patients on warfarin therapy there was a 1.4% risk of major bleeding (3/213). For patients on ASA/clopidogrel there was a 0.6% risk of major bleeding (2/319). This suggests that the risk of bleeding in this trial was similar to reported event rates for warfarin or clopidogrel.

- There was one report of an Unanticipated Serious Adverse Device Event (UADE) involving a “tingling sensation” in a control patient which was adjudicated by the CEC as not device/system related. There were two reports of Serious Adverse Device Events (SADE), due to hemoptysis and a blood clot, both of which resolved without permanent sequelae. The CEC adjudicated both events as device/system related. There were no reports of Unanticipated Serious Adverse Device Events (UADE) or Serious Adverse Device Events (SADE) after the 6 month period.

<u>Creatinine (mg/dL) and GFR (mL/min/1.73m²) at Screening and 6 Months</u>

- There were no significant differences in mean creatinine levels between treatment and control at screening (1.40 vs. 1.35) or 6 months (1.49 vs. 1.41). Likewise, there were no significant differences in mean GFR between treatment and control at screening (60.4 vs.

61.8) or 6 months (57.3 vs. 61.7).

Complications of Heart Failure Therapy

- A sensitivity analysis was performed to evaluate the impact of complications, which may have occurred due to HF therapy, on the primary endpoints. For the primary safety endpoint, freedom from DSRC plus CHFT was 94.8% (95% CI 92.6% - 96.5%, p<0.0001). For the primary efficacy endpoint, the treatment group had a hospitalization rate (HFR plus CHFT) of 0.38 vs. the control group hospitalization rate of 0.48 (p=0.0102). The safety and efficacy endpoints remained significant even with the addition of the CHFT hospitalizations.

- Over the study duration, the freedom from DSRC plus CHFT was 90.1% (95% CI 87.32% - 92.42%, p<0.0001). For the primary efficacy endpoint over the study duration, the treatment group had a hospitalization rate (HFR plus CHFT) of 0.55 vs. the control group rate of 0.79 (p<0.0001). The safety and efficacy endpoints remained highly significant over study duration with the addition of the CHFT hospitalizations.

Sensor Performance

- Based on CardioMEMS database monitoring, the estimated rate of freedom from recalibration was 96.7%, with a 95% lower confidence of 94.9%. Comparative data (sensor vs. Swan-Ganz) over an average of 265.0 ±168.5 days after implant demonstrated good concordance between the sensor and Swan-Ganz PA mean measurements.

3 STUDY OBJECTIVE

The objective of the study is to evaluate the safety and efficacy of the Champion HF Monitoring System in a subset of subjects suffering from HF.

4 STUDY DESIGN

This is a prospective, multi-center, open-label clinical trial to be conducted at between 45 and 200 sites in the US. The timeline for enrollment is based on initiating the study in the first quarter of 2012; dates will change based on the actual start date of the study, the date enrollment begins, and/or the actual enrollment rate (Appendix A).

Subjects who sign the informed consent form and meet the eligibility criteria at the Baseline Visit will be eligible for the trial. Subjects will undergo the study-related procedures, including clinical laboratory measurements and body mass index (BMI) calculation. Once the Investigator has reviewed the laboratory values against the inclusion/exclusion criteria, the site will contact all subjects to inform them of their eligibility for the study. Subjects deemed ineligible for the study will be documented as screen failures. Note that for study related procedures/visits Investigator refers to the Principal Investigator or designee.

Eligible subjects will be scheduled to return to the hospital for the Implant Visit (HF pressure sensor implant in conjunction with a RHC procedure). Subjects with a BMI > 35 will require a measurement of the chest circumference (axillary level). If the chest circumference is < 52 inches, the subject will be considered eligible for the study. If chest circumference is > 65 inches, the subject is excluded. Additionally, subjects must also have an appropriately sized (7mm - 15mm diameter) pulmonary artery branch identified prior to Sensor implant. Subjects who do not meet these inclusion criteria will not receive the HF Pressure Sensor implant and will be considered ineligible for the study. These subjects will be documented as consented not implanted and will be followed 30 days for safety.

Subjects meeting all angiographic requirements will receive the Wireless Implantable Hemodynamic Sensor implant.

Following the Champion Sensor implant, at the investigator's discretion, subjects may be discharged once stable or hospitalized overnight for observation and evaluation.

Prior to hospital discharge, subjects will be trained by a CardioMEMS representative, or designee, on the home monitoring system and instructed to take his/her pulmonary artery pressure measurements daily (at the same time each morning). CardioMEMS will supply each subject with a CardioMEMS patient implant identification card, a Home Monitoring User's Manual, and a Helpline phone number that will be available for questions.

After discharge, the subject will take daily pressure measurements in the morning at home utilizing the Champion HF Monitoring System. These measurements will be transmitted via modem to a secure data base.

The Investigator or designee will review the PA pressure measurements from the home monitoring unit. Pressure thresholds are automatically set as described in Appendix D. The Investigator or designee can be notified by CardioMEMS if those parameters are exceeded. If the PA pressures are elevated, the Investigator or designee should make medication changes according to the guidelines in Appendix D. In addition, the Investigator or designee will review the HF pressure measurements on a weekly basis at a minimum to clinically manage subjects appropriately. Medication changes can be made immediately after implant.

Follow-up study visits will be scheduled at Month 1, Month 6, and every 6 months thereafter. Follow-up visits will include a physical exam, evaluation of NYHA Class, AE assessment, medication review and any hospitalizations. Subjects will be followed for long-term safety and efficacy for two years (see Appendix B for the Schedule of Events).

5 STUDY POPULATION

Study subjects must meet the following inclusion and none of the exclusion criteria to be eligible for the study:

5.1 INCLUSION CRITERIA

1. Written informed consent obtained from subject or legal representative
2. Male or female, at least 18 years of age
3. Diagnosis of HF ≥ 3 months

4. Diagnosis of NYHA Class III HF

5. At least 1 HF hospitalization within 12 months of baseline Visit

6. Subjects with a BMI $\leq$ 35. Subjects with BMI >35 will require additional screening. Note: If the BMI is > 35, and the chest circumference is > 52 inches but < 65 inches, the distance from skin on subject's back to the pulmonary artery must be < 10 cm and confirmed by angiogram of the lateral view during the RHC prior to placement of the pressure sensor. If this distance is > 10 cm the subject will not receive a sensor and will not be eligible for the study

7. Subjects with pulmonary artery branch diameter sized between 7mm and 15mm (implanted vessel)

8. Female subjects of childbearing age with a negative urine or serum pregnancy test (at Baseline Visit), and who have agreed to use a reliable mechanical or hormonal form of contraception during the study will be allowed to enter the study. Note: A female is considered of child-bearing potential unless she is postmenopausal for 2 years, has had a total hysterectomy, or has had a bilateral tubal ligation.

9. Subjects willing and able to comply with the follow up requirements of the study

5.2 EXCLUSION CRITERIA

1. Subjects with an active infection

2. Subjects with history of recurrent (> 1) pulmonary embolism or deep vein thrombosis

3. Subjects, in the Investigator's opinion, unable to tolerate a right heart catheterization

4. Subjects who have had a major cardiovascular event (e.g., myocardial infarction, stroke) within 2 months of Baseline Visit

5. Subjects with Cardiac Resynchronization Device (CRT) implanted $\leq$ 3 months prior to enrollment

6. Subjects with a Glomerular Filtration Rate (GFR) <25 ml/min who are non-responsive to diuretic therapy or who are on chronic renal dialysis

7. Subjects with congenital heart disease or mechanical right heart valve(s)

8. Subjects with known coagulation disorders

9. Subjects with a hypersensitivity or allergy to aspirin, and/or clopidogrel

10. Subjects enrolled in concurrent studies that may confound the results of this study

5.2.1 Appropriate Medical Therapy for Heart Failure

At the baseline visit and throughout the study, all subjects will receive appropriate dietary education especially pertaining to sodium restriction and fluid restriction per current ACC/AHA guidelines.

