Clinical Investigation Plan

SJM-CIP-10147

CardioMEMS™ HF System OUS Post Market Study

Version Number	C
Date	April 18, 2018
Coordinating Investigator	Martin Cowie, MD
Planned Number of Sites and Region(s)	85 clinical sites Outside the United States
Clinical Investigation Type	Prospective, multi-center, open-label clinical trial
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Electronic Data Capture Software	Oracle Clinical
CIP Author of Current Version	Marie-Elena Brett

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
CEC	Clinical Events Committee
CRF	Case Report Form
CRT-D	Cardiac Resynchronization Therapy Defibrillator
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HF	Heart Failure
HFH	Heart Failure Hospitalization
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IEC	Independent Ethics Committee
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NYHA	New York Heart Association
OPC	Objective Performance Criterion
PA	Pulmonary Artery
PMS	Post Market Study
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RHC	Right Heart Catheterization
RF	Radio Frequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

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2. PROTOCOL SYNOPSIS

Sponsor:	St. Jude Medical, Atlanta, GA
Protocol Title:	CardioMEMS HF System OUS Post Market Study
Document Control Number:	SJM-CIP-10147
Device:	The CardioMEMS™ HF System consists of a wireless, battery-less pressure sensor implanted into the pulmonary artery and an external electronics that powers and communicates with the sensor and transmits pulmonary artery pressure waveforms and measurements to a secure website for Investigator review and patient management.
Purpose:	The purpose of this Post Market Study (PMS) is to evaluate the use of the CardioMEMS™ HF System in patients with Class III Heart Failure in a real-world setting.
Objective:	The objective of this PMS is to confirm safety and effectiveness in a real-world setting.
Study Population:	Adults with New York Heart Association (NYHA) Class III Heart Failure (HF) who have experienced a heart failure hospitalization within the past 12 months. The patients will serve as their own historical controls for effectiveness (1 year prior to implantation). All subjects who sign the informed consent form and satisfy the inclusion/exclusion criteria. Ejection fraction data must be taken within the last 6 months or prior to implantation.
Study Design:	This is a prospective, multi-center, open-label trial conducted in centers located outside of the United States (US). All subjects who sign the informed consent form and satisfy the inclusion/exclusion criteria will be enrolled into the CardioMEMS™ HF System PMS and will be scheduled for follow-up visits at 1 month and every 6 months for 2 years. Following sensor implant and hospital discharge, subjects will take PA pressure measurements on a daily basis, or as directed by the investigator. These measurements will be automatically transmitted to the secure patient database (Merlin.net website).
Timeline:	Study visits will be scheduled at Month 1, Month 6, and every 6 months thereafter for 2 years or until study termination.

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Number of Subjects	Up to 800 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 up to 85 sites.
Safety Measures:	Primary safety endpoints will be evaluated at 2 years: 1) freedom from device/system related complications and 2) freedom from pressure sensor failure. Safety will also be assessed throughout the study by the frequency of Adverse Device Effects (ADEs), Serious Adverse Events (SAEs), and Serious Adverse Device Effects (SADEs).
Effectiveness Measures:	The primary effectiveness endpoint is the annualized HF hospitalization rate at 1 year. Supplemental analyses include mortality at 1 year, HF hospitalization or death at 1 year, patient compliance over the trial, training evaluation, and subgroup analyses. Information regarding all hospitalization and deaths will be collected throughout the study.
Statistical Considerations:	Primary Safety Endpoints The primary safety hypotheses are that the device / system-related complication-free proportion of subjects will be at least 80% at 24 months (OPC used in the CHAMPION trial) and that the pressure sensor failure-free proportion of subjects will be at least 90% at 24 months (OPC used in the CHAMPION trial). Plotting and analysis of safety endpoints will also be displayed using Kaplan-Meier methods. All safety analyses will be performed on the safety population. Primary Effectiveness Endpoint The primary effectiveness evaluation will compare the annualized HF hospitalization rate at 1 year compared to the HF hospitalization rate in the year prior to enrollment. The effectiveness population consists of all subjects who received a sensor implant regardless of study completion status. Supplemental Analyses Mortality at 1 year will be analyzed. Plotting and analysis of mortality will be displayed using Kaplan-Meier methods. The annualized HF hospitalization or death rate at 1 year in study will be compared to the HF hospitalization rate in the year prior to enrollment.

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	Patient compliance over the trial will be examined. The total number of PA pressure readings taken will be reported as a percentage of patient days at home. Effectiveness analyses will be performed by the following subgroups: Women, Men, Reduced Ejection Fraction (< 40%), Preserved Ejection Fraction (≥ 40%), Ischemic Etiology, Non-ischemic Etiology, With ICD/CRT-D, and Without ICD/CRT-D. Frequency, purpose and outcome of all contacts made between site staff and implanted subjects post the implant visit will be examined.
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3. BACKGROUND AND RATIONALE

3.1. Introduction

Heart failure (HF) is a clinical syndrome characterized by frequent hospitalization, poor quality of life, multiple comorbidities, high mortality and a complex therapeutic regimen. Affected individuals have a variety of symptoms such as dyspnea, fatigue, limited exercise tolerance, fluid retention, pulmonary congestion and peripheral edema. Patients suffer impairment in functional capacity and quality of life.

The incidence of HF is on the rise, affecting more than 5 million people in the US alone. Despite current guideline recommended therapies, rates of heart failure hospitalization remain high. Heart failure is the primary diagnosis in >1 million hospitalizations annually. Patients hospitalized for HF are at high risk for all-cause re-hospitalization, with a 1-month readmission rate of 25% (Go, et al., 2013).

3.2. CHAMPION Trial Results

The CHAMPION trial demonstrated that management of heart failure using pulmonary artery pressure information obtained with the CardioMEMS HF System, in addition to traditional signs and symptoms, reduced HF hospitalizations.

The CHAMPION trial was conducted at 64 U.S. centers and enrolled 550 patients with NYHA Class III heart failure who had been hospitalized for heart failure in the previous year. All patients were implanted with a sensor and then randomized to Treatment (heart failure management on the basis of pulmonary artery pressure and standard of care) or Control (heart failure management on the basis of standard of care). CHAMPION met its primary endpoint of reduction in the rate of heart failure hospitalizations at 6 months with Treatment patients having 28% fewer heart failure hospitalizations compared to Control patients; benefit was sustained with a 37% reduction in heart failure hospitalizations over the full randomized study duration (Abraham, et al., 2011). All secondary endpoints were met with reduction in pulmonary artery pressures, reduction in proportion of patients hospitalized for heart failure, increase in days alive outside the hospital and improved quality of life.

The CardioMEMS™ HF System received CE Mark in 2011 and the current certificate was issued by BSI on May 1st 2014. The system received Food and Drug Administration (FDA) approval on May 28th 2014 for use in the United States.

3.3. Indication for Use

The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and with the goal of reducing heart failure hospitalizations.

3.4. CardioMEMS™ HF System

The CardioMEMS™ HF System provides pulmonary artery (PA) hemodynamic data used for the monitoring and management of heart failure (HF) patients. The system measures changes in PA pressure which physicians use to initiate or modify heart failure treatment.

The system includes the following components:

- Implantable wireless sensor with delivery catheter
- Patient or hospital electronics system
- Patient database (Merlin.net Website)

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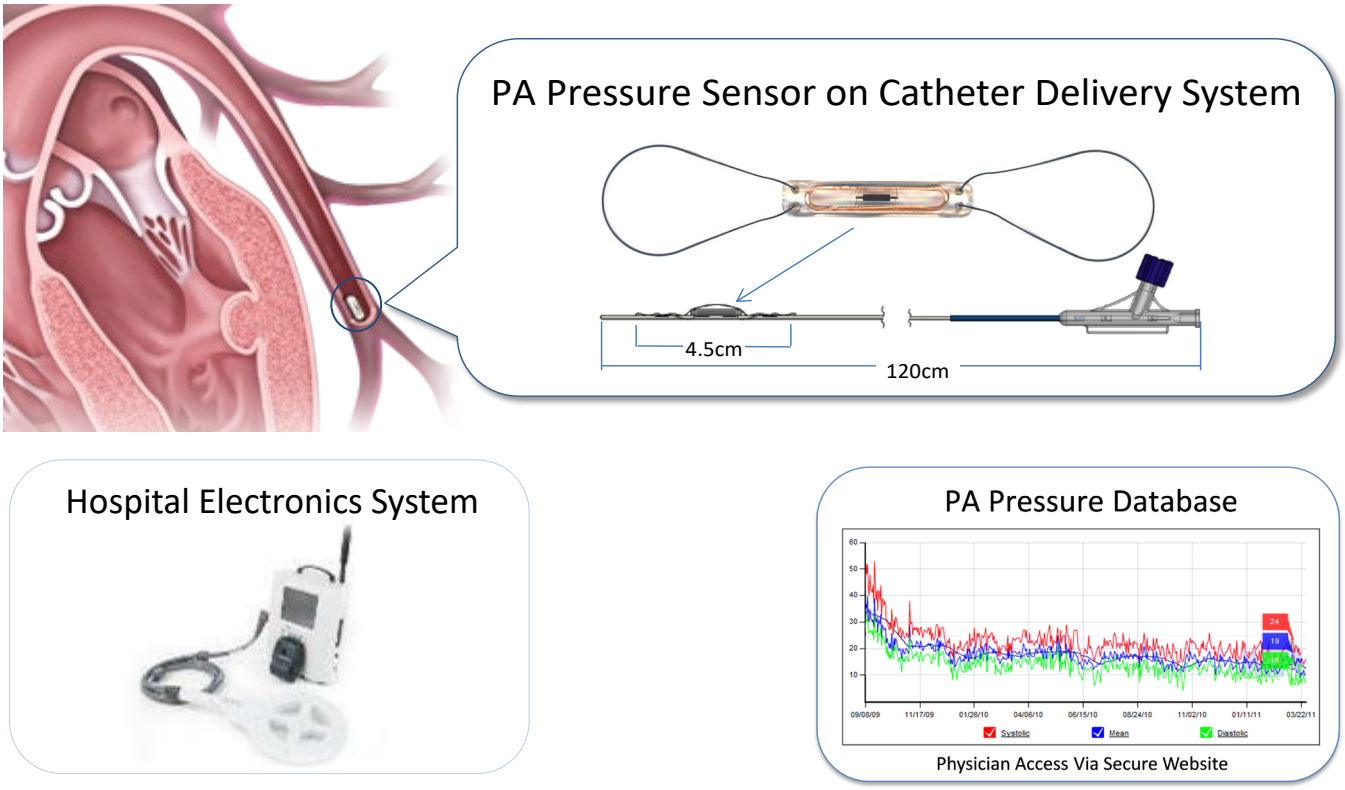
Figure 1. CardioMEMS HF System



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; the sensor baseline is set to the mean PA pressure using a pulmonary artery catheter. Daily PA hemodynamic measurements are taken by the patient in a supine position at home. The patient measurement system consists of an 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 is transmitted to the website which is accessible via a secure website to the patient's physician or nurse.

Implantable Sensor

The sensor measures pulmonary artery pressure using MEMS (micro-electromechanical systems) technology and requires neither batteries nor leads. It is silicon wafer fabricated and measures 15 mm in length, 3.4 mm in width and 2 mm in thickness. The sensor is permanently implanted in a branch of the left or right pulmonary artery via a catheter. The Patient Electronics Unit provides both wireless communication and power to the sensor.

Implantable Sensor Delivery System

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The sensor is tethered to an over-the-wire delivery catheter. A right heart catheterization is performed, and a hand injected selective pulmonary angiogram is performed via the pulmonary artery catheter to define the distal pulmonary artery branch anatomy. A 0.018" guidewire is then advanced through the pulmonary artery catheter into the distal pulmonary artery. The pulmonary artery catheter is removed, and the delivery system is advanced over the guidewire. Once it is optimally positioned, the sensor is separated from the delivery system by releasing the tether wires and delivery system is then removed.

Patient Electronics System

The electronics unit uses an antenna to transmit low power pulses of radiofrequency energy to power and communicate with the sensor. The electronics unit transmits the PA pressure information to the Merlin.net website.

Merlin.net website

The Merlin.net website provides a secure user interface through a website for the clinician to review the PA pressure data from the CardioMEMS HF System.

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4. STUDY OBJECTIVE

The objective of this Post Market Study is to provide safety and effectiveness data regarding the use of the CardioMEMS™ HF System in a commercial setting

5. STUDY DESIGN

This is a prospective, multi-center, open-label clinical trial to be conducted up to 85 sites in centers located outside of the US.

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. Note that for study related procedures/visits Investigator refers to the Principal Investigator or designee.

Eligible subjects will be scheduled for the Implant procedure (PA sensor implant in conjunction with a RHC procedure).

Subjects must also have an appropriately sized (≥7mm diameter) pulmonary artery branch identified by a selective pulmonary angiogram prior to Sensor implant. Subjects who do not meet this inclusion criteria will be documented as consented not implanted and will be followed for 30 days for safety.

Prior to hospital discharge, subjects will be trained on the home monitoring system and instructed to take pulmonary artery pressure measurements daily or as directed by their physician. Subjects will be supplied with a patient implant identification card, a Patient System Manual, and a Helpline phone number.

After discharge, the subject will take PA pressure measurements at home, as directed by the investigator, utilizing the CardioMEMS HF System. These measurements will be transmitted via modem to a secure data base. Patient compliance will be monitored by the sponsor and reported to the Investigator.

The Investigator or designee will review the PA pressure measurements transmitted from the home monitoring unit. Pressure thresholds are automatically set as described in Appendix C. These threshold notifications are intended to guide the Investigator to review the Merlin.net website. If the PA pressures are elevated or low, the Investigator or designee should make medication changes according to the guidelines in Appendix C. The Investigator or designee will review the PA pressure measurements on a weekly basis at a minimum and appropriately utilize the information obtained to assist in the clinical management of subjects. Weekly logins to the database will be monitored by the sponsor. Reminders will be sent to the clinical sites if there are no logins noted during the course of a 7 day window. Clinical and technical support will be available to the Investigator as needed.

- Follow-up study visits will be scheduled at Month 1, Month 6, and every 6 months thereafter for 2 years. Follow-up visits will include a physical exam, evaluation of NYHA Class (Appendix B), AE assessment, heart failure medications review, quality of life assessment, and assessment of any hospitalizations (including HF hospitalizations), that may have occurred between visits.

In addition, all contacts between site staff and study subjects post implant will be recorded on a log to capture frequency, purpose and outcome of each contact.

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6. STUDY POPULATION

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

6.1. Inclusion Criteria

1. Written informed consent obtained from subject
2. ≥ 18 years of age
3. Diagnosis of NYHA Class III Heart Failure
4. At least 1 HF hospitalization within 12 months of Baseline visit
5. Subjects with reduced LVEF heart failure should be receiving a beta blocker for 3 months and an ACE-I or ARB for one month unless in the investigator's opinion, the subject is intolerant to beta blockers, ACE-I or ARB.
6. Subjects with a BMI ≤ 35. Subjects with BMI >35 will require their chest circumference to be measured at the axillary level, if > 65 inches the patient will not be eligible for the study.
7. Subjects with pulmonary artery branch diameter ≥ 7mm - (implant target artery - assessed during the RHC)
8. Subjects willing and able to comply with the follow-up requirements of the study

6.2. Exclusion Criteria

1. Subjects with an active infection
2. Subjects with history of recurrent (> 1) pulmonary embolism or deep vein thrombosis
3. Subjects who, in the Investigator's opinion, are unable to tolerate a right heart catheterization
4. Subjects who have had a major cardiovascular event (e.g., myocardial infarction, open heart surgery, stroke, etc.) within 2 months of Baseline Visit
5. Subjects with Cardiac Resynchronization Device (CRT) implanted < 3 months prior to enrollment
6. Subjects with a Glomerular Filtration Rate (GFR) < 25 ml/min (obtained within 2 weeks of the baseline visit) 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 likely to undergo heart transplantation or VAD within 6 months of baseline visit
9. Subjects with known coagulation disorders
10. Subjects with a hypersensitivity or allergy to aspirin, and/or clopidogrel (not applicable for subjects taking anti-coagulation therapy or other approved anti-platelets therapy).

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7. STUDY OR SITE TERMINATION

The Sponsor or the Investigator has the right to discontinue the study at any time. As much as possible, this should occur after mutual consultation. The Investigator (or sponsor, where appropriate) is responsible for informing the Independent Ethics Committee (IEC) 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 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 IEC under investigation

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8. STUDY PROCEDURES

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 A for the Schedule of Events).

8.1. Screening Visit

During the screening visit, the following procedures/assessments will be performed to determine subject eligibility:

- Informed Consent prior to the conduct of any study-related procedures
- Physical examination including vital signs (temperature, heart rate, blood pressure), weight, height, BMI calculation (refer to Appendix D)
- Medical and surgical history including ejection fraction data must be taken within the last 3 months to enroll in the study. If ejection fraction data is older than six months, ejection fraction data is required to be obtained at screening visit or prior to implantation.
- Patient history of all heart failure hospitalizations in the 12 months previous to the baseline visit as documented with information provided by the patient's cardiologist, internist, or referring physicians and review of all source documents of any heart failure hospitalizations reported in the previous year.
- Demographics
- NYHA Functional Classification
- Calculation of GFR (requires creatinine - refer to Appendix E)
- Assessment of medications
- Assessment of enrollment eligibility (inclusion/exclusion criteria)
- Completion of Quality of Life Questionnaire EQ-5D-5L

Eligible subjects will be scheduled for the Implant procedure. Subjects on anticoagulation therapy (e.g. warfarin) may 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.

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8.2. Right Heart Catheterization and Implant Procedure (Baseline Visit)

Before the RHC, the following procedures/assessments will be performed:

- Abbreviated physical examination (i.e., vital sign assessments and significant changes since Screening Visit) and weight
- Confirmation of enrollment eligibility (other than angiographic criteria)
- PT/PTT with International Normalized Ratio (INR) per institution standards for subjects previously on warfarin
- Assessment of heart failure medications
- Record any changes in medical history that occurred since screening visit.

The patient will then undergo a standard RHC. A selective, hand injected pulmonary angiogram will be performed via the pulmonary artery catheter to identify a suitable pulmonary artery branch for sensor implantation. Subjects must have an appropriately sized (≥ 7mm diameter) pulmonary artery branch. These procedures are considered standard of care for the sensor implant and are described in the User Manual. Subjects who do not meet this inclusion criterion will not receive the PA 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. Patients with a suitable target pulmonary artery branch will undergo:

- Wireless implantable hemodynamic sensor implant
- Pulmonary artery catheter measurements (pulmonary systolic, pulmonary diastolic, heart rate, pulmonary mean, cardiac output) done 3 times consecutively with sensor measurements for setting of sensor baseline.
- Provide post-procedure vascular access site care per standard procedure
- At the Investigator's discretion, subjects should be discharged once stable with respect to the procedure and their heart failure.
- Please see User's Manual for implant details

Subjects who are currently on anticoagulant therapy (warfarin or other approved anticoagulants) will restart treatment. The subject's INR should be checked per the institutions standards. Those subjects not on chronic warfarin will be placed on aspirin and clopidogrel or other approved anti-platelet daily for 1 month starting on the day of Sensor placement. Any approved anticoagulant or anti-platelet therapy may be used as well. After 1 month, the subject will continue with aspirin therapy and clopidogrel (or other approved anti-platelet therapy) will be discontinued.

8.3. Study Follow-Up Visits 1, 2, 3, 4, and 5 (Months 1, 6, 12, 18, and 24)

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Implanted subjects will be evaluated at Month 1 (± 7 days) and at Months 6, 12, 18, and 24 (± 30 days) and the following procedures/assessments will be performed:

- Updated medical and surgical history
- Assessment of SAEs, ADEs, and SADEs that occurred since the last visit
- Reporting of any HF hospitalizations that have occurred since the last visit
- Abbreviated physical examination (significant changes since previous visit) including vital signs (heart rate, blood pressure), and weight
- Assessment of NYHA functional class
- Completion of Quality of Life Questionnaire EQ-5D-5L (6, 12, 18, and 24 month visits)
- Heart failure medication review
- PA pressure measurements may be obtained at the Investigator's discretion

Subjects will be reminded to obtain pulmonary artery pressure measurements utilizing the CardioMEMS HF System as directed. Subjects will be reminded of the current ACC/AHA guidelines or of the ESC guidelines regarding sodium and fluid restrictions.

8.4. Subject contact throughout the study

All contacts between site staff and study subjects post implant will be documented on a Subject Contact Log and the following information will be captured:

- Date of contact
- Reason for contact
- Ability to reach the subject (Call success)
- Name and role of person contacting the patient
- Call outcome (Instructions given)
- Other action required

8.5. Subject Home PA Pressure Readings

Following the sensor implant procedure, subjects will be instructed on how to take their own pulmonary artery pressure measurements, utilizing the CardioMEMS™ HF System. Subjects will provide returned demonstration 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 padded, flat antenna. It is recommended that 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 measurement.

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The home electronics system 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. St. Jude Medical will provide instructions for use and a help line will be available. Please refer to subject's Patient System Guide for more detailed information.

8.6. PA Pressure Readings in the hospital

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

Following sensor implant, subsequent RHC procedures or pulmonary artery catheter insertions must be performed under fluoroscopic guidance.

Resetting of the sensor baseline will be performed as deemed necessary by Sponsor. Baseline resetting may require an echocardiogram or a RHC procedure.

Following the sensor implant, should a RHC procedure or PA catheter evaluation be clinically warranted, comparative pulmonary artery pressures utilizing the CardioMEMS™ HF System should also be obtained utilizing the hospital electronics unit.

8.7. 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 that other treatment is warranted to protect the health and safety of the subject
3. Investigator determines that the 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 (e.g., 2 – 3 phone calls, followed by 1 certified letter, documentation of repetitive missed study visits, etc.)

The Investigator will notify the Sponsor and document on the appropriate CRF the reason/circumstances for early discontinuation. All subjects who withdraw from the study should have the following study exit procedures performed if possible:

- Assessment of SAEs, ADEs, and SADEs, that occurred since the last visit
- Reporting of any HF hospitalizations that have occurred since the last visit
- Abbreviated physical examination (only significant changes since Enrollment) including vital signs (temperature, heart rate, blood pressure), and weight
- Assessment of NYHA functional class
- Heart failure Medication Review
- PA pressures may be obtained at the Investigator's discretion

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All reasonable efforts should be made to retain subjects in the clinical trial until its completion. If a patient moves from the geographic area of their investigator, St. Jude Medical will attempt to place the patient with another investigator.

8.8. Deviations from CIP

A deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. The investigator should not deviate from the CIP.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects; such non-compliance exposes subjects to unreasonable risks. Examples: failure to adhere to the inclusion/exclusion criteria, failure to report SAEs within given timeframe as per CIP, etc. Investigators should seek to minimize such risks by adhering to the CIP.

The PI must maintain accurate, complete, and current records, including documents showing the date of and reason for each deviation from the CIP. Relevant information for each deviation will be documented as soon as possible on the applicable CRF. The site will submit the CRF to the Sponsor.

The PI is required to adhere to local regulatory requirements for reporting deviations to the site IEC.

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9. SAFETY ANALYSES

9.1. Primary Safety Endpoints

Primary safety endpoints will be evaluated at 2 years:
1) Freedom from device/system related complications
2) Freedom from pressure sensor failure

9.1.1. Device / System-related Complication Criteria

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 has at least one of the following characteristics:

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

9.1.2. Sensor Failure Criteria

A Sensor failure occurs when no readings can be obtained from it after troubleshooting the system to rule out any problems with the external electronics.

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10. EFFECTIVENESS ANALYSES

10.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint will compare the annualized HF hospitalization rate at 1 year in the study to the HF hospitalization rate in the year prior to enrollment.

10.2. Supplemental Analyses

10.2.1. Mortality

The mortality rate at 1 year in study will be analyzed.

10.2.2. HF Hospitalization or Death

The annualized HF hospitalization or death rate at 1 year in the study will be compared to the HF hospitalization rate in the year prior to enrollment.

10.2.3. Patient Compliance

Patient device usage over the course of the trial will be examined.

10.2.4. Quality of Life Evaluation

Quality of Life will be measured using the EuroQOL Five Dimensions Questionnaire (EQ-5D-5L).

10.2.5. Subgroup Analyses

The effectiveness analyses will be evaluated in each of the following subgroups: Women, Men, Reduced Ejection Fraction (< 40%), Preserved Ejection Fraction (≥ 40%), Ischemic Etiology, Non-ischemic Etiology, With ICD/CRT-D, and Without ICD/CRT-D.

10.2.6. Subject Contact

Frequency, purpose and outcome of all contacts between site staff and study subjects post implant will be examined.

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11. ADVERSE EVENTS

11.1. Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation.

Note 1: This definition includes events related to the medical device under investigation or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to medical devices under investigation.

11.2. Serious Adverse Event (SAE)

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,

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

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function, or
3. in-patient hospitalization or prolongation of existing hospitalization, or
4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
5. chronic disease

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

Note: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

11.3. Device-Relatedness

An AE or SAE that is definitely or possibly related to the device or the insertion procedure should be considered device-related. A serious adverse device effect (SADE) is an event that meets any of the above SAE criteria and is considered definitely or possibly related to the device or the insertion procedure by the Investigator. All other events considered definitely or possibly related to the device or insertion procedure are non-serious adverse device effects (ADEs).

If it is not certain that an event meets the above definitions, contact the Study Manager.

11.4. Device Deficiency

Device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Device deficiencies will not be collected on the case report forms for this study.

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All device deficiencies should be reported to Sponsor via email: CardioMEMS_Complaints@sjm.com or contacting your local representative (Australia, Canada, and New Zealand can report deficiencies by calling 1- 877-696-3754, European Countries can call +46 847 44147.

11.5. Procedures for Reporting Adverse Events

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical investigation. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical study or the subject withdraws from the clinical study. All ADEs, SAEs, and SADEs, including deaths, will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF.

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local EC according to the institution's EC reporting requirements.

11.6. Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs, SADEs and ADEs to the country regulatory authority, per local requirements.

11.7. Anticipated Adverse Events

Risks associated with the CardioMEMS™ PA Sensor or the implant procedure (in conjunction with RHC) or post-implantation complications, together with their likely incidence, are described in the User's Manual.

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12. STATISTICAL ANALYSIS

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 for continuous or categorical variables, respectively.

The primary time point for safety analyses is 24 months post enrollment. Enrollment is defined as having a successful Sensor implant. The primary time point for effectiveness analyses is 12 months post enrollment.

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

12.1. 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, 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 and did not receive the 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.

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

Pooled Safety Population: The Pooled Safety Population will consist of the Safety Population from this study and the Safety Population from other similar study(ies) (demonstrated to be poolable with this study) that have been combined to form a larger safety analysis population to permit more robust analyses.

Pooled Effectiveness Population: The Pooled Effectiveness Population will consist of the Effectiveness Population from this study and the Effectiveness Population from other similar study(ies) (demonstrated to be poolable with this study) that have been combined to form a larger effectiveness analysis population to permit more robust analyses.

12.2. Sample Size Considerations

Effectiveness Sample Size Determination
For the primary effectiveness endpoint of HF hospitalization rate during 1 year, 250 subjects will provide greater than 90% power to meet the efficacy goal, using a one-sample, one-sided Poisson rate test with alpha of 0.025.

The HF hospitalization (HFH) rate for Control and Treatment groups at 1 year in Part 1 of the CHAMPION trial were 0.75 and 0.52 (HFH/patient-year), respectively. For this trial, HF hospitalization rates at 1 year will be compared to the rate observed in the trial subjects 1 year prior to enrollment (i.e., 1.0 or greater). Using a one-sample, 1-sided Poisson rate test with alpha of 0.025 (equivalent to 2-sided test at alpha of 0.05) (see table below), at least 149 subjects will provide >90% power to show a difference between a Treatment rate as high as 0.75 (conservative estimate) and the subject's own

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historical rate from the year prior estimated at a minimum of 1.0. To account for early withdrawal, and to allow additional countries to enroll sufficient number of subjects each, 800 subjects will be enrolled.

Numeric Results for a One-Sample Poisson Rate Test

Null Hypothesis: λ1 ≥ λ0 Alternative Hypothesis: λ1 < λ0

Power	n	Target Alpha	Actual Alpha	λ0	λ1	Diff (λ1-λ0)	Effect Size	Beta
0.9052	36	0.0250	0.0224	1.00	0.52	-0.48	0.6656	0.0948
0.9048	42	0.0250	0.0221	1.00	0.55	-0.45	0.6068	0.0952
0.9012	55	0.0250	0.0213	1.00	0.60	-0.40	0.5164	0.0988
0.9030	73	0.0250	0.0232	1.00	0.65	-0.35	0.4341	0.0970
0.9034	102	0.0250	0.0238	1.00	0.70	-0.30	0.3586	0.0966
0.9016	149	0.0250	0.0247	1.00	0.75	-0.25	0.2887	0.0984

Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.
n is the size of the sample drawn from the population. To conserve resources, it should be small.
Alpha is the probability of rejecting a true null hypothesis. It should be small.
λ0 is the value of the population mean rate under the null hypothesis.
λ1 is the value of the population mean rate under the alternative hypothesis.
Diff is the value of λ1 - λ0, the difference being tested.
Effect Size is the value of (λ1 - λ0) / √(λ1).
Beta is the probability of accepting a false null hypothesis. It should be small.

12.3. Safety Sample Size Determinations

The freedom from device-related complications observed in CHAMPION over 2 years was 98.6%. For the two-year primary safety endpoint of freedom from device-related complications, using an exact one-sided test for one-sample binomial proportions with alpha of 0.025 (equivalent to 2-sided test at alpha of 0.05) (see table below), a sample size of 137 subjects will provide greater than 90% power to detect a difference as small as 10% from the null proportion rate of 0.80 (i.e., objective performance criterion of 80%). For sensor failures at 2 years, a sample size of 292 subjects provides greater than 90% power to detect a difference as small as 5.0% from the null proportion rate of 0.90 (i.e., objective performance criterion of 90%)(see table below).

To account for early withdrawal, and to allow additional countries to enroll sufficient number of subjects each, 800 subjects will be enrolled.

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Tests for One Proportion - Freedom from Device-related Complications

Numeric Results for Testing One Proportion using the Exact Test
Alternative Hypothesis: One-Sided (H0: P ≤ P0 vs. H1: P > P0)

Power*	n	Proportion Given H0 P0	Proportion Given H1 P1	Difference P1-P0	Target Alpha	Actual Alpha*	Reject H0 If R ≥
0.91001	137	0.8000	0.9000	0.1000	0.0250	0.0245	119
0.90023	107	0.8000	0.9100	0.1100	0.0250	0.0233	94
0.90756	88	0.8000	0.9200	0.1200	0.0250	0.0238	78
0.92186	75	0.8000	0.9300	0.1300	0.0250	0.0243	67
0.92273	62	0.8000	0.9400	0.1400	0.0250	0.0238	56
0.90933	48	0.8000	0.9500	0.1500	0.0250	0.0248	44
0.91958	41	0.8000	0.9600	0.1600	0.0250	0.0244	38
0.91882	34	0.8000	0.9700	0.1700	0.0250	0.0226	32
0.90520	26	0.8000	0.9800	0.1800	0.0250	0.0227	25

* Power and actual alpha were computed using binomial enumeration of all possible outcomes.

Tests for One Proportion – Freedom from Sensor Failures

Numeric Results for Testing One Proportion using the Exact Test
Alternative Hypothesis: One-Sided (H0: P ≤ P0 vs. H1: P > P0)

Power*	n	Proportion Given H0 P0	Proportion Given H1 P1	Difference P1-P0	Target Alpha	Actual Alpha*	Reject H0 If R ≥
0.90193	292	0.9000	0.9500	0.0500	0.0250	0.0242	273
0.91154	193	0.9000	0.9600	0.0600	0.0250	0.0242	182
0.91132	127	0.9000	0.9700	0.0700	0.0250	0.0250	121
0.90879	85	0.9000	0.9800	0.0800	0.0250	0.0245	82
0.96665	70	0.9000	0.9900	0.0900	0.0250	0.0242	68

* Power and actual alpha were computed using binomial enumeration of all possible outcomes.

Report Definitions
Power is the probability of rejecting the null hypothesis when it is false. It should be close to one.
n is the size of the sample drawn from the population. To conserve resources, it should be as small as possible.
P0 is the value of the population proportion under the null hypothesis.
P1 is the value of the population proportion under the alternative hypothesis.
P1-P0 is the difference to be detected by the study.
Alpha (significance level) is the probability of rejecting the null hypothesis when it is true. It should be small.
Target Alpha is the significance level that the study design is meant to achieve.
Actual Alpha is the significance level that is actually achieved by the design.
Reject H0 If... gives the critical value(s) for the test.

References for Sample Size Calculations

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12.4. Missing Data

Missing data will be tracked in the Electronic Data Capture system; queries will be generated and provided to the site. In addition, St. Jude Medical representative, or designee will routinely perform remote data check and on site monitoring per monitoring plan. Data queries will be addressed until resolution. Missing data that are not resolved will not be imputed unless specified below.

12.5. Subject Accountability and Baseline Information

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

12.6. 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.

12.7. Safety Analyses

The safety analyses will be performed using the Safety Population. 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.

12.7.1. Primary Safety Endpoints

The primary safety analysis will be based on the following objective performance criteria: the lower limit of the one-sided 97.5% confidence interval on the freedom from device / system-related complication rate at 24 months is greater than 80% and b) the lower limit of the one-sided 97.5% confidence interval on the freedom from pressure sensor failure rate at 24 months is greater than 90%. 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., $p<0.025$).

Mathematically stated, the primary safety hypotheses are:

H_0: $P_{\text{(Freedom from device / system-related complications at 24 months)}} \leq 80\%$

H_a: $P_{\text{(Freedom from device / system-related complications at 24 months)}} > 80\%$

a) H_0: $P_{\text{(Freedom from pressure sensor failure at 24 months)}} \leq 90\%$

H_a: $P_{\text{(Freedom from pressure sensor failure at 24 months)}} > 90\%$

Plotting and analysis of safety endpoints will also be displayed using Kaplan-Meier methods.

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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 serious adverse device effects (USADEs), and device / system-related complications by relationship to the device via Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Physical examination, and subject survival data through 24 months will be tabulated across study period assessments.

12.8. Effectiveness Analyses

Effectiveness analyses will be conducted in the effectiveness population. 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.

12.8.1. Primary Effectiveness Endpoint

The primary time point for analyses is 12 months post-enrollment. The primary effectiveness endpoint will compare the annualized HF hospitalization rate parameter, γ, at 1 year versus the HF hospitalization rate in the year prior to enrollment using a one-sample, one-sided Poisson rate test. If the one-sided, upper 97.5% confidence interval for the PMS rate parameter is less than the rate in the year prior to enrollment, then the primary effectiveness endpoint will be met.

Mathematically stated, the primary effectiveness hypothesis is:

H_0: $\gamma_{\text{(12 month HF Hospitalization Rate)}} \geq \gamma_{\text{(HF hospitalization rate in year prior to enrollment)}}$

H_a: $\gamma_{\text{(12 month HF Hospitalization Rate)}} < \gamma_{\text{(HF hospitalization rate in year prior to enrollment)}}$

where $\gamma_{\text{(12 month HF Hospitalization Rate)}}$ = the HF hospitalization rate parameter at 1 year in the PMS and $\gamma_{\text{(HF hospitalization rate in year prior to enrollment)}}$ = the HF hospitalization rate in the year prior to enrollment.

12.8.2. Supplemental Analyses

12.8.2.1. Mortality

The mortality rate over 1 year in study will be reported. Plotting and analysis of survival data will be displayed using Kaplan-Meier methods.

12.8.2.2. HF Hospitalization or Death

The annualized HF hospitalization or death rate parameter, λ, at 1 year will be compared to the HF hospitalization rate in the year prior to enrollment using a one-sample, one-sided Poisson confidence

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interval. If the one-sided, upper 97.5% confidence interval for the PMS rate parameter is less than that in the year prior to enrollment, then the hypothesis will be met.

Mathematically stated, the hypothesis is:

H_0: $\lambda_{(12\ month\ HF\ Hospitalization\ or\ Death\ Rate)} \geq \lambda_{(HF\ hospitalization\ rate\ in\ year\ prior\ to\ enrollment)}$

H_a: $\lambda_{(12\ month\ HF\ Hospitalization\ or\ Death\ Rate)} < \lambda_{(HF\ hospitalization\ rate\ in\ year\ prior\ to\ enrollment)}$

where $\lambda_{(12\ month\ HF\ Hospitalization\ or\ Death\ Rate)}$ = the HF hospitalization or death rate parameter at 1 year in the PMS and $\lambda_{(HF\ hospitalization\ rate\ in\ year\ prior\ to\ enrollment)}$ = the HF hospitalization rate in the year prior to enrollment.

12.8.2.3. Patient Compliance

Patient device usage over the course of the trial will be examined. The total number of PA pressure readings taken will be reported as a percentage of patient days at home.

12.8.2.4. Quality of Life (QoL)

Patient improvement in Quality of Life will be reported. The difference between the Quality of Life scores at 6 months, 12 months, 18 months, and 24 months will be compared to the baseline values. Quality of Life will be measured using the EuroQOL Five Dimensions Questionnaire (EQ-5D-5L)

12.8.2.5. Subgroup Analyses

The effectiveness analyses will be evaluated in each of the following subgroups:

1) Women
2) Men
3) Reduced Ejection Fraction (< 40%)
4) Preserved Ejection Fraction (≥ 40%)
5) Ischemic Etiology
6) Non-ischemic Etiology
7) With ICD/CRT-D
8) Without ICD/CRT-D

12.8.2.6. Subject Contact

All contact between site staff and study subjects post implant will be documented and the frequency, purpose and outcome of all contacts will be examined to estimate resource utilization.

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13. DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

13.1. Data Collection and Reporting

Electronic CRFs (eCRFs) will be utilized. Site staff will enter the information required by the protocol onto eCRFs using a validated sponsor system that conforms to IEC 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 study site using an electronic data query system that includes an automated audit trail of the corrections.

Monitoring personnel of St. Jude Medical, 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.

13.2. Site Qualification

A site visit will be performed by St. Jude Medical 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.

13.3. Training

Detailed training to cover aspects of the hemodynamic management of heart failure (HF), identification of prospective patients, HF sensor implant procedures, the use of the heart failure electronic units, and the use of the Merlin.net website to view the patient's hemodynamic parameters will occur for all sites prior to enrollment of patients.

13.3.1. Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical investigation personnel will include, but is not limited to, the CIP requirements, investigational device usage, electronic case report form completion, and clinical investigation personnel responsibilities. All Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site. The CardioMEMS™ HF System physician training plan (document CL1002501) is designed to provide essential didactic and field training.

13.4. Study Monitoring

St. Jude Medical 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.

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Clinical Monitors will periodically audit 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 St. Jude Medical personnel or agents of St. Jude Medical 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).

13.5. 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.).

13.6. 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.

13.7. 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 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 government regulatory agency auditors, the Sponsor and the 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, and to other government agencies.

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14. ETHICAL CONSIDERATIONS AND STUDY ADMINISTRATION

14.1. 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 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, and by the person who conducted the informed consent discussion (Investigator or designee). The subject 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, 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 IEC.

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

The IEC must be notified of completion of the study and a final report must be provided to the 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 IEC, including a list of all reports and documents submitted. Adverse experiences which are reported to the regulatory agencies, as Expedited Safety Reports, must be submitted promptly to the IEC.

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

14.2. 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 IEC. Protocol modifications that impact subject safety or the validity of the study must be approved by the IEC and submitted to the appropriate regulatory agencies before initiation.

14.3. Retention of Records

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

14.4. 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.

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15. REFERENCES

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16. APPENDIX A: Schedule of Events

	Screening	Baseline (Implant)	Month 1	Months 6 and every 6 Months thereafter until Study Termination
Procedures	Prior to Implant	(within 30 days of Screening)	Visit 1 (30 ± 7 days)	Visits 2-5 or Study Termination (± 30 day window)
Informed Consent	X			
Demographics	X			
Past Medical & Surgical History. Ejection Fraction is part of this assessment and must be obtained within 3 months of the baseline visit or prior to implantation.	X			
Inclusion/Exclusion Criteria Review	X	X		
GFR (within 2 weeks of the implant procedure)	X			
INR (if indicated)		X		
Pulmonary artery measurement		X		
Physical Examination (including weight)	X[1]	X[2]	X[2]	X[2]
NYHA HF Classification	X		X	X
Pulmonary Artery Angiography		X		
Sensor Implant		X		
Sensor Measurements		X	X (Investigator discretion)	X (Investigator discretion)
Adverse Events Assessment		X	X	X
HF Hospitalizations	X		X	X
Quality of Life Assessment (EQ-5D-5L)	X			X (6, 12, 18, 24 months)
Medication Assessment (heart failure)	X	X	X	X
Subject Contact Log[3]			X	X

[1] Includes weight, height and vital signs (temperature, blood pressure, pulse, respirations).

[2] Includes weight, vital signs and significant changes from previous physical examination

[3] To be completed each time contact is made between the site staff and a study subject

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17. APPENDIX B: 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.

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18. APPENDIX C: Management of Hemodynamic Parameters

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

Pulmonary Artery Pressure Ranges:

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

Initially, thresholds will be set automatically at the acceptable range. The physician can adjust the thresholds specifically for each patient. These threshold notifications are intended to guide the physician to review the Merlin.net website. Every attempt should be made to keep the pulmonary artery pressures within the specified pulmonary artery pressure ranges utilizing the guidelines. In order to clinically manage patient's PA pressures, the physician must review the PA pressure measurements on a frequent basis, for example, some patients may require a daily review of their PA pressure measurements, while some patients may need a weekly review. The physician or designee has unlimited access to the Merlin.net website.

An elevation of pressures beyond the patient's pressure ranges should be considered a volume overloaded status and should be managed according to the hyper-volemic guidelines (see below). Diuretics and vasodilators should be adjusted based on the patient's baseline diuretic requirement, knowledge of the patient's prior response to these agents, and clinician judgment to accomplish the pressure goals set forth in this guideline.

A decrease in the pulmonary pressures below the patient's pressure ranges should be considered a volume depletion event and managed according to the hypo-volemia guidelines (see below) (see below). Diuretic therapy should be held and the chronic dose should be lowered.

In addition to these specific guidelines, the physician should also incorporate the recommendations set forth in the ACC/AHA 2013 Guidelines for the Diagnosis and Management of Heart Failure in the Adult or in the ESC Guidelines on Acute and Chronic Heart Failure 2016.

The PA pressure readings should be used in addition to weights, signs and symptoms, laboratory values and other traditional markers of volume in the management of heart failure. It is important to review the trend of PA pressures. As with all other diagnostic information, physicians should consider the entire medical history of each patient when initiating or modifying therapies.

Elevated PA Pressures (Hyper-volemic)

Hyper-volemic Definitions

- Subject symptoms: Congestive symptoms (wet)

- CardioMEMS HF System Parameters: above the acceptable range
- Daily trends: elevated trend data outside the acceptable range
- Weekly trends: elevation in trend data

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 CardioMEMS HF System at least 2 – 3 days per week until optivolemic
- Add or increase vasodilators including long-acting nitrates
- 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

Low PA Pressures (Hypo-volemic)

Hypo-volemic Definitions

- Subject symptoms: poor perfusion in absence of signs and symptoms of congestion
- CardioMEMS HF System Parameters: below the acceptable range
- Daily trends: decrease in trend data outside the acceptable range
- Weekly trends: decrease in trend data

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 CardioMEMS HF System Review

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

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19. APPENDIX D: 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.

20. APPENDIX E: 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.

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21. APPENDIX F: Protocol Definitions

Enrollment – After signing the Informed consent, meeting study inclusion criteria and following successful Sensor implant, subjects are considered enrolled.

HF Hospitalization – A HF hospitalization of greater than or equal to 24 hours in a hospital

Active Infection- Febrile, elevated WBC, left shift, on antibiotics, positive cultures (blood, sputum or urine).

PI – Appropriate clinician designated as the Principal Investigator on the "Investigator Agreement" received and approved by St. Jude Medical. For study related procedures/visits PI refers to the PI or his/her designee.

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 St. Jude Medical.

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.

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22. APPENDIX G: CIP Revision History

Revision History				
Amendment Number	Version	Date	Rationale	Details
Not Applicable	A	06 June 2016	First release of CIP	NA
1	B	18 July 2016	Additional data collection is added for documentation of contact between site and study subjects. This data will be used to analyze resource utilization post implant. As all data is submitted via electronic Case Report Forms (eCRFs) there is no need for the site to fax the SAE/ADE/SADE forms to SJM. There will be no Clinical Events Committee (CEC) for this study. This study will completed using only centers outside of the United States.	A Subject Contact log will be completed by the site to document the frequency, purpose and outcome of all contacts between site staff and study subjects. Removed the fax, email and telephone numbers for the reporting of adverse events. Removed references to CECs that were included in error. References to the FDA were removed where appropriate. References to the ESC guidelines were added Removed legal representative

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			Informed consent process Ethics approval Adverse event definition revised For unexpected serious adverse device effect, the term UADE is used for studies following FDA regulations and USADE for studies following ISO 14155 regulations Reporting SAE, ADE, SADE timelines revised Revise the anticipated adverse events list to ensure consistency between study documentation (CIP, Informed Consent Template and the device User's Manual)	No annual approval renewal needed for countries OUS Adverse event definition clarified UADEs replaced by USADEs Reporting SAE, ADE, SADE timelines revised Added Allergic reaction, bruising, chest pain, nausea and sepsis to the CIP; added hemoptysis and sepsis to the PIS
2	C	18Apr2018	Study Population Number of subjects/sites International Normalized Ratio (INR)	Removed requirement for 35% women; this was only required by FDA for US PAS Increased to 800 subjects/85 sites in order to expand to other countries in EU, AUS The INR has been revised to reflect institution standards.

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			Aspirin dose	Specific dosages have been removed from this section.
			Adverse Events	Updated definitions and reporting requirements language to align with harmonized CIP template (Rev. E); added 3 day reporting requirement for SAEs; Removed USADEs as not applicable to post-market study
			Deviations from CIP	New section to describe in detail expectations for protocol deviations
			Retention of Records	Language updated to reflect harmonized CIP template (Rev. E)
			Appendix G	Removed ICF; will now route separately
			Cover Page/Document Template	Revised formatting
			Document Title Change	The title has been changed from Post Approval Study to Post Market Study in order to accurately reflect study type.
			Ejection Fraction	The time window of ejection fraction measurement has been increased from 3 months to 6 months as decompensation of ejection fraction is not

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				that volatile. Additionally, if ejection fraction has not been measured prior to screening, it can be measured at the screening visit or prior to implantation.
			Device Tracking	Device tracking is not a requirement of a Post Market Study, therefore this section has been removed.