Reference:
SJM-CIP-10105

CardioMEMS European Monitoring Study for Heart Failure
MEMS-HF

Clinical Investigation Plan (CIP)

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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I have read and agree to adhere to the clinical investigational plan and all regulatory requirements applicable in conducting this clinical study.

Principal Investigator

Printed name: _____

Signature:_____

Date: _____

CLINICAL COORDINATING INVESTIGATOR SIGNATURE PAGE

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Date: _____

CO-CLINICAL COORDINATING INVESTIGATOR SIGNATURE PAGE

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CO-Clinical Coordinating Investigator

Printed name: _____

Signature:_____

Date: _____

Contents

1.0 **SYNOPSIS**

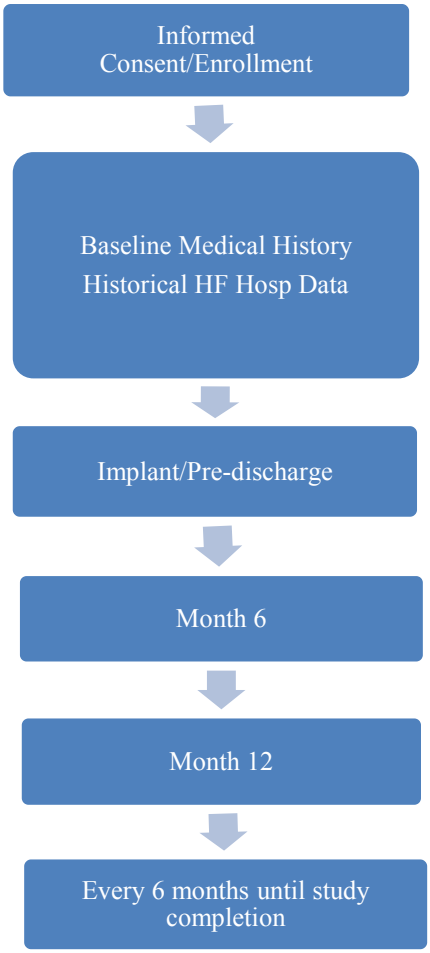
Title:	Cardio**MEMS** European Monitoring Study for **H**eart **F**ailure
Acronym:	MEMS-HF
Purpose:	The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure in New York Heart Association (NYHA) Class III heart failure patients (without regard to ejection fraction) 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. Studies to date have demonstrated a reduction in HF-related hospitalizations and improved quality of life in patients using the CardioMEMS™ HF System when compared with patients receiving standard of care in the United States. The purpose of this study is to characterize the use of the CardioMEMS™ HF System when used in a real-world setting.
Objectives:	The primary objective of this study is to demonstrate the safety and to report clinical performance of the CardioMEMS™ HF System. The secondary objective is to report the ability of experienced heart failure physicians and health care professionals to manage the treatment of NYHA Class III HF patients with a recent heart failure hospitalization (within the last 12 months) and a CardioMEMS sensor implanted when compared to the patient's outcome over the year prior to receiving the CardioMEMS™ HF System.
Endpoints:	Primary Endpoints: The primary safety endpoints are freedom from device/system related complications (Serious Adverse Device Effects) and freedom from pressure sensor failure at 12 months post-implant. The primary clinical performance endpoint is patient data transmission success at 12 months. Secondary Endpoint: The secondary endpoint is the annualized HF hospitalization rate at 12 months compared to the annualized HF hospitalization rate for 12 months prior to implant.
Additional Data Analyses:	Additional Analyses: • HF hospitalization or all-cause death at 12 months post-implant • Change in pressure from baseline using an area under the curve analysis • Characterize ability to use the CardioMEMS™ HF System by

	follow up center type (patient is followed by implanting center, patient is followed by a central follow up center, or other follow up type). The following information will be reported by center type: ○ Annualized HF hospitalization rate at 12 months compared to the annualized HF hospitalization rate for the 12 months prior to implant ○ Number of medication changes ○ Patient compliance for taking pressure readings ○ HF care provider compliance for weekly readings • Change in Quality of Life (QoL) between baseline and 12 months Quality of life will be measured using the following questionnaires: ○ EuroQOL Five Dimensions Questionnaire (EQ-5D) ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) ○ Patient Health Questionnaire (PHQ-9)
Design:	This study is a prospective, non-randomized, open-label, multi-center, post-market study designed to characterize the use of the CardioMEMS™ HF System in a real-world setting. The duration of the study is expected to be approximately 36 months consisting of approximately 24 months of enrollment plus 12 months of follow up. All subjects will be followed until the last subject completes their 12-month visit. The endpoints and additional analyses will be evaluated using data obtained through each subject's 12-month visit. This study will be conducted in approximately 35 centers. All centers regardless of location will conduct the study in the same way as to ensure consistent data collection and as directed in the protocol to ensure data poolability. A total of 230 subjects will be implanted. Interim annual progress reports will be submitted to comply with Post Market Clinical Follow up requirements.
Devices used:	The CardioMEMS™ HF System consists of a wireless, battery-less pressure sensor implanted into the pulmonary artery and external electronics that power and communicate with the sensor and that transmit pulmonary artery pressure waveforms and measurements to a secure website for physician/health care professional review and patient management.
Study Population	Subjects enrolled into this trial will be comprised of male and female subjects of at least 18 years of age with New York Heart Association (NYHA) Class III heart failure who have been hospitalized for heart failure in the previous 12 months, who meet all eligibility criteria and have provided written informed consent.
Inclusion/Exclusion Criteria	<u>Inclusion Criteria</u> • Indicated to receive a CardioMEMS sensor implant per the CardioMEMS™ HF System User's Manual ○ <u>≥</u> 18 years of age

	○ Diagnosis of NYHA Class III Heart Failure at the time of sensor implantation ○ Hospitalization for worsening HF within 12 months prior to the CardioMEMS HF System implant. For the purposes of this study, a HF hospitalization is defined as an overnight stay in the hospital with signs and symptoms of congestion requiring intensification of treatment for HF ○ Subjects with reduced Left Ventricular Ejection Fraction (LVEF) must be on stable Guideline Directed Medical Therapy (GDMT) as tolerated ○ Written informed consent obtained from subject <u>Exclusion Criteria</u> • Known coagulation disorders or inability to take two types of blood thinning medications for one month after the sensor is implanted • Subjects deemed a candidate for transplant, Ventricular Assist Device, or hospice care in the next 12 months or are otherwise not expected to be able to complete the study follow up
Data Collection	<u>Study Visits</u> Subjects will be followed until the last subject completes their 12-month visit. ○ Study visits will occur at Baseline (confirmation of eligibility), Implant, Pre-discharge, 6 months, 12 months, and every 6 months until study completion. Follow-up visits will include a physical examination (including an assessment of NYHA classification), Adverse Event (AE) assessment (Serious Adverse Events (SAE), Adverse Device Effects (ADE), and Serious Adverse Device Effects (SADE)), HF medication review, Quality of Life assessments, and reporting of any HF hospitalizations that have occurred since the subject was last seen (see table 2). ○ Prior to discharge, HF therapy should be optimized and the subject should receive instructions on important aspects of HF management including signs and symptoms, medications, the need for treatment adherence, life style, exercise and self-monitoring of HF signs and symptoms such as body weight, blood pressure, and heart rate. The subject will be instructed to take daily readings using the Patient Electronics System and trend data will be reviewed by a healthcare professional experienced in the management of heart failure at least once every 7 days. Between study visits, the subject will be followed remotely using the CardioMEMS™ HF System for the collection of pulmonary artery pressure (PAP) measurements. The

	subject should also be followed in the frame of basic standardized aftercare (see below). Heart failure medication or treatment regimen changes will be reported along with the reason for change (e.g., PAP increase/decrease, signs/symptoms, etc.). The measurements will be automatically transmitted to a secure patient database for viewing. All telephone contacts between site staff and the subject should be documented using the Subject Contact Log. The log will include information such as purpose, duration, and outcome of the contact (refer to Appendix K). **Guidelines for Standardized Post-discharge HF Care** The subject should be contacted by telephone weekly during the first month and two weekly (NYHA class III/IV subjects) and four weekly (NYHA class I/II subjects) thereafter depending on HF symptoms severity, to ensure optimal HF medication including drug up-titration, adherence to therapy and standardized HF monitoring and education. A standardized 14-item questionnaire (structured interview) addressing general health, indicators of worsening heart failure, state of mood, well-being, and medication should be used to drive and to document the interaction between the subject and site staff (refer to Appendix L). A self-assessment booklet and a booklet containing information on HF-associated symptoms should be provided to the subject together with appropriate training on the content of both documents. If the subject is contacted off-schedule to perform PAP guided medication changes, the subject does not need to be contacted again per the recommended standardized schedule during that time.

1.1 STUDY FLOW CHART



1.2 STUDY CONTACTS

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2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

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 suffer from impairment of functional capacity and have a variety of symptoms such as dyspnea, fatigue, limited exercise tolerance, fluid retention, pulmonary congestion and peripheral edema.

HF is a progressive disease associated with high patient morbidity and mortality and a poor quality of life. Prognosis following a diagnosis of heart failure is poor and 5-year survival rates compare badly with those of most cancers[1]. Heart failure is incurable and while patients may die from other causes not directly linked to heart failure once diagnosed with heart failure, they will not be cured of the syndrome by any currently available therapy.

Estimates of the prevalence and incidence of heart failure vary due to differences in definition and assessment of heart failure, there is no gold-standard assessment to diagnose the presence of the disease[2,3]. The prevalence of heart failure is generally accepted to be 1-2% of the population in the western world with the incidence approaching 5 – 10 people per 1000 per year[3,4]. The total population of 28 EU member states by January 2013 was estimated to be 505,674,965[5] giving an estimated number of heart failure patients of between five and ten million (1 – 2%) in the EU.

The Rotterdam study, a population based study of cardiovascular, locomotor, neurologic and ophthalmologic diseases of the elderly, invited all inhabitants aged 55 and over of Ommoord, a suburb

of Rotterdam, to participate. Seven thousand nine hundred eighty three (7,983) of 10,275 agreed to participate[2]. Heart failure prevalence at baseline was assessed following the definition of heart failure published by the European Society of Cardiology[6]. Prevalence in this population was 6.7% in 1998 and sharply rose with age (0.9% aged 55 – 65; 4.0% aged 65 – 74; 9.7% aged 75 – 84 and 17.4% in subjects 85 years old and over). Overall incidence was 14.4 / 1000 person years and increased with age from 1.4 / 1000 patient years for those aged 55-59 to 47.4 / 1000 patient years for those aged 90 and over[2].

This highly prevalent disease leads to over 1,000,000 hospitalizations each year for decompensation requiring acute medical care. Over 90% of patients hospitalized for heart failure are congested with excess body volume resulting in increased pulmonary artery pressures. Current disease management tools are insensitive in estimating pulmonary artery pressures and are of limited utility in remotely monitoring the patient. New technology development has led to a fully implantable leadless and battery-less sensor that can provide pulmonary artery pressures by remote interrogation from the patient's home.

The CardioMEMS™ HF System consists of a wireless, battery-less pressure sensor implanted into the pulmonary artery and external electronics that power and communicate with the sensor and that transmit pulmonary artery pressure waveforms and measurements to a secure website for physician/health care professional review and patient management.

The CHAMPION trial[7] 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[13]. All secondary endpoints were met demonstrating 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.

2.1 PURPOSE OF THE STUDY

The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure in New York Heart Association (NYHA) Class III heart failure patients (without regard to ejection fraction) who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management, with the goal of reducing heart failure hospitalizations.

Studies to date have demonstrated a reduction in HF-related hospitalizations and improved quality of life in patients using the CardioMEMS HF System when compared with patients receiving standard of care in the United States. The purpose of this study is to characterize the use of the CardioMEMS HF System when used in a real-world setting.

2.2 JUSTIFICATION FOR THE PROPOSED DESIGN

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force has identified the Prospective Observational Study design as an appropriate method to assess the comparative effectiveness of a new technology in a real-world setting and provided under the usual circumstances of health care practice.

The ISPOR describes a single group (longitudinal) prospective observational design where the pretest period is defined as the time before the intervention or exposure and the post-test period as the time after the intervention or exposure. Subjects serve as their own controls in that outcomes observed in the post-test period are compared to the same outcomes observed in the pretest period for each subject. The main advantage of this design relates to the benefits of using a subject to serve as his or her own control so that unmeasured time-invariant factors are differenced out. The main disadvantage of this design is the inability to control for unmeasured time-varying confounding or to rule out that improvements in the outcomes would have occurred naturally over time. However, in advanced progressive disease states like NYHA class III heart failure, these disadvantages are less relevant as patient outcomes are expected to worsen over time (i.e., in the absence of any intervention, post-test outcomes are expected to worsen compared to pretest outcomes). Thus, this study design is a conservative and appropriate choice for testing the CardioMEMS HF System. In order to establish robust, favorable comparative effectiveness, the CardioMEMS HF System must improve post-test outcomes compared to pretest outcomes despite the increased likelihood that post-test outcomes would worsen in the absence of intervention.

Data from this study will also be provided to the governing agency for CE Mark in order to provide post market clinical follow up data. The MEDDEV definition of a post market clinical follow up study is stated as “A study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of a device when used in accordance with its approved labelling (MEDDEV 2.12/2 rev.2)”. At this time, there are no known residual risks associated with the use of the CardioMEMS™ HF System. Therefore, the Primary and Secondary endpoints of this study evaluating safety of the device and the ability of the device to function in a variety of clinical environments is believed to be sufficient to satisfy these reporting requirements.

3.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

3.1 DESCRIPTION OF SUBJECT POPULATION

Subjects enrolled into this trial will be comprised of male and female subjects of at least 18 years of age with New York Heart Association (NYHA) Class III Heart Failure who have been hospitalized for heart failure in the previous 12 months, who meet all eligibility criteria and have provided written informed consent.

3.2 ANTICIPATED CLINICAL BENEFITS

The information collected in this clinical investigation will be added to the current knowledge and understanding of treatment options for patients with New York Heart Association (NYHA) Class III heart failure. The anticipated clinical benefit is that the hemodynamic data used by physicians for heart failure management will result in fewer HF hospitalizations. As each HF hospitalization indicates a higher risk for the patient being re-hospitalized, avoiding these hospitalizations may have a favorable impact on the patient’s long-term outcome.

3.3 ANTICIPATED ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

Events associated with the sensor implant procedure (in conjunction with the Right Heart Catheterization) or post-implant complications are considered anticipated and include, but are not limited to the following:

- Air embolism
- Allergic reaction
- Abnormal heart rate or rhythm
- Bleeding
- Bruising
- Chest pain
- Nausea
- Stroke
- Infection
- Sepsis
- Delayed wound healing
- Atrial dysrhythmia
- Thrombus formation
- Hematoma
- Venous trauma
- Valve damage
- Pulmonary infarct
- Pulmonary embolism
- Heart attack (myocardial infarction)
- Death
- Hemoptysis
- Sensor does not detach from delivery system

3.4 RESIDUAL RISKS ASSOCIATED WITH THE DEVICE UNDER INVESTIGATION

There are no residual risks associated with the study device. In approximately 2% of the cases, a re-calibration of the device may be required.

3.5 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL STUDY

There are no further risks associated with participation in the clinical study.

3.6 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS AND/OR CONCURRENT MEDICAL INTERVENTIONS

There are no known interactions of the CardioMEMS™ HF System with concomitant medical treatment or with any previously implanted active devices (IPG, ICD, or CRT). Please refer to the User's Manual of the CardioMEMS™ HF System for information related to MRI compatibility.

3.7 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS

The risks identified through a pre-market clinical investigation (CHAMPION Trial) represent the most up-to-date understanding of risks associated with CardioMEMS™ HF System implantation. The sponsor will employ measures throughout the course of this study to minimize these risks (e.g. clearly defined inclusion and exclusion criteria to ensure that only appropriate subjects are enrolled, proper consenting process, selection of investigational sites that have a sufficient level of clinical expertise, investigator selection, appropriate training for all involved in the study activities etc.).

3.8 RISK-TO-BENEFIT RATIONALE

Implantation of the CardioMEMS™ HF System may offer certain advantages. Studies to date have demonstrated a reduction in HF-related hospitalizations and improved quality of life in patients using the CardioMEMS™ HF System when compared with patients receiving standard of care. Risks associated with the implantation and use of the device are minor, generally without serious consequences, and occur at a low rate. The CHAMPION Clinical Trial[7] reported no pressure sensor failures, and device/system Related Complications occurred in only 1% of the cases with an additional 1% of the patients experiencing a Procedure-related adverse event. Therefore, there is reasonable evidence that the clinical benefits for this procedure outweigh the risks and thus provide justification for proceeding with this observational study.

4.0 STUDY DESIGN

4.1 PURPOSE

The purpose of this study is to characterize the use of the CardioMEMS™ HF System when used in a real-world setting.

4.2 STUDY DESIGN AND SCOPE

This study is a prospective, non-randomized, open-label, multi-center, post-market study designed to characterize the use of the CardioMEMS™ HF System in a real-world setting.

The duration of the study is expected to be approximately 36 months consisting of approximately 24 months of enrollment plus 12 months of follow up. All subjects will be followed until the last subject completes their 12-month visit. The endpoints and additional analyses will be evaluated using data obtained through each subject's 12-month visit.

This study will be conducted in approximately 35 centers. All centers regardless of location will conduct the study in such a way as to ensure consistent data collection and as directed in the protocol to ensure data poolability. A total of 230 subjects will be implanted in the study. Interim annual progress reports will be submitted to comply with Post-Market Clinical Follow up requirements.

4.2.1 Number of subjects required to be included in the study

A total of 230 subjects will be implanted in the study (refer to section 12.2 (sample size)). Study enrollment will be closed when a total of 230 subjects are implanted.

4.2.2 Estimated time needed to enroll this subject population

The enrollment period is expected to be approximately 24 months.

4.3 OBJECTIVES

4.3.1 Primary Objective

The primary objective of this study is to demonstrate the safety and to report clinical performance of the CardioMEMS™ HF System.

Primary Safety Objectives:

- To demonstrate freedom from device/system-related complication at 12 months is greater than 80%
- To demonstrate freedom from pressure sensor failure at 12 months is greater than 90%

Primary Clinical Performance Objective

- To report patient data transmission success at 12 months.

4.3.2 Secondary objective

The secondary objective is to report the ability of experienced heart failure physicians and health care professionals to manage the treatment of NYHA Class III HF patients with a recent HF hospitalization (within the last 12 months) and a CardioMEMS sensor implanted when compared to the patient's outcome over the year prior to receiving the CardioMEMS™ HF System.

4.4 ENDPOINTS

4.4.1 Primary Endpoints

Primary Safety Endpoints:
The primary safety endpoints are freedom from device/system related complications (Serious Adverse Device Effects) and freedom from pressure sensor failure at 12 months post-implant.

- A device/system related complication (Serious Adverse Device Effects) is an adverse event that is, or is possibly, related to the device/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 right heart catheterization which is used for diagnostic purposes)
  - results in death of the subject
  - results in the explant of the device
- A pressure sensor failure occurs when no readings can be obtained after troubleshooting the system to rule out any problems with the external electronics.

Primary Clinical Performance Endpoint:
The primary clinical performance endpoint is patient data transmission success at 12 months post implant.

4.4.2 Secondary Endpoint

The secondary endpoint is the annualized HF hospitalization rate at 12 months compared to the annualized HF hospitalization rate for the 12 months prior to implant.

4.5 ADDITIONAL ANALYSES

- HF hospitalization or all-cause death at 12 months post-implant
- Change in pressure from baseline using an area under the curve analysis
- Characterize ability to use the CardioMEMS™ HF System by follow up center type (patient is followed by implanting center, patient is followed by a central follow up center, or other follow up type). The following information will be reported by center type:
  - Annualized HF hospitalization rate at 12 months compared to the annualized HF hospitalization rate for the 12 months prior to implant
  - Number of medication changes
  - Patient compliance for taking pressure readings
  - HF care provider compliance for weekly readings
- Change in Quality of Life (QoL) between baseline and 12 months
  Quality of life will be measured using the following questionnaires:
  - EuroQOL Five Dimensions Questionnaire (EQ-5D)
  - Kansas City Cardiomyopathy Questionnaire (KCCQ)
  - Patient Health Questionnaire (PHQ-9)

4.6 INCLUSION AND EXCLUSION CRITERIA

A subject, who meets all of the inclusion criteria, and none of the exclusion criteria, is eligible to participate in this study.

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented in a patient identification log, assigning an identification code linked to their names, alternative identification or contact information.

This log will be kept up to date throughout the clinical study by the principal investigator or his/her authorized designee. To ensure subject privacy and confidentiality of data this log must be maintained throughout the clinical study at the clinical site.

To participate in this clinical study, the subject must meet all of the following inclusion criteria:

4.6.1 Inclusion Criteria

- Indicated to receive a CardioMEMS sensor implant per the CardioMEMS™ HF System User's Manual
- ≥ 18 years of age
- Diagnosis of NYHA Class III Heart Failure at the time of sensor implantation
- Hospitalization for worsening HF within 12 months prior to the CardioMEMS HF System implant. For the purposes of this study, a HF hospitalization is defined as an overnight stay in the hospital with signs and symptoms of congestion requiring intensification of treatment for HF.
- Subjects with reduced Left Ventricular Ejection Fraction (LVEF) must be on stable Guideline Directed Medical Therapy (GDMT)[14] as tolerated
- Written informed consent obtained from subject

Subjects are not eligible for clinical study participation if they meet any of the following exclusion criteria:

4.6.2 Exclusion Criteria

- Known coagulation disorders or inability to take two types of blood thinning medications for one month after the sensor is implanted.
- Subjects deemed a candidate for transplant, Ventricular Assist Device, or hospice care in the next 12 months or are otherwise not expected to be able to complete the study follow up.

4.7 SUBJECT POPULATION

4.7.1 Subject Screening

All subjects presenting at the investigational site can be screened by a member of the investigational team previously trained on the CIP and delegated to do so.

Subjects who do not meet the inclusion or meet the exclusion criteria will not be eligible to participate in this study (screening failures).

The Principal Investigator or the delegated study personnel must maintain patients who are screened (including screening failures) in screening logs.

Subjects meeting the inclusion criteria and none of the exclusion criteria will be fully informed about the study and asked to participate in the study. If the subject agrees, a duly signed and dated Patient Informed Consent (PIC) will be obtained.

4.7.2 Point of Enrollment

Subjects are considered enrolled in the study from the moment the subject has provided written Patient Informed Consent.

4.8 INFORMED CONSENT PROCESS

4.8.1 General process

Prior to enrolling in the clinical study and conducting study-specific procedures, all subjects will be consented, as required by applicable regulations and the center's Ethics Committee (EC). Informed consent must be obtained from each subject prior to any study related procedures. The consent form must be signed and dated by the subject and by the person obtaining the consent.

The principal investigator or his/her authorized designee will conduct the informed consent process. This process will include a verbal discussion with the subject on all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study.

The subject shall be provided with the informed consent form (ICF) that is written in a language that is understandable to the subject and has been approved by the center's EC. Failure to obtain informed consent from a subject prior to study enrollment should be reported to St. Jude Medical within 5 working days and to the reviewing center's EC consistent with the center's EC reporting requirements.

5.0 DEVICE UNDER INVESTIGATION

5.1 DEVICE DESCRIPTION

The CardioMEMS™ HF System is CE-Marked. The legal manufacturer of the CardioMEMS™ HF System is St. Jude Medical, 387 Technology Circle NW, Atlanta, Georgia 30313 USA.

5.2 INTENDED INDICATION

The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure in New York Heart Association (NYHA) Class III heart failure patients (without regard to ejection fraction) 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.

Instructions for use, storage and handling instructions, preparation for use and any precautions can be found in the CardioMEMS™ HF System User's Manual.

5.3 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 (Integrated Merlin.net website for Patient Data Management)

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 cardiac catheterization laboratory; the sensor baseline is set to the mean PA pressure and cardiac output derived from a pulmonary artery catheter. Patients generally are discharged from the catheterization laboratory after a period of observation. Once home, daily PA hemodynamic measurements are taken by the patient in a supine position using the patient electronic unit provided as part of the system. The patient electronic unit 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 are encrypted and then transmitted to the secured website (Merlin.net) which is accessible via a secure login by 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 during the daily interrogation procedure.

Implantable Sensor Delivery System
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. The target implant vessel must be more than 7 mm in diameter, which is assessed during the limited angiogram. An 0.018" guidewire is then advanced through the pulmonary artery catheter into the distal pulmonary artery. The pulmonary artery catheter is removed, and the sensor 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 patient 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.

Hospital Electronics System
The hospital electronics unit uses an antenna to transmit low power pulses of radiofrequency energy to power and communicate with the sensor. The hospital electronics unit is used to set the implanted sensor baseline using simultaneous measurements from the sensor and a PA catheter as a reference. The "set the baseline" sequence is performed during the implant procedure. The hospital electronics unit may be used to obtain PA pressure data during subsequent HF hospitalizations or clinic visits.

Integrated Merlin.net website for Patient Data Management
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.

Table 1. Description of Proposed Devices

Device Component	Model/Type	Investigational or Market Released
Sensor and delivery catheter	CM2000	Market Released
Hospital Electronics System	CM3000	Market Released
Patient Electronics System	CM1000 (GSM), CM1010 (land line), and any subsequent commercially approved model(s)	Market Released
Integrated Merlin.net website for Patient Data Management	V8.5, and any subsequent commercially approved version(s)	Market Released

Site personnel (e.g. implanting physician, heart failure physician) that will use at least one of the device components will be trained according to SJM CardioMEMS HF System training program prior to implant.

5.4 DEVICE ACCOUNTABILITY

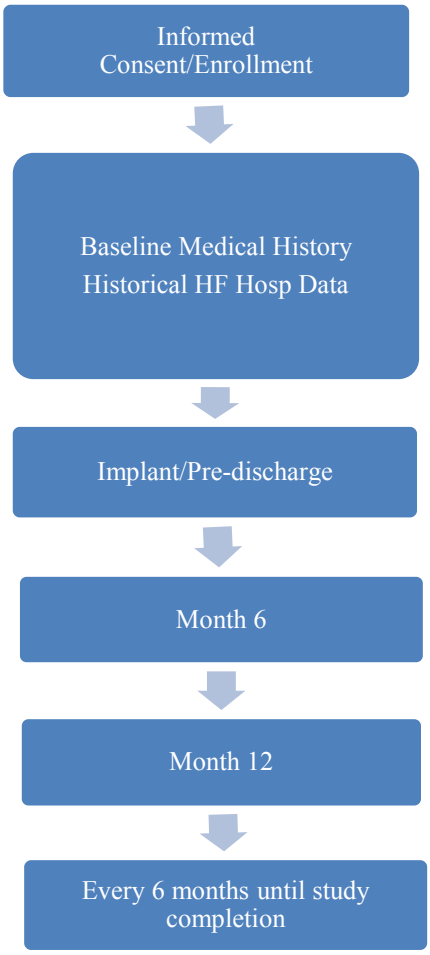
Device accountability is not required for this study.

5.5 DEVICE HANDLING AND STORAGE

Please refer to the product labeling for device handling and storage.

6.0 PROCEDURES

6.1 STUDY FLOW CHART



6.2 PROCEDURES

The clinical study will be conducted in accordance with the Clinical Investigation Plan (CIP). All parties participating in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

The clinical study will not commence until St. Jude Medical receives written approval from the EC and relevant regulatory authorities (if applicable) and all required documents have been collected from the site(s).

Table 2: List of all study specific activities/procedures

Visit / Study Activity	Baseline (Enrollment)	Implant	Pre-discharge	6 Month post-implant ± 30days	12 Month post-implant ± 30days	Every 6 months ± 60days	Unscheduled
Informed Consent Process	X						
Demographics	X						
Medical & surgical history	X						
History of HF hospitalizations (last 12 months)	X						
Inclusion/ Exclusion Criteria Review	X						
Physical Examination	X			X	X		
NYHA HF Classification	X		X	X	X		
Heart Failure medications	X		X	X	X	X	X
Subject Contact Log[1]				X	X	X	X
Structured Interview[1]				X	X	X	X
Optimization of HF treatment, subject education on HF symptoms, and subject instructions for self-monitoring[2]			X				
Cardiac Device history	X						
Anticoagulant/ antiplatelet medications	X		X	X	X	X	X
Sensor Calibration		X					
Patient training			X[3]				
PA Pressure reading			(X)	(X)	(X)	(X)	(X)
EQ-5D assessment	X			X	X		
KCCQ assessment	X			X	X		
PHQ-9 assessment	X			X	X		
Adverse event and HF hospitalization assessment	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Deviation	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Termination	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Death	(X)	(X)	(X)	(X)	(X)	(X)	(X)

(X) if applicable (PA pressure measurements during study visits may be obtained at the investigator's discretion)
[1]The subject contact log should to be completed each time contact is made between the site staff and a study subject The structured interview should be administered weekly during the first month and two (NYHA class III/IV) to four weekly (NYHA class I/II) thereafter
[2]Recommended as part of the guidelines for Standardized Post-discharge HF Care
[3]Prior to discharge, subjects will be trained to take daily readings at home

6.3 ENROLLMENT VISIT

The following enrollment activities are performed after the subject has been screened and must occur before any study procedure/visit.

- The principal investigator or delegated study personnel are responsible for screening all potential subjects to determine subject eligibility for the study.
- Record enrollment information (name of the study, date of consent and inclusion/exclusion information) in the hospital records and complete and submit the CRF enrollment form in a timely manner (recommended within 5 days).
- Notification of enrollment to the sponsor will take place only when the sponsor receives the enrollment form.

NOTE: As soon as the subject signs the Patient Informed Consent, adverse events need to be reported according to the guidelines in section 8.0

If a subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject cannot participate in the study and should not be consented.

6.4 BASELINE VISIT

- The following medical information will be collected at this visit
    - Demographics including subject's year of birth and gender
    - Physical examination including vital signs (heart rate and blood pressure), weight, height (for Body Mass Index (BMI) calculation)
    - Medical history including documentation of comorbidities and ejection fraction data
    - Surgical history
    - Cardiac device (IPG, ICD, and CRT) history
    - Patient history of heart failure hospitalizations in the 12 months prior to the implant as documented in information provided by the patient's cardiologist, internist, or referring physicians and collection of source documents of any heart failure hospitalization(s) reported in the previous 12 months. It will be the responsibility of the enrolling physician to perform a review of the patient's record over the last 12 months and to determine if the hospitalizations were due to HF. This review should include actual record review and not rely on patient self-reported history. For the purposes of this study, a HF hospitalization is defined as an overnight stay in the hospital with signs and symptoms of congestion requiring intensification of treatment for HF. Elective or planned hospitalizations are not included in this definition
    - NYHA Functional Classification
    - Heart failure medication history
- The following activity must be completed prior to implant
    - Completion of the EuroQOL Five Dimensions Questionnaire (EQ-5D)
    - Completion of Kansas City Cardiomyopathy Questionnaire (KCCQ)
    - Completion of Patient Health Questionnaire (PHQ-9)

6.5 IMPLANT VISIT

Following completion of informed consent and collection of the baseline visit, subjects will have a sensor implant. All subjects must have complete implant information provided. The implant procedure will be performed according to the User's Manual/Instructions For Use and the hospital standard of care.

Consented subjects who undergo the implant procedure but without a suitable target pulmonary artery branch will not receive the PA Sensor implant and will be withdrawn from the study after being followed for 30 days for safety (unscheduled visit and withdrawal CRF to be completed). In addition, any subject with a failed PA sensor implant due to any other reasons will be followed for 30 days for safety, then withdrawn from the study, and will resume his/her regular standard of care with his/her physician (unscheduled visit and withdrawal CRF to be completed). If an AE occurred during that period of 30 days, an AE CRF needs to be completed.
If a subject was consented to participate in the study and was implanted but does not meet inclusion/exclusion criteria, this is considered a protocol deviation (PD). A PD form needs to be completed and the sponsor must be informed. The EC and Competent Authority (CA) should be notified (if applicable) about any deviations related to the eligibility criteria.

- The following medical information will be collected at this visit
  - Right Heart Catheterization/implant procedure information
    - Catheter access information
    - Confirmation of target vessel size
    - Initial PA catheter measurement (PA pressures, Cardiac Output (preferably by measured Modified FICK or thermodilution))
    - Implant location
    - Device and PA catheter measurements (PA Pressures, Heart Rate, Cardiac Output)

  - Device information
    - Sensor serial number

Prior to hospital discharge, subjects will be trained on the home monitoring system and instructed to take pulmonary artery pressure measurements daily. It is recommended that the pressure measurements be taken at the same time in the morning. Subjects will be supplied with a patient implant identification card, a patient system manual, and a helpline phone number.

It is recommended that subjects who are not being treated with chronic anticoagulant therapy be placed on dual antiplatelet therapy for 1 month following the procedure.

After discharge, the subject will take daily PA pressure measurements at home, utilizing the CardioMEMS HF™ System. These measurements will be transmitted via modem to a secure database. Subject compliance will be monitored by the investigator and the sponsor by review of uploaded information on the Merlin.net website.

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 E but can be customized to adapt to patient specific needs. 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 E. 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.

6.6 SCHEDULED FOLLOW-UPS

Study visits will occur at Pre-discharge, 6 months, 12 months and every 6 months thereafter until completion of the study. Day 1 starts from the implant procedure.

The following procedures/assessments will be performed:

- Pre-Discharge visit
  - NYHA classification assessment
  - Adverse event assessment (SAEs, SADEs, and ADEs that occurred since implant)
  - Heart failure medication review
  - Anticoagulant/antiplatelet medication review
  - PA pressure measurements may be obtained at the investigator's discretion

Prior to discharge, HF therapy should be optimized and the subject should receive instructions on important aspects of HF management including signs and symptoms, medications, the need for treatment adherence, life style, exercise and self-monitoring of HF signs and symptoms such as body weight, blood pressure, and heart rate. Sites should provide practical training in the self-monitoring of the blood pressure and heart rate and should ensure that a blood pressure measurement device and an electronic scale are available to the subject.
A self-assessment booklet and a booklet containing information on HF-associated symptoms should be provided to the subject together with appropriate training on the content of both documents.

- 6 Months Follow-up (± 30 days)
  - Physical examination including vital signs, weight, and NYHA classification
  - Adverse event assessment (SAEs, SADEs, ADEs that occurred since the subject's last visit)
  - Heart failure medication review
  - Anticoagulant/antiplatelet medication review
  - PA pressure measurements may be obtained at the investigator's discretion
  - Reporting of any HF hospitalizations that have occurred since the subject was last seen
  - Completion of EQ-5D, KCCQ, and PHQ-9 by the subject

- 12 Months Follow-up (± 30 days)
  - Physical examination including vital signs and NYHA classification
  - Adverse event assessment (SAEs, SADEs, ADEs that occurred since the subject's last visit)
  - Heart failure medication review
  - Anticoagulant/antiplatelet medication review
  - PA pressure measurements may be obtained at the investigator's discretion
  - Reporting of any HF hospitalizations that have occurred since the subject was last seen
  - Completion of EQ-5D, KCCQ, and PHQ-9 by the subject

6.7 EVERY 6 MONTHS THEREAFTER AND UNSCHEDULED VISITS

Visits occurring after the 12 month visit should occur every 6 months until completion of the study (18 months ± 60 days, 24 months ± 60 days etc. after the implant). An unscheduled follow-up is defined as a visit that occurs between two scheduled study visits where the subject is examined for either a physician or investigator requested follow-up or for an adverse event. The following assessments will be performed at these visits:

- Adverse event assessment (SAE, ADE, SADE that occurred since the last study visit)
- Heart failure medication review
- Anticoagulant/antiplatelet medication review

- PA pressure measurements may be obtained at the investigator's discretion
- Reporting of any HF hospitalization that have occurred since the subject was last seen

The data collected must be documented by completing the appropriate CRF.

Between study visits, the subject will be followed remotely using the CardioMEMS HF System for the collection of pulmonary artery pressure measurements. Subjects will be instructed to take daily readings and trend data will be reviewed by a healthcare professional experienced in the management of heart failure at least once every 7 days. Medication or treatment regimen changes as a result of PAP data review will be reported.

All telephone contacts between site staff and the subject should be documented using the Subject Contact Log (refer to Appendix K) and the following information should 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) with the reason medication was changed, if applicable (PAP guided or signs and symptoms guided)
- Other action required

Guidelines for Standardized Post-discharge Heart Failure Care
The subject should be contacted by telephone weekly during the first month and two weekly (for NYHA class III/IV subjects) and four weekly (for NYHA class I/II subjects) weekly thereafter depending on HF symptoms severity to ensure standardized HF monitoring and education. A standardized 14-item questionnaire (structured interview) addressing general health, indicators of worsening HF, state of mood, well-being, and medication should be used to drive and to document the interaction between the subject and site staff (refer to Appendix L). A self-assessment booklet and a booklet containing information on HF-associated symptoms should be provided to the subject together with appropriate training on the content of both documents.
If the subject is contacted off-schedule to perform PAP guided medication changes, the subject does not need to be contacted again per the recommended standardized schedule during that time.

6.8 DESCRIPTION OF ACTIVITIES PERFORMED BY SPONSOR REPRESENTATIVES

Trained sponsor personnel may perform certain activities to ensure compliance to the clinical investigation plan and may provide technical expertise.

Sponsor personnel will not perform the informed consent process, practice medicine, provide medical diagnosis or treatment to subjects, discuss a subject's condition or treatment with a subject without the approval and presence of a health care practitioner, or independently collect clinical investigation data.

6.9 SUBJECT STUDY COMPLETION

Upon completion of the study, the subject's participation will be considered completed. When the subject's participation in the clinical study has been completed the subject will return to medical care as per physician's recommendation.

6.10 ANY KNOWN OR FORSEEABLE FACTORS THAT MAY COMPROMISE THE OUTCOME OF THE CLINICAL STUDY OR THE INTERPRETATION OF THE

RESULTS

All foreseeable factors that may compromise the outcome have been taken into account by clinical study design and well defined subject selection criteria.

Subject recruitment and retention will be monitored throughout the study and include (but are not limited to) the following activities: evaluation of the site and investigators, training of site personnel, and developing site support materials.

6.11 DESCRIPTION OF THE METHODS THAT WILL BE USED TO ADDRESS POTENTIALLY CONFOUNDING FACTORS IN THE CLINICAL STUDY DESIGN

This is a single arm study so there are no known confounding factors to be addressed for the primary safety endpoints and the primary clinical performance endpoint. The study design of using subjects serving as their own controls and within-subject comparisons of outcomes during 12 months following implant in the study and outcomes during 12 months prior to implant using frailty model accounts for unmeasured confounding factors for the secondary endpoint.

6.12 CRITERIA AND PROCEDURES FOR SUBJECT WITHDRAWAL OR DISCONTINUATION

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled and withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the study.

Reasons for subject's withdrawal include, but are not limited to:

- Subject refuses to continue participating in the study
- Subject does not meet the inclusion/exclusion criteria and does not require additional follow-up for safety reasons.
- Subject is deceased (cause must be documented)
- Subject's non-compliance
- Subject's participation is terminated by the PI or investigator, although the subject consented, since participation is no longer medically appropriate
- Subject is lost to follow up: subject does not adhere to the scheduled follow up visits but has not explicitly requested to be withdrawn from the clinical study (this does not apply to missed visits). Site personnel should at all times make all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow up visits:
  1. A subject will be considered 'Lost to Follow Up' after a minimum of 2 phone calls of a physician or delegate at the investigational site to the subject or contact. These 2 phone calls need to be documented in the subject's hospital records.
  2. If these attempts are unsuccessful, a letter should be sent to the subject's last known address or general practitioner (GP) and a copy of this letter should be maintained in the subject's hospital records.

Note: If a subject misses the 6-month visit, this will be considered as a missed visit. The subject may therefore still return for the 12-month visit and will not be excluded from the study.

If a subject withdraws from the clinical study, the site will record the subject's reasons for withdrawal on a withdrawal CRF.

When subject withdrawal from the clinical study is due to an adverse event, the subject will be followed until resolution of that adverse event or determination that the subject's condition is stable. The status of the subject's condition should be documented at the time of withdrawal.

Prior to withdrawal, the subject should be seen for a final study visit. At this final study visit, the subject will undergo the following evaluations:

- Adverse event assessment (SAEs, SADEs, ADEs that occurred since the last visit)
- Heart failure medication review
- Anticoagulant/antiplatelet medication review
- Reporting of any HF hospitalizations that have occurred since the subject was last seen.

7.0 **COMPLIANCE TO CIP**

7.1 STATEMENTS OF COMPLIANCE

The study will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki, ISO14155 and any regional and/or national regulations.

The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining EC approval and Competent Authority (CA) approval, if applicable, and authorization from the sponsor in writing for the study.

In case additional requirements are imposed by the EC or CA, those requirements will be followed, if appropriate. If any action is taken by an EC and/or CA with respect to the study, that information will be forwarded to St. Jude Medical.

As sponsor, St. Jude Medical has taken up general liability insurance in accordance with the requirements of the applicable local laws.

If required, additional subject coverage or a study specific insurance will be provided by the sponsor as well.

7.2 ADHERENCE TO THE CLINICAL INVESTIGATION PLAN

A deviation is defined as an event where the clinical investigator, site personnel, sponsor or sponsor representative did not conduct the clinical study according to the Clinical Investigational Plan (CIP), EC requirements or the Investigator Agreement. The investigator is not allowed to deviate from the CIP, except as specified under emergency circumstances.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects, since the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the sponsor to exclude subjects for whom the device is not beneficial and the use involves unreasonable risks. This may be considered failure to protect the rights, safety and well-being of the enrolled subject. Similarly, failure to perform safety assessments intended to detect adverse events

may be considered failure to protect the rights, safety and well-being of the enrolled subject. Investigators should seek minimization of such risks by adhering to the CIP.

Simultaneously, in the event that adhering to the CIP might expose the subject to unreasonable risks, the investigator is also required to protect the rights, safety and well-being of the subject by intentionally deviating from the requirements of the CIP, so that subjects are not exposed to unreasonable risks.

It is the responsibility of the investigator to provide adequate medical care to a subject enrolled in a study.

Regulations require that the PI maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the Clinical Investigational Plan. Relevant information for each deviation will be documented on a Deviation Case Report Form (CRF). The site will submit the CRF to St. Jude Medical.

Regulations require investigators to obtain approval from St. Jude Medical and the EC (as required) before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well-being of a subject in an emergency. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible, but no later than 5 working days.

Prior approval must be requested when the PI anticipates, contemplates, or makes a conscious decision to depart from the CIP, except when unforeseen circumstances are beyond the investigator's control (e.g. a subject who fails to attend a scheduled follow-up visit, a subject is too ill to perform a CIP-required test, etc.). All deviations, including those beyond the investigator's control, must be reported on a deviation CRF.

To obtain approval, the PI may call or email and discuss the potential deviation with St. Jude Medical or designee prior to initiating any changes.

All deviations must be reported to appropriate CA in specified timelines (if appropriate). The Investigator is required to adhere to local regulatory requirements for reporting deviations to EC.

7.3 REPEATED AND SERIOUS NON-COMPLIANCE

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the sponsor, a Clinical Research Associate or clinical representative will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator
- Contacting the investigator by telephone
- Contacting the investigator in writing
- Retraining of the investigator

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical study.

8.0 ADVERSE EVENT, ADVERSE DEVICE EFFECT, DEVICE DEFICIENCY

8.1 DEFINITIONS

8.1.1 Medical device

Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article

- Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of
  - Diagnosis, prevention, monitoring, treatments or alleviation of disease,
  - Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
  - Investigation, replacement, modification, or support of the anatomy or of a physiological process,
  - Supporting or sustaining life,
  - Control of conception,
  - Disinfection of medical devices and
- Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

8.1.2 Adverse Event (AE)

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 investigational medical device under study.

This definition includes events related to the investigational medical device or the comparator.
This definition includes events related to the procedures involved.

8.1.3 Serious Adverse Event (SAE)

An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury OR
  - A permanent impairment to a body structure or a body function OR
  - An in-patient or prolonged hospitalization OR
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function OR
- Fetal distress, fetal death or a congenital abnormality or birth defect

A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered a serious adverse event.

8.1.4 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from the use error or from intentional misuse of the investigational medical device.

8.1.5 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.1.6 Anticipated Serious Adverse Device Effect (ASADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

8.2 PROCEDURE FOR ASSESSING, RECORDING, AND REPORTING ADVERSE EVENTS, DEVICE DEFICIENCIES/COMPLAINTS, ADVERSE DEVICE EFFECTS, SERIOUS ADVERSE EVENTS, AND SERIOUS ADVERSE DEVICE EFFECTS:

Safety surveillance within this study and the safety reporting both performed by the investigator, starts as soon as the subject is enrolled in this study (date of signature of the informed consent). The safety surveillance and the safety reporting will continue until the last investigational visit has been performed, the subject is deceased, the subject/investigator concludes his participation into the study or the subject/investigator withdraws the subject from the study, except as otherwise specified in the CIP.

For the list of anticipated adverse events and adverse device effects please refer to the section 3.3 of this CIP.

Reportable events to sponsor are considered:

- All Serious Adverse Events (whether or not the event is considered device or procedure related)
- All procedure and device-related Adverse Events (whether or not the event is considered serious).

All above events will be reported to the sponsor, as soon as possible, but no later than 72 hours of first learning of the event.

The investigator will report the event to the EC and CA (if applicable) per national and local laws and regulations.

The sponsor will ensure that all events are reported to the relevant authorities as per regulations. Additional information may be requested, when required, in order to support the reporting of AEs to regulatory authorities.

All reportable adverse event data including deaths will be collected throughout the clinical study and will be reported to the sponsor on a dedicated CRF through the Electronic Data Capture (EDC) system.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Adverse events will be monitored until they are adequately resolved. The status of the subject's condition should be documented at each visit.

8.3 SUBJECT DEATH

8.3.1 Procedure for recording and reporting subject death

All subject deaths are to be documented and reported to the sponsor within 72 hours after becoming aware of the event.

Should death occur, the investigator is requested to record death information in the hospital records and immediately document the information on the Death form. By completing the form the sponsor will be notified.

8.4 DEVICE DEFICIENCY /COMPLAINTS

A Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling.

All device deficiency/ complaints in St. Jude Medical market-released products must be reported to St. Jude Medical (SJM). The investigator should notify the SJM representative **or** SJM Product Surveillance Department by emailing the information about a complaint to the following e-mail address: CardioMEMS_Complaints@sjm.com or calling at: 877-696-3754 as soon as possible after becoming aware of a complaint.

9.0 DATA MANAGEMENT

Overall, the sponsor will be responsible for the data handling.

The sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

Data will be analyzed by the sponsor and may be transferred to the sponsor's locations outside of Europe and/or any other worldwide regulatory authority in support of a market-approval application.

St. Jude Medical respects and protects personally identifiable information that we collect or maintain. As part of our commitment, St. Jude Medical is certified to the U.S. - European Union Framework and U.S. – Swiss Safe Harbor Framework Agreements regarding human resources and subject clinical trial personal information. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, EC review and CA inspections. As required, the Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

9.1 DATA MANAGEMENT PLAN

A detailed Data Management Plan (DMP) will be established to ensure consistency of the data. This document will include procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the study duration. All revisions will be tracked and document controlled.

CRF data will be captured in a validated electronic database management system hosted by St. Jude Medical.

Only authorized site personnel will be permitted to enter the CRF data through the electronic data capture (EDC) system deployed by St. Jude Medical. An electronic audit trail will be used to track any subsequent changes of the entered data.

9.2 DOCUMENT AND DATA CONTROL

9.2.1 Traceability of documents and data

The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports.

9.2.2 Recording data

Source documents will be created and maintained by the investigational site team throughout the clinical study.

The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

The CRFs will be validated (eCRF) by the authorized site personnel.

10.0 MONITORING

It is the responsibility of St. Jude Medical as the sponsor of the study to ensure the study is conducted, recorded, and reported according to the approved protocol, subsequent amendment(s), applicable regulations, and guidance documents. Monitoring will be conducted according to the St. Jude Medical Clinical Monitoring standard operating procedure.

Prior to beginning the study, St. Jude Medical will contact the investigator or designee to discuss the study and data requirements. A St. Jude Medical monitor will periodically review the subject records and associated source documents.

The investigator shall make subject and study records available to the clinical monitor for monitoring.

11.0 REGULATORY INSPECTIONS

The investigator and/or delegate should contact St. Jude Medical immediately upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the investigator and/or delegate in preparing for the audit.

An investigator who has authority to grant access will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An investigator, or any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the sponsor or EC have not been submitted or are incomplete, inaccurate, false or misleading.

12.0 STATISTICAL CONSIDERATIONS

12.1 STATISTICAL DESIGN, HYPOTHESES, METHOD AND ANALYTICAL PROCEDURES

This study has two primary safety hypotheses (1) freedom from device/system-related complications at 12 months and (2) freedom from pressure sensor failure at 12 months. Both hypotheses must be met in order to declare the study successful. Additionally, patient data transmission success at 12 months will be summarized to characterize the primary clinical performance endpoint.

12.1.1 Freedom from Device/System-related Complications at 12 months

The hypothesis is formulated as:

H_0: Freedom from device/system-related complications at 12 months ≤ 0.80
H_a: Freedom from device/system-related complications at 12 months > 0.80

where device/system-related complication is defined in Section 4.4.1.

Sample Size

The CHAMPION Clinical Trial observed 98.6% freedom from device/system-related complications (DSCR) at 12 months[7]. The study size of 230 implanted subjects provides at least 85% power to reject the null hypothesis at the significance level of 5% using exact test for a binomial proportion, under the conservative assumption that freedom from device/system-related complications at 12 months is as low as 87%. The sample size was estimated using PASS 13 (NCSS LLC.).

Subject Group

All subjects who are consented and received a sensor implant or undergo the implant procedure but did not receive a sensor implant regardless of study completion status will be included in the analysis.

Analysis

The desired outcome is to reject the null hypothesis. Subjects not experiencing DSRC prior to withdrawal will be treated as not experiencing a DSRC event. The endpoint will be evaluated using the exact test for a binominal proportion. The null hypothesis will be rejected if the 95% lower confidence bound (LCB) is greater than 0.8.

The freedom from device/system-related complications at 12 months will also be reported using the Kaplan-Meier method.

12.1.2 Freedom from Pressure Sensor Failure at 12 Months

The hypothesis is formulated as:

H_0: Freedom from pressure sensor failure at 12 months ≤ 0.90
H_a: Freedom from pressure sensor failure at 12 months > 0.90

where pressure sensor failure is defined in Section 4.4.1.

Sample Size
The CHAMPION Clinical Trial observed 100% freedom from pressure sensor failure at 12 months[7]. The study size of 230 implanted subjects provides at least 85% power to reject the null hypothesis at the significance level of 5% using exact test for a binomial proportion under the conservative assumption that the freedom from pressure sensor failure at 12 months is as low as 95%. The sample size was estimated using PASS 13 (NCSS LLC.).

Subject Group
All subjects who are consented and successfully implanted with a pressure sensor regardless of study completion status will be included in the analyses.

Analysis
The desired outcome is to reject the null hypothesis. Subjects not experiencing pressure sensor failure prior to withdrawal will be treated as not experiencing a pressure sensor failure event. The endpoint will be evaluated using the exact test for a binominal proportion. The null hypothesis will be rejected if the 95% lower confidence bound (LCB) is greater than 0.9.

The freedom from pressure sensor failure at 12 months will also be reported using the Kaplan-Meier method