5.3 SCREEN FAILURES

Subjects who do not meet all inclusion/exclusion criteria prior to the completion of the Visit 1 (Baseline) procedures will be defined as screen failures. They will not be allowed to continue their participation in the study.

Subjects who do not meet the angiographic inclusion criterion at Visit 2 (Implant), will not receive the sensor implant. These subjects will be defined as consented not implanted. These subjects may remain in the hospital overnight for observation at the Investigators discretion. They will not be allowed to continue their participation in the study, yet will be followed 30 days for safety.

5.4 CRITERIA FOR WITHDRAWAL

Subjects may be withdrawn from the study for any of the following reasons:

1. Subject withdraws his/her consent
2. Investigator determines other treatment is warranted to protect the health and safety of the subject
3. Subject is noncompliant with study related procedures
4. Subject is lost to follow-up: site must document attempts made to contact the subject for an early discontinuation visit (i.e., 2 – 3 phone calls, followed by 1 certified letter, and two consecutive visits pass without an investigator receiving data.)
5. Pregnancy: If an enrolled subject becomes pregnant at any time during the study, the subject must be withdrawn from the study, and the early discontinuation procedures will be completed. The Investigator must inform the sponsor immediately upon knowledge of the pregnancy. The Investigator will send written notification of the pregnancy including study number, site number, and subject number to the Medical Monitor.

The Investigator will document on the appropriate CRF page the reason/circumstances for early discontinuation. All subjects who prematurely withdraw from the study should have their study exit procedures performed (including CRF Study Completion Form) when possible.

CardioMEMS, Inc. or its designee should be consulted before withdrawing any subject from the study.

5.5 STUDY OR SITE TERMINATION

The sponsor or the Investigator has the right to discontinue the study at any time. As far as possible, this should occur after mutual consultation. The Investigator (or sponsor, where appropriate) is responsible for informing the Independent Ethics Committee/Institutional Review Board (IEC/IRB) of trial closure.

Conditions may arise during the study that could prompt termination of the study or the study sites. Conditions that may prompt such considerations include, but are not limited to, the following:

- The discovery of unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of Sponsor to suspend, discontinue, or shorten the study
- Study conduct at the study site may warrant termination under conditions that include the following:
  - Failure of Investigator(s) to enroll eligible subjects into the study
  - Failure of Investigator(s) to comply with the Food and Drug Administration (FDA), or country-specific regulations
  - Submission of false information from the research facility to Sponsor, the Clinical Monitor, or a regulatory authority
  - Insufficient adherence to protocol requirements
  - A conflict of interest of the Investigator, his/her institution, or site personnel that would negatively impact the integrity of the clinical trial
  - Institution or IRB/IEC under investigation for cause by a federal agency

In the event of premature discontinuation of the study, all materials (completed, partially completed or blank CRFs, study supplies, etc.) must be returned to the sponsor, as if the trial had been completed.

6 STUDY PROCEDURES BY VISIT

All subjects will be followed for 2 years. A subject is considered to have successfully completed the study upon completion of the 2 year visit (see Appendix B for the Schedule of Events).

6.1 ON-STUDY EVALUATIONS

6.1.1 Study Visit 1 (Baseline Visit)

During Study Visit 1, the following procedures/assessments will be performed to determine subject eligibility:

- Informed Consent prior to the conduct of any study-related procedures
- Abbreviated physical examination including vital signs (temperature, heart rate, respiratory rate, blood pressure), weight, height, BMI calculation (refer to Appendix E)

All physical examinations will be conducted by a licensed physician, or designee, in accordance with local laws and regulations.

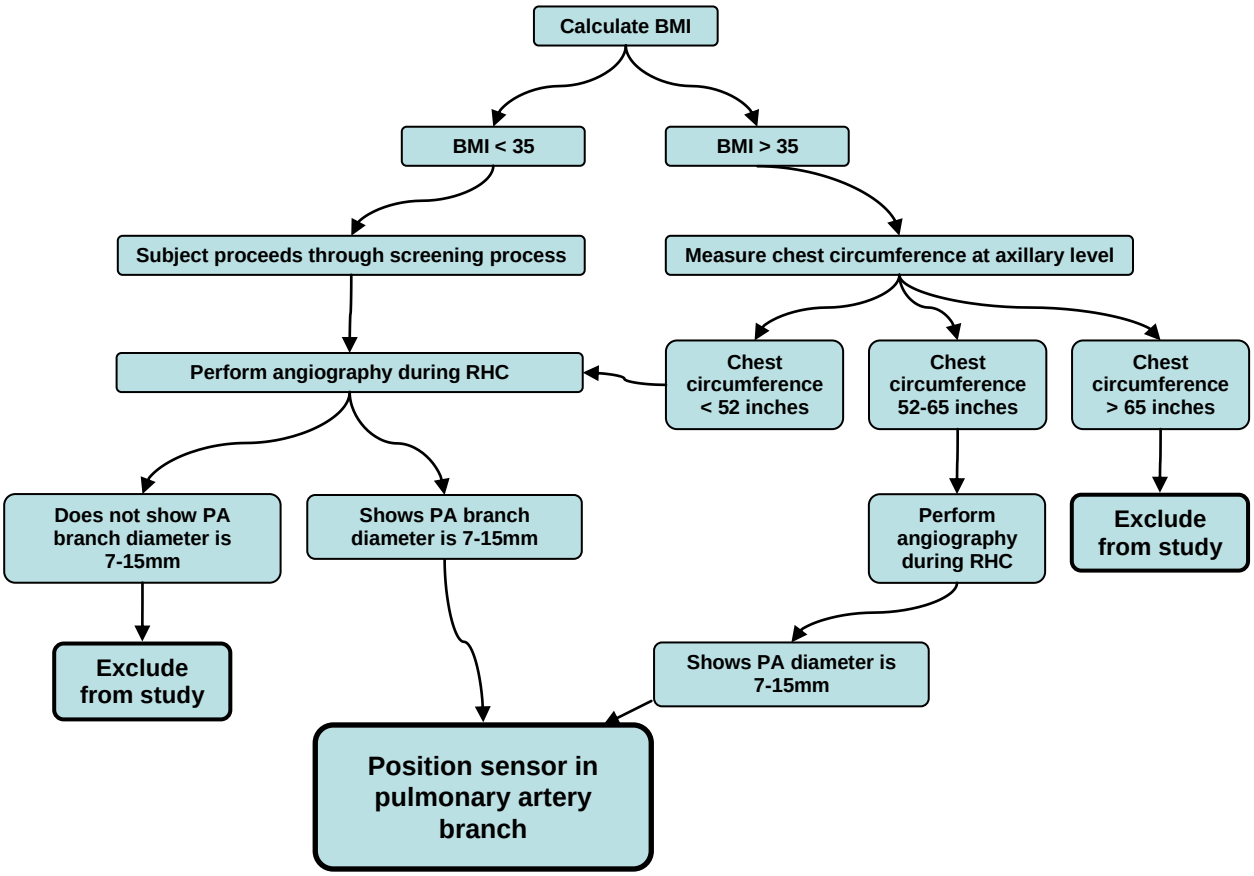
- Medical and surgical history
- Demographics
- Subject questionnaire to assess acceptable support to set up and maintain the CardioMEMS home monitoring system
- NYHA Functional Classification for HF
- Blood Chemistry (including creatinine and BUN)
- Calculation of GFR (refer to Appendix F)
- Pregnancy test (urine or serum) in females of child-bearing potential
- Assessment of medications
- Assessment of enrollment eligibility (inclusion/exclusion criteria)

Once the Investigator has reviewed the lab values against the inclusion/exclusion criteria, the site will contact all subjects to inform them of their eligibility for the study. Eligible subjects will be scheduled to return to the hospital for the Implant Visit and procedure. Subjects on anticoagulation therapy will be instructed by the Investigator to discontinue use 1-2 days prior to pressure sensor placement. The investigator should consider utilizing enoxaparin (Lovenox) per the site's standard of care as bridge therapy to sensor placement in subjects who were on anticoagulation therapy.

For subjects at risk for gastro-intestinal bleeding during the period in which dual antiplatelet therapy is given, the investigator should consider a proton pump inhibitor such as omeprazole (Prilosec). Subjects at risk include the elderly; those with a history of gastroduodenal ulcers, GERD, esophagitis, intestinal polyps or cancer. Subjects who smoke or who are using steroids or non-steroidal anti-inflammatory drugs may also be at risk.

6.1.2 Study Visit 2 (Implant Visit)

Eligibility will be reconfirmed at the implant visit. Subjects with a BMI > 35 will require a measurement of the chest circumference (axillary level). If the chest circumference is < 52 inches, the subject will be considered eligible to continue evaluation. If chest circumference is > 65 inches, the subject is excluded. Additionally, subjects must also have an appropriately sized ($\geq$ 7mm and $\leq$ 15mm diameter) pulmonary artery branch identified prior to Sensor implant. Subjects who do not meet these inclusion criteria will not receive the HF Pressure Sensor implant and will be considered ineligible for the study. These subjects will be documented as consented not implanted and will be followed for 30 days for safety.


Calculate BMI
BMI < 35
BMI > 35
Subject proceeds through screening process
Measure chest circumference at axillary level
Perform angiography during RHC
Chest circumference < 52 inches
Chest circumference 52-65 inches
Chest circumference > 65 inches
Does not show PA branch diameter is 7-15mm
Shows PA branch diameter is 7-15mm
Perform angiography during RHC
Exclude from study
Exclude from study
Shows PA diameter is 7-15mm
Position sensor in pulmonary artery branch

At Study Visit 2 the following procedures/assessments will be performed:

- Abbreviated physical examination (i.e., vital sign assessments and significant changes since Screening) and weight
- Confirmation of enrollment eligibility (inclusion/exclusion criteria)
- NYHA Functional Classification for HF
- PT/PTT with International Normalized Ratio (INR) of 1.5 or less for subjects previously on warfarin
- Right Heart Catheterization with sensor implant
- Wireless implantable hemodynamic sensor implant, calibration, and measurements
- Swan-Ganz measurements (cardiac output, pulmonary systolic, pulmonary diastolic, pulmonary mean) done 3 times consecutively with sensor measurements (for calibration)
- Assessment of medications
- Record any AEs that occurred since the last follow-up visit. See Section 8, Adverse Events

NOTE: Recalibration of the Champion HF Monitoring System will be performed as deemed necessary by Sponsor.

Subjects, who are currently on anticoagulant therapy (warfarin), or for those in whom chronic warfarin therapy is indicated for their HF, will restart treatment. The subject's INR should be checked periodically to ensure that it is in the therapeutic range. Those subjects who will not be treated with chronic warfarin will be placed on aspirin (81 mg or 325 mg) and clopidogrel (75 mg) daily for 1 month starting on the day of Sensor placement. After 1 month, the subject will continue with aspirin therapy only.

6.1.2.1 Sensor Implant and HF Pressure Measurements

All eligible subjects will undergo a right heart catheterization with pressure sensor implant procedure at the Implant Visit (Study Visit 2). The RHC must be performed according to each site's standard of care.

CardioMEMS personnel will be available during the implant procedure and at any time to support the site staff with any additional training needs they may have.

Implant Procedure of Wireless Pressure Sensor:

- Prep in accordance with standard technique
- Perform right heart catheterization in accordance with standard of care
- Identify target Sensor deployment site
- Implant and calibrate Sensor
- Provide vascular access site care per standard procedure

- At investigator's discretion, subjects may be discharged once stable or hospitalized overnight for observation and evaluation.
- Please see IFU for implant details

Prior to discharge, the subject will be instructed on how to take their own pulmonary artery pressures at home utilizing the Champion HF Monitoring System. This training will enable the subject to determine the appropriate position in which to obtain the optimum Sensor signal. Subjects will be instructed to take sensor pressure measurements daily (at the same time each morning). Subjects will be reminded of the current ACC/AHA guidelines regarding sodium and fluid restrictions.

Initially, guidelines and thresholds will be set automatically according to Appendix D. It is recommended the Investigator or designee review the home readings daily during the first week of home monitoring. Medication changes may be made immediately. . The Investigator or designee,should review the PA pressure measurements weekly at a minimum in order to clinically manage subject's PA pressure appropriately. However, the Investigator or designee has as needed access to the Champion HF Monitoring System in order to manage subjects. Guidelines for the frequency of review are listed in Appendix D. The physician will use his/her discretion to determine if additional diagnostic procedures are warranted based on the Sensor pressure data.

Subjects will be instructed to contact a CardioMEMS representative immediately if they are having any problems using the Champion HF Monitoring System in obtaining daily readings.

6.1.3 Study Visit 3 (Month 1)

Subjects will be evaluated at Month 1 (+ 7 days) from the Implant visit and the following procedures/assessments will be performed:

- Updated medical and surgical history
- Assessment of AEs that occurred since the last visit
- Abbreviated physical examination (only significant changes since Enrollment) including vital signs (temperature, heart rate, respiratory rate, blood pressure), and weight
- Assessment of NYHA functional class
- Medication Review
- Creatinine level

Subjects will be reminded to obtain daily pulmonary artery pressure measurements utilizing the Champion HF Monitoring System. Subjects will be reminded of the current ACC/AHA guidelines regarding sodium and fluid restrictions.

6.1.4 Study Visits 4, 5, 6, and 7 (Month 6, 12, 18, and 24)

All subjects will be evaluated at Month 6, 12, 18, and 24 (± 30 days) and the following procedures/assessments will be performed:

- Updated medical and surgical history
- Assessment of AEs that occurred since the last visit
- Abbreviated physical examination (only significant changes since Enrollment) including vital signs (temperature, heart rate, respiratory rate, blood pressure), and weight
- Assessment of NYHA functional class
- Medication Review
- Creatinine level

Subjects will be reminded to obtain daily pulmonary artery pressure measurements utilizing the Champion HF Monitoring System. Subjects will be reminded of the current ACC/AHA guidelines regarding sodium and fluid restrictions.

6.1.5 Early Termination

All subjects who withdraw from the study must have their study exit procedures performed (including CRF Study Completion Form). The following procedures/assessments will be performed:

- Updated medical and surgical history
- Assessment of AEs that occurred since the last visit
- Abbreviated physical examination (only significant changes since Enrollment) including vital signs (temperature, heart rate, respiratory rate, blood pressure), and weight
- Assessment of NYHA functional class
- Medication Review
- Creatinine level

All subjects who withdraw from the study prior to Study Visit 10 must have their study exit procedures performed (including CRF Study Completion Form).

All reasonable efforts will be made to retain subjects in the clinical trial until its completion. If a patient moves from the geographic catchment area of their investigator, CardioMEMS will first attempt to place the patient with another investigator. If it is not possible to place the patient with another investigator, CardioMEMS will request that the patient's new physician forward the patient's study information to the investigator. Patients lost to follow-up will be withdrawn only after a minimum of two documented phone calls are made by personnel at the study center to the

patient or emergency contact, a certified letter is sent to the last known address, and two consecutive visits pass without an investigator receiving data.

6.1.6 Unscheduled Visit

If a subject is hospitalized, seen in the emergency room (ER) or has an unscheduled clinic visit, the Champion HF Monitoring System may be used to obtain pulmonary artery pressure measurements at the investigators discretion.

If a subject is hospitalized and a RHC procedure or Swan-Ganz catheter evaluation is clinically warranted, pulmonary artery pressures utilizing the Champion HF Monitoring System should also be obtained utilizing the hospital electronics unit. Three pulmonary artery pressure measurements should be obtained at post-exhalation from both the Swan-Ganz and the Champion HF Monitoring System.

Additional procedures/assessments should also be performed:

- Updated medical and surgical history
- Assessment of AEs that occurred since the last visit
- Abbreviated physical examination (only significant changes since Enrollment) including vital signs (temperature, heart rate, respiratory rate, blood pressure), and weight

These assessments should be documented on the Unscheduled Visit / Hospitalization / AE Case Report Forms as appropriate.

7 DEVICE INFORMATION

7.1 DESCRIPTION, PACKAGING, LABELING, AND STORAGE

7.1.1 Wireless Implantable Hemodynamic Sensor

The Wireless implantable hemodynamic sensor is a small, oval shaped device with rounded edges. The implantable sensor is designed and fabricated using tools, techniques and design rules largely inspired by recent breakthroughs in the field of micro-electronics. The Sensor is composed of ultra miniaturized electrical components (three dimensional coil and a pressure sensitive capacitor) encased in a fused silica housing. The housing is encapsulated in medical grade silicone. A change in local pressure (outside the silica housing) results in a change in electrical behavior of the components enclosed inside the housing. The Sensor membrane is quite rigid and much less compliant than any biological material (e.g.: blood clot, tissue) that may grow, adhere to or be deposited onto it. This allows the sensor to remain accurate in biological environments as has been demonstrated in the aortic and heart failure applications.

The coil allows for wireless communication with the Sensor without requiring an on-board source of energy, such as a battery. Thus, when the Sensor is located in the pulmonary artery, it is possible to measure the blood pressure in a simple, noninvasive procedure by remotely interrogating the Sensor.

Two platinum/iridium marker bands at each end of the Sensor (total of 4 marker bands) allow the device to be visualized under fluoroscopy during the insertion procedure (and on imaging during follow-up visits) and indicate the position of the sensor.

A tether system keeps the Sensor connected to the Delivery System until the physician determines that the Sensor is properly positioned within the distal pulmonary artery. Once the Sensor is in position, the tether system is removed, releasing the Sensor.

The fused silica assembly is completely encased in medical grade silicone.

No particular storage conditions are needed for the Sensor.

7.1.2 Delivery System

The Sensor is attached by a tether wires to an over-the-wire delivery catheter. The delivery catheter (with Sensor) is introduced over a guidewire through a sheath.

7.1.3 External Electronics

The function of the external electronics is to effectively and efficiently obtain information from the wireless implantable hemodynamic sensor. There are 2 main components comprising the external electronics: the antenna and main unit.

The antenna is used to interrogate the Sensor. During a reading, the antenna is placed in the vicinity of the Sensor and the antenna powers the passive Sensor using bursts of RF energy. When the Sensor is energized, it returns a signal with pressure information. This signal is received by the antenna and sent to the main unit for processing.

The external electronics are labeled with a unique serial number, voltage requirements, electrical safety information and CardioMEMS name.

7.1.4 Home Monitoring

Prior to hospital discharge, subjects will be instructed on how to take their own pulmonary artery pressure measurements, utilizing the Champion HF Monitoring System each day. Subjects will be trained on: setting up the unit, connecting the system to a phone line, proper positioning for obtaining the optimum sensor signal, taking and transmitting the daily pressure measurements. The unit will transmit the data to a database using the system's modem.

The home measurements will be taken while the subject is lying down (supine) in bed positioned on a flat antenna. The antenna assembly will rest on a foam pad with shielding material attached to the bottom of the pad. The subject can cover the assembly with a bed sheet or large pillow cover. It is recommended subjects obtain home measurements in a supine position however, if the subject is unable to lie flat, measurements can be obtained in a sitting or reclined position. It is important the anatomical position is consistent for every daily measurement.

The home electronics unit is small enough for placement on a bedside table. The unit will provide audio and visual prompts for the subject to guide them through signal acquisition. Once the subject is positioned and a signal is acquired, the subject will be notified of the successful reading and the data is automatically transmitted to a remote database. CardioMEMS will provide instructions for use and a help line will be available for questions. Please refer to Subject's Home Monitoring User Manual for more detailed information.

7.1.5 Software Program for Wireless Pressure Measurements

The CardioMEMS Champion HF Monitoring System is intended for measuring pulmonary artery pressures within the body in real time. The Software User's Manual covers the operation of that software. The software is used exclusively in conjunction with the CardioMEMS external electronics.

7.2 SHIPPING INFORMATION

The CardioMEMS Champion HF Monitoring System may be shipped to the subject or hand-carried to the clinical site. Records will note the serial number of each external electronic system (which corresponds to the other components) as well as the lot number of each Sensor with Delivery System. CardioMEMS will maintain device accountability records for each site. In addition, each center will maintain device accountability records for each Sensor implanted.

8 ASSESSMENT OF SAFETY

Safety will be assessed throughout the study by the frequency of Adverse Events (AEs), Adverse Device Events (ADEs), Serious AEs (SAEs), Serious Adverse Device Event (SADEs), Unanticipated Adverse Device Events (UADEs), pressure sensor failure rate, and device / system-related complications by relationship to the device, and severity using absolute and relative frequencies via Medical Dictionary for Regulatory Activities (MedDRA, Version 6.0 or later) preferred term. Creatinine levels, physical examination, and subject survival data through 24 months will be tabulated across study period assessments.

8.1 DEFINITIONS OF ADVERSE EVENT (AE), ADVERSE DEVICE EVENT (ADE), DEVICE/ SYSTEM-RELATED COMPLICATION, AND PRESSURE SENSOR FAILURE

8.1.1 Adverse Event (AE) and Adverse Device Event (ADE)

An AE is any untoward medical occurrence (e.g., noxious or pathological changes) in a subject or clinical investigation subject compared with pre-existing conditions that may occur during any part of the clinical study. An AE is defined as being independent of assumption of any causality (e.g., primary or concomitant disease or study design).
An ADE is any undesirable clinical event in a subject considered possibly or definitely related to the device or the insertion procedure by the Investigator. An ADE may occur at any time after exposure to the Investigational Device.
All AEs and ADEs should be documented in the CRF.

8.1.2 Serious Adverse Event (SAE) and Serious Adverse Device Events (SADE)

For this study, an SAE is defined as any untoward medical occurrence that:

- results in death
- is immediately life-threatening – an event in which the subject was at risk of death at the time of the event
- requires admission and hospitalization (> 24 hours) or prolongation of existing hospitalization

- results in disability/incapacity
- results in a congenital anomaly/birth defect
- requires intervention to prevent one of the above

A Serious ADE (SADE) is an event that meets any of the above criteria and is considered possibly or definitely related to the device or the insertion procedure by the Investigator.

The cause of death of any subject after enrollment must be documented on the AE CRF and reported as an SAE. The information should include the date expired, cause of death, what attempts were made to treat the condition, the performance and functioning of the Sensor prior to the event and causal relationship to the Sensor. An autopsy should be encouraged.

If it is not certain that an event meets the above definitions of an SAE or an SADE, contact the Medical Monitor.

8.1.3 Procedures for Reporting Serious Adverse Events (SAEs)

It is the responsibility of the Investigator or Sub-Investigator(s) to perform periodic assessments of all AEs as well as identifying SAEs. The AE and SAE reporting period for this study is from the Baseline visit through study termination.

AEs, ADEs, SAEs and SADEs that occur during the study should be treated by established standards of care that will protect the life and safety of the subjects.

Any SAEs and SADEs are to be reported by the Investigator via telephone or facsimile to the Safety Monitor within 24 hours of knowledge of the event, followed by a written confirmation by the Investigator within 10 days. The site must complete an SAE Report Form for all SAEs, including SADEs, and submit it by fax to:

Bradley Jeffries, MD, MS

Medical Safety Monitor

Fax: (877) 293-3816

Phone: (404) 432-6882

If at the time the Investigator submits an initial SAE form and the SAE has not resolved, the Investigator must provide a follow-up report as soon as the event resolves (or upon receipt of significant information if the event is still ongoing).

All SAEs must be followed until resolution/stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator. Additionally, the Investigator is responsible for reporting SAEs to his or her IRB/IEC in accordance with local IRB/IEC procedures.

8.1.4 Definition for Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect is defined as any serious adverse effect on health or safety or life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the

investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

8.1.5 Procedures for reporting Unanticipated Adverse Device Effects (UADEs)

Any UADEs are to be reported immediately by the Investigator by telephone or by facsimile to the Safety Monitor within 24 hours of knowledge of the event, followed by a written confirmation by the Investigator within 10 days. The site must complete a UADE Report Form and submit it by fax to:

Brad Jeffries, MD, MS
Medical Safety Monitor
Fax: (877) 293-3816
Phone: (404) 432-6882

8.1.6 Relatedness (Causality)

Causality assessment is required for AEs (and SAEs) that occur during clinical investigations. There is currently no standard international nomenclature to describe the degree of causality or relatedness of an AE with the Investigational Device (ICH, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, 1994). The following terms will be used during this study:

- Definite - An AE that has a clear temporal association with the Investigational Device;
- Possible - There is a reasonable likelihood that the event is due to the Investigational Device, as evidenced by one of the following:
  - There may be temporal association with the Investigational Device (e.g., within 24 hours of implant), or
  - The event, or level of severity of the event, is unlikely to be explained by other etiologies (known to be related to the study disease, subject's baseline medical condition, or concomitant medication).
- Unlikely - The AE is not temporally related to the Investigational Device, or is known to be related to one of the following:
  - Morbidity associated with underlying medical condition,
  - Concomitant medication, or
  - A relationship to Investigational Device is not biologically plausible
- Not related - The AE is definitely not related to the Investigational Device.

8.1.7 Anticipated Adverse Events Associated with the sensor implant procedure or post-implant complications

Anticipated AEs associated with the sensor implant procedure (in conjunction with RHC) or post-implant complications should be recorded on the AE page of the CRF and include the following:

- Air embolism

- Abnormal heart beats or heart rate
- Bleeding
- Delayed wound healing
- Infection
- Hematoma
- Thrombus (blood clot) formation at catheter insertion site
- Venous trauma (e.g., perforation, dissection)
- Valve damage

8.1.8 Anticipated Serious Adverse Events (SAEs) or Anticipated Serious Adverse Device Events (SADEs) associated with the sensor implant procedure or post-implant complications

Anticipated SAEs or SADEs associated with the sensor implant procedure (in conjunction with RHC) or post-implant complications should be recorded on the AE CRF and include the following:

- Pulmonary infarct
- Pulmonary embolism

8.1.9 Device / System-related Complication

A device / system-related complication is an adverse event that is, or is possibly, related to the system (wireless pressure sensor or external electronics) and at least one the following:

- is treated with invasive means (other than intramuscular medication or a right heart catheterization with a Swan-Ganz measurement which is used for diagnostic purposes)
- results in the death of the subject
- results in the explant of the device

8.1.10 Pressure Sensor Failure

A pressure sensor failure occurs when the sensor malfunctions to the point that no readings can be obtained from it after all attempts are exhausted including troubleshooting the system to rule out any problems with the electronic components.

NOTE: Recalibration of the Champion HF Monitoring System will be performed as deemed necessary by Sponsor.

8.2 OTHER SAFETY MEASUREMENTS

8.2.1 Physical Examinations

A physical examination will be performed at each visit. All physical examinations will be conducted by a licensed physician, or designee, in accordance with local laws and regulations.

Subject weight (kg/lb) will be recorded at each study visit along with vital signs.

8.2.2 Clinical Laboratory Assessments

Creatinine will be evaluated for renal function at baseline and every 6 months for all subjects. Additional laboratory assessments may be made per the Investigator discretion during the study.

9 ASSESSMENT OF EFFICACY

Information regarding HFR hospitalizations will be collected throughout the study and will be adjudicated by the CEC.

10 STATISTICAL CONSIDERATIONS

The data will be summarized using univariate statistics (e.g., N, mean, standard deviation, median, minimum and maximum) or frequency (e.g., N, %) as appropriate.

The primary time point for safety analyses is 24 months post enrollment. The primary time point for efficacy analyses is 12 months post enrollment.

Unless otherwise specified, all statistical tests will be conducted using a 2-sided significance level of 0.05.

10.1 POPULATIONS FOR ANALYSIS

Safety Population: The Safety Population consists of all subjects who received a sensor implant or underwent the implant procedure but were never implanted (e.g., AE prevented implantation), regardless of study completion status. All safety analyses will be performed on the Safety population.

Subjects who are found not to have an appropriately sized pulmonary artery branch or the distance from the back to the target vessel was not < 10 cm and did not receive the HF Pressure Sensor implant will be considered ineligible for the study. However, these subjects will be followed for 30 days for safety and all safety related data for these subjects will be provided in separate data listings.

Efficacy Population: The efficacy population consists of all subjects who received a sensor implant regardless of study completion status. All efficacy analyses will be performed on the efficacy population.

10.2 SAMPLE SIZE CONSIDERATIONS

10.2.1 Efficacy Sample Size Determination

For the primary efficacy endpoint of HFR hospitalizations at 1 year, 538 patients will provide 90% power to show a difference in rates as small as 0.09 between treatment and historical control using a one-sided, one-sample Poisson test with an alpha of 0.05.

10.2.2 Safety Sample Size Determinations

For the freedom from device / system-related complication rate, using an exact test for one-sample binomial proportions with a two-sided alpha of 0.05, a sample size of 600 subjects will provide greater than 90% power to detect a difference as small as 6% from the null proportion rate of 80%.

For the freedom from pressure sensor failure rate, using the exact test for one-sample binomial proportions with a two-sided alpha of 0.05, a sample size of 600 subjects will provide greater than 90% power to detect a difference as small as 4% from the null proportion rate of 90%.

The sample size is driven by the safety endpoints. Given a 6 month attrition rate of 9.5% in the CHAMPION trial, or a two year attrition rate of 38%, 967 subjects will be enrolled.

10.3 MISSING DATA

Missing data will be tracked in the Electronic Data Capture system; queries will be generated and sent to the site. In addition, a CardioMEMS representative, or designee will routinely perform monitoring visits at each site. During the monitoring visits, missing data queries will be addressed until resolution. Missing data that are not resolved will not be imputed unless specified below.

10.4 SUBJECT ACCOUNTABILITY AND BASELINE INFORMATION

Descriptive summaries will be generated to describe the disposition of all enrolled subjects.

10.5 DEMOGRAPHIC AND BASELINE INFORMATION

Descriptive summaries will be generated for all relevant baseline variables. These variables include, but are not limited to, demographic data and conditions at the time of enrollment.

Medication data will be analyzed across study period assessments.

10.6 SAFETY ANALYSES

The safety analyses will be performed using the Safety Population.

The primary safety analyses will be based on the following objective performance criteria: a) the lower limit of the two-sided 95% confidence interval on the freedom from device / system-related complication rate at 24 months is at least 80% and b) the lower limit of the two-sided 95% confidence interval on the freedom from pressure sensor failure rate at 24 months is at least 90%. These primary safety endpoints will be tested hierarchically in order to control for multiplicity. First, the freedom from device / system-related complication rate will be tested. If

the result is statistically significant (i.e., $p<0.050$), then the freedom from pressure sensor failure rate will also be tested for significance (i.e., $p<0.050$). The study will be judged to have provided positive safety results if both tests of the primary safety analysis endpoints are statistically significant (i.e., $p<0.050$).

Mathematically stated, the primary safety hypotheses are:

a) H_0: $P_{\text{(Freedom from device / system-related complications at six months)}} < 80\%$
   H_a: $P_{\text{(Freedom from device / system-related complications at six months)}} \geq 80\%$

b) H_0: $P_{\text{(Freedom from pressure sensor failure at six months)}} < 90\%$
   H_a: $P_{\text{(Freedom from pressure sensor failure at six months)}} \geq 90\%$

Safety will also be assessed throughout the study by the frequency of Adverse Events (AEs), Adverse Device Events (ADEs), Serious AEs (SAEs), Serious Adverse Device Event (SADEs), unanticipated adverse device events (UADEs), and device / system-related complications by relationship to the device, and severity using absolute and relative frequencies via Medical Dictionary for Regulatory Activities (MedDRA, Version 6.0 or later) preferred term. Creatinine levels, physical examination, and subject survival data through 6 months will be tabulated across study period assessments.

10.7 EFFICACY EVALUATION

Efficacy evaluation will be conducted on both the ITT and the PP populations. The data will be summarized using univariate statistics (e.g., N, mean, standard deviation, median, minimum and maximum) or frequency (e.g., N, %) as appropriate.

The primary time point for analyses is 12 months post enrollment. The primary efficacy evaluation will compare the annualized HFR hospitalization rate at 1 year compared to the patients' historical control HFR hospitalization rate in the year prior to enrollment in CHAMPION PAS using a one-sided, one-sample Poisson test.

Mathematically stated, the primary efficacy hypothesis is:

H_0: $\gamma_{\text{(12 month Treatment HFR Hospitalization Rate)}} \geq \gamma_{\text{(12 month Historical Control HFR Hospitalization Rate)}}$
H_a: $\gamma_{\text{(12 month Treatment HFR Hospitalization Rate)}} < \gamma_{\text{(12 month Historical Control HFR Hospitalization Rate)}}$

Secondary Efficacy Endpoint

The secondary efficacy evaluation will compare the annualized HFR hospitalization rate at 2 years compared to the patients' historical control HFR hospitalization rate in the year prior to enrollment in CHAMPION PAS using a one-sided, one-sample Poisson test.

In addition, HFR hospitalizations at 12 and 24 months will be analyzed by the following subgroups: gender, left ventricular systolic function (EF ≥ 40% vs. EF <40%), and HF type (ischemic cardiomyopathy vs. non-ischemic cardiomyopathy).

10.8 SUBJECT SURVIVAL RATE

Subject survival rate will be measured from the Implant date to the date of death, or censored at last date known alive. HFR Hospitalization-free mortality will also be analyzed. Plotting and analysis of survival data will be accomplished using Kaplan-Meier methods.

11 CLINICAL EVENT CLASSIFICATION COMMITTEE

An independent clinical events committee will be formed to review clinical data. The committee will be comprised of physicians, who will not participate in the enrollment or treatment of subjects in this trial. All endpoints or suspected endpoints will be reviewed by this committee according to the CEC Committee charter. Any event listed in the CEC Committee charter reported in an SAE report or the CRF will trigger the accumulation of a portfolio of pertinent documents from the hospital admission. These documents will be collected and copies distributed to members of the CEC Committee. The interpretation of the event as classified and adjudicated by the clinical events committee will be used in the final efficacy and safety analyses, and when available, for any interim safety and efficacy analyses.

The composition and function of the CEC Committee is described in Appendix H.

12 DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

12.1 DATA COLLECTION AND REPORTING

Electronic CRFs (eCRFs) using data capture will be utilized. Site staff will enter the information required by the protocol onto eCRFs using a validated software/database that conforms to FDA requirements for electronic data capture. All data fields will be completed where appropriate. However, if data are not available (i.e., missed visit, etc.), the site will receive instruction regarding electronic documentation. As data are entered, automated cross-check programs will search for any data discrepancies in the eCRFs. Appropriate error messages will be generated, allowing for the modification or verification of the entered data. Queries will generally be sent to the investigational site using an electronic data query system that includes an automated audit trail of the corrections.

Monitoring personnel of CardioMEMS, Inc., or its designee, will review the eCRFs for completeness and accuracy and will instruct site personnel to make any corrections or additions.

The Investigator, or designee, will certify that the data are complete and accurate by applying an electronic signature to the eCRF. Any subsequent alterations, corrections, or additions will be reviewed and electronically signed by the Investigator prior to database lock.

12.2 Site Qualification

For sites that did not participate in the CHAMPION protocol, a site visit will be performed by CardioMEMS, Inc. or designee prior to the start of the study to review the protocol in detail, to ensure the availability of appropriate trial personnel, adequate resources and to assess their ability to properly conduct the study according to ICH-GCP guidelines and local requirements.

12.3 Study Monitoring

CardioMEMS, Inc. or designee will monitor the study to meet the sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guidelines, and applicable regulatory requirements and to ensure that study initiation, conduct, and closure are adequate.

Clinical Monitors will periodically audit all CRFs/eCRFs and corresponding source medical records for each subject. The monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of CRFs/eCRFs, to resolve any inconsistencies in the study records, and to assure that all protocol requirements, applicable regulatory or country-specific regulations, other requirements, and Investigator's obligations are being fulfilled.

The Investigator and his/her staff will be expected to cooperate with CardioMEMS, Inc. personnel or agents of CardioMEMS, Inc. and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information.

The Investigator(s)/institution(s) will permit direct access to source data/documents for trial-related monitoring, audits, IRB/IEC and regulatory inspection(s).

12.4 Source Data Verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (e.g., subject files, physician notes, discharge summaries, operative records, etc.). All data reported on the CRF should be supported by source documents.

12.5 Definition of Source Data

Source data includes all information in source documents (original records, certified copies of original records, and original data recorded on customized worksheets) and includes all original recordings or certified copies of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

12.6 Data Disclosure and Subject Confidentiality

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection

upon request by FDA or other government regulatory agency auditors, the Sponsor's Clinical Monitor (or designee) and the IRB/IEC.

The information developed in this clinical study will be used by the Sponsor in the clinical development of the study device and therefore may be disclosed by the Sponsor as required for disclosure as to other clinical Investigators, to other companies, to the FDA and to other government agencies.

13 ETHICAL CONSIDERATIONS AND STUDY ADMINISTRATION

13.1 HUMAN SUBJECTS PROTECTION

Subject's informed consent has to be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Before initiation of this study, the Investigator or designee and the Sponsor will jointly develop the consent form. Written IRB/IEC approval of the protocol and the consent form must be provided to the Sponsor prior to enrollment of subjects. This approval must refer to the consent form and to the study title and protocol number as given by the Sponsor on the cover page of the protocol.

Prior to participation in the study, the written informed consent form must be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated informed consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for trial-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

The informed consent form should be updated or amended whenever new information becomes available that may be relevant to the subject. The subject should then sign the revised informed consent form as directed by the IRB.

A list of IRB/IEC voting members, their titles or occupations, and their institutional affiliations should be provided to the Sponsor before study initiation.

The IRB/IEC must be notified of completion of the study and a final report must be provided to the IRB/IEC. A copy of these reports must be forwarded to the sponsor. The Investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. Adverse experiences which are reported to the FDA and/or to other regulatory agencies, as Expedited Safety Reports, must be submitted promptly to the IRB/IEC.

At least once per year, the IRB/IEC must review and give written approval to continue the study. A copy of this written approval, referring to the study by protocol title and number, as given by the Sponsor, must be provided to the Sponsor.

This trial will be conducted in accordance with FDA regulations and ICH-GCP.

13.2 PROTOCOL AMENDMENTS

The Investigator will not modify the protocol without first obtaining concurrence in writing from the Sponsor. If an amendment is required, this must be made in written form and receive

approval according to the appropriate SOP. All changes to the protocol must be submitted to the IRB/IEC. Protocol modifications that impact subject safety or the validity of the study must be approved by the IRB/IEC and submitted to the FDA or country-specific regulatory agency before initiation.

13.3 Device Accountability

The Sponsor will provide the study center with the CardioMEMS HF Pressure Measurement System in adequate quantities to complete the study. The Devices may only be used for subjects enrolled in this clinical investigation under the supervision of the Investigator and according to the terms outlined in this protocol.

It is the responsibility of the Investigator to ensure that the device is securely stored where access is limited to the Investigator, Sub-Investigators and approved study personnel. It is also the responsibility of the Investigator to maintain complete and accurate device accountability records throughout the duration of the clinical study.

Any unused or damaged Investigational Devices will be returned to the Sponsor. At the end of the clinical study, the Monitor will conduct a final inventory of unused product and reconcile the inventory with the inventory logs kept by the Sponsor.

13.4 Retention of Records

FDA and ICH GCP guidelines require that an Investigator retain subject identification codes, subject files, and source data for the maximum period of time permitted by the hospital, institution, or private practice, but not less than 2 years after the Investigational Device is approved by the FDA or withdrawn from clinical investigation.

13.5 Finance, Insurance, and Publication

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in separate agreements as appropriate.

14 REFERENCES

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Hunt, S. A., Abraham, W. T., Chin, M. H., Feldman, A. M., Francis, G. S., Ganiats, T. G., et al. (2009). AHA 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults- A Report of the ACC Foundation/AHA Task Force on Practice Guidelines Developed in Collaboration with the ISHLT. *Journal of the American College of Cardiology , 53* (15), e1-e90.

Setoguchi, S. N. (2009). Maximum potential benefit of implantable defibrillators in preventing sudden cardiac death after hospital admission because of heart failure. *Canadian Medical Association Journal , 180* (6), 611-16.

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APPENDIX A ANTICIPATED STUDY TIMELINE

Time = 0 *March 2012*	**Time = month 1** *July 2012*	**Time = month 2** *August 2012*	**Time = month 3**	**Time = month 4**	**Time = month 5**	**Time = month 6** *December 2012*	**Time = month 7**	**Time = month 8**	**Time = month 9** *March 2013*
Study Initiation	5 sites with IRB approval First enrollment	15 sites with IRB approval	30 sites with IRB approval	40 sites with IRB approval	50 sites with IRB approval	60 sites with IRB approval	70 sites with IRB approval	80 sites with IRB approval	100 sites with IRB approval
	Estimated enrollment = 5	Estimated enrollment = 15	Estimated enrollment = 30	Estimated enrollment = 40	Estimated enrollment = 50	Estimated enrollment= 50	Estimated enrollment = 50	Estimated enrollment = 50	Estimated enrollment = 50
	5	20	50	90	140	190	240	290	340

Time = month 10 *April 2013*	**Time = month 11**	**Time = month 12** *June 2013*	**Time = month 13**	**Time = month 14**	**Time = month 15**	**Time = month 16**	**Time = month 17**	**Time = month 18** *December 2013*	**Time = month 19**	**Time = month 20**	**Time = month 21** *March 2014*
125 sites with IRB approval	150 sites with IRB approval	200 sites with IRB approval									Enrollment complete
390	440	490	540	590	640	700	760	820	880	940	967

Time = month 22 *April 2014*	**Time = month 23**	**Time = month 24**	**Time = month 25**	**Time = month 26**	**Time = month 27**	**Time = month 28**	**Time = month 29**	**Time = month 30**	**Time = month 31**	**Time = month 32**	**Time = month 33** *March 2015*
Patient follow-up											

Time = month 34 *April 2015*	**Time = month 35**	**Time = month 36**	**Time = month 37**	**Time = month 38**	**Time = month 39**	**Time = month 40**	**Time = month 41**	**Time = month 42**	**Time = month 43**	**Time = month 44**	**Time = month 45** *March 2016*
Patient follow-up											

Study follow-up complete *April 2016*		**Study Report complete** *June 2016*

APPENDIX B: SCHEDULE OF EVENTS

	Baseline	Implant	Month 1	Months 6 and every 6 Months thereafter until Study Termination
Procedures	**Visit 1**	**Visit 2 (≤ 2 weeks of Visit 1)**	**Visit 3 (30 ± 7 days)**	**Visits 4-7 or Study Termination (± 30 day window)**
Informed Consent	X			
Serum or Urine Pregnancy Test	X[1]			
Demographics	X			
Past Medical & Surgical History	X			
Blood Chemistry (including Creatinine and BUN)	X			
Creatinine	X		X	X
Inclusion/Exclusion Criteria Review	X	X		
GFR	X			
INR (if indicated)		X		
Swan-Ganz measurement		X		
Physical Examination (including weight)	X[2]	X(Abbreviated PE)[3]	X[3]	X[3]
NYHA HF Classification	X	X	X	X
Pulmonary Artery Angiography		X		
Sensor Implant		X		
Sensor Measurements		X		
HF Sensor Support Questionnaire	X			
Adverse Events Assessment	X	X	X	X
Medication Assessment	X	X	X	X

[1] Females of child bearing potential
[2] Includes weight, height and vital signs (temperature, blood pressure, pulse, respirations).
[3] Includes weight, vital signs and significant changes since Enrollment

APPENDIX C: NYHA FUNCTIONAL CLASSIFICATION FOR HEART FAILURE

The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying heart disease (originally cardiac failure), useful for pre operative and post operative assessment. It places subjects in one of four categories, based on how much they are limited during physical activity:

Class I (Mild): Subjects with no limitation of activities; they suffer no symptoms.

Class II (Mild): Subjects with slight, mild limitation of activities and suffer mild symptoms (slight swelling of extremities).

Class III (Moderate): Subjects with marked limitation of activity; they are comfortable only at rest.

Class IV (Severe): Subjects who are unable to do any physical activity without discomfort; they suffer with HF symptoms at rest and are confined to bed or chair.

APPENDIX D: MANAGEMENT OF HEMODYNAMIC PARAMETERS

The Champion HF Monitoring System allows intermittent assessment of pulmonary artery systolic, diastolic and mean pulmonary artery pressures**.** Hemodynamic information obtained by the system should be used for the basis of clinical decision making in addition to symptoms, weights or physical examination (traditional markers of volume).

Guidelines for managing heart failure using pulmonary artery pressures

Pulmonary Artery Pressure Ranges:

PA Systolic	15 - 35 mmHg
PA Diastolic	8 - 20 mmHg
Mean PA pressure	10 - 25 mmHg

An elevation of pressures beyond these reference ranges should be considered a volume overloaded status. Diuretic therapy should be adjusted to reduce these pressures to within pressure goals unless the following occurs:

1. Serum creatinine increases by 20%
2. If systemic systolic blood pressure drops by 20 mmHg when changing from supine to a standing position
3. Symptomatic systemic hypotension

If diuresis causes the above mentioned clinical events and the pulmonary pressures stay higher than the reference range, the suggestion is to attempt to reduce the pulmonary pressures with vasodilator therapy, primarily using long-acting nitroglycerin therapy as needed. If the pressures are outside the reference range after vasodilator therapy and maximally tolerated diuretics, then other etiologies should be investigated. If the pressures remain high after the above steps are taken, then the reference ranges may be reset for the individual patient and the new values should be considered “optivolemic”. Medication adjustments and patients’ responses must be documented prior to changing the goal ranges.

Diuretics and vasodilators should be adjusted based on the subject’s baseline diuretic requirement, knowledge of the subject’s prior response to these agents, and clinician judgment to accomplish the pressure goals set forth in this guideline. Consultation with the national PI’s is encouraged to optimize the success of medical management of PA pressures.

A decrease in the pulmonary pressures below the established ranges should be considered a volume depletion event and diuretic therapy should be held and chronic dose should be lowered.

In addition to these specific guidelines, the investigator should also incorporate the recommendations set forth in the AHA 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in the Adult.

Opti-volemic

Opti-volemic Definitions

- Subject symptoms: minimal symptoms and minimal evidence of poor perfusion
- Invasive Hemodynamic Monitoring:
- Pulmonary artery systolic pressure 15 – 35 mmHg
- Pulmonary artery diastolic pressure 8 – 20 mmHg
- Pulmonary artery mean pressure 10 – 25 mmHg
- Champion HF Monitoring System Parameters:

The initial parameters will be set to the above values. After all guidelines for managing HF using pulmonary artery pressures as described on the previous page have been implemented and documented, the Investigator may reset the values to an acceptable range for individual subjects and establish the range in mmHg in the secure website.

Opti-volemic Treatment Recommendations

- No medication changes based on hemodynamic data obtained from the Champion HF Monitoring System
- Baseline chronic aggressive therapy (reduced LVEF)
    a. ACE inhibitor (ARB or other vasodilator if ACE not tolerated) to target dose
    b. Digoxin, diuretic and electrolyte replacement advised
    c. Consider spironolactone as indicated in subjects with stable renal function and potassium handling
    d. Nitrates to appropriate doses as tolerated
    e. Beta-blocker administration and/or uptitration according to guidelines when subject is not hypervolemic.

If the subject has signs of poor perfusion (cold), consider other interventions, such as:

a. Admission for monitoring and further adjustment of medical management
b. Intravenous (IV) pharmacotherapy
c. Increase vascular volume if still without evidence of congestion at rest
d. Consider invasive hemodynamic monitoring for determination of Cardiac Output if indicated

Hyper-volemic

Hyper-volemic Definitions

- Subject symptoms: Congestive symptoms (wet)
- Champion HF Monitoring System Parameters: above the pre-determined opti-volemic range
- Daily trends: elevated trend data outside the pre-determined opti-volemic range
- Weekly trends: elevation in trend data

Hyper-volemic Treatment Recommendations

- Add or increase diuretic (and appropriate electrolyte replacement)
  a. Increase or add loop diuretic
  b. Change to another loop diuretic
  c. Add thiazide diuretic (with caution)
  d. IV doses of loop diuretic
  e. Serum electrolyte evaluation with change in baseline medication
  f. Re-assess pulmonary artery pressure utilizing the Champion HF Monitoring System at least 2 – 3 days per week until optivolemic
- Add or increase nitrates
- Start or re-educate in salt intake and fluid restriction
- If subject has signs and symptoms of poor perfusion (cold) in addition to being hyper-volemic:
  a. Consider admission if clinical evidence suggests need for IV diuretics, telemetry monitoring or the IV therapeutic agents
  b. Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated

Hypo-volemic

Hypo-volemic Definitions

- Subject symptoms: poor perfusion in absence of signs and symptoms of congestion
- Champion HF Monitoring System Parameters: below the pre-determined opti-volemic range
- Daily trends: decrease in trend data outside the pre-determined opti-volemic range
- Weekly trends: decrease in trend data

Hypo-volemic Treatment Recommendations

- Lower or discontinue diuretic
  a. If on a thiazide diuretic with loop diuretic, lower or discontinue the dose of thiazide (and adjust electrolyte replacement)
  b. If on only loop diuretic, lower the dose or discontinue
  c. Consider liberalization of oral fluid restriction and salt restriction
- If postural hypotension, hold or lower vasodilators and/or oral nitrates, especially if hypotensive when sitting or supine
- If worsening renal function, hold or lower ACE/ARB dose, especially if hypotensive
- If subject had signs and symptoms of poor perfusion (cold) in addition to being hypo-volemic:
  a. Consider admission if clinical evidence suggests need for IV fluid repletion, telemetry monitoring or the use of IV therapeutic agents
  b. Consider invasive hemodynamic monitoring for determination of Cardiac Output, if indicated

Recommended Frequency of Champion HF Monitoring System Review

Subject Status	Weekly	At least 2– 3 times per week until optivolemic	At least 2 – 3 times per week until pressure stabilizes
Opti-volemic	X		
Hyper-volemic		X	
Hypo-volemic		X	
Medication modifications			X
Significant deviations in trend data			X

APPENDIX E: BMI CALCULATOR

To calculate subjects Body Mass Index using the website below:

http://www.nhlbisupport.com/bmi/bmi-m.htm

Enter the subjects Weight and Height and then calculate BMI (print screen for source documentation)

Formulas used to calculate Body Mass Index:

English BMI Formula
BMI = Weight in pounds/ (height in inches x height in inches) x 703

Metric BMI Formula
BMI = Weight in kilograms/ (height in meters x height in meters)

Note that BMI may also be calculated within the eCRF.

APPENDIX F: GLOMERULAR FILTRATION RATE

To calculate subjects Glomerular Filtration Rate use the website below:

http://www.nephron.com/cgi-bin/CGSI.cgi

Enter the subjects Creatinine level, Age, Race, Gender then calculate (print screen for source documentation)

GFR (mL/min/1.73 m^2) = 186 x$(S_{cr})^{-1.154}$ x $(Age^{)-0.203}$ x (0.742 if female) x (1.210 if African American)

Note that GFR may also be calculated within the eCRF.

APPENDIX G: PROTOCOL DEFINITIONS

Enrollment – After meeting study inclusion criteria and following implant, subjects are considered enrolled

Hospitalization – Greater than or equal to 24 hours in a hospital

HF-related Hospitalization – hospitalization determined to be related to heart failure as determined by the CEC

PI – Appropriate clinical personal designated as the Principle Investigator on the "Investigator Agreement" received and approved by CardioMEMS

*Note: For study related procedures/visits PI refers to the PI or his/her designee.

Post-exhalation – Subjects breathing with normal rate will exhale completely, in which time pulmonary artery pressures will be obtained from a Swan-Ganz catheter and the Champion HF Monitoring System.

Premature Discontinuation – Withdrawal of a patient from the trial prior to the patient's completion of all protocol-defined visits.

Source documents – Primary study documentation including electronic, paper, phone messages, etc. containing study-pertinent information such as visit information, clinical history, medications, (S)AE reporting, etc. These documents are originals and should be treated as such. Information from these documents will be transferred from and compared against information reported in study CRFs

Sub-investigator – Clinical personnel designated as a sub-investigator on the "Investigator Agreement" received and approved by CardioMEMS

Worksheets –Source documents used for calculation of clinical values such as BMI or EGFR from screening to end of study. Worksheets may also be used during the sensor implant or follow-up visits to capture information not captured in the medical record. In order for these worksheets to be considered valid, the Investigator must sign and date the worksheet.

APPENDIX H: COMPOSITION, FUNCTION AND PROCEDURES OF THE CLINICAL EVENTS CLASSIFICATION (CEC) COMMITTEE

The hospitalizations in this study will be monitored by a Clinical Events Classification (CEC) Committee. The committee will be comprised of physicians, who will not participate in the enrollment or treatment of subjects in this trial. CardioMEMS will name individuals to the CEC and transmit their CVs to regulatory agencies, as required. The CEC members will have agreed with the study design and protocol. CEC members are independent and cannot be removed based on difference of opinion on study-related matters with CardioMEMS, Investigators, or any CardioMEMS contractor.

The members of the CEC are responsible for reviewing the safety data and providing an assessment of the data according to their individual expertise. The CEC Committee will evaluate all SAEs to determine whether or not the SAE is device / system-related.

A summary of all CEC meetings will be signed by the CEC Chair and will be provided to CardioMEMS.

The role and procedures of the CEC Committee will be finalized in the CEC charter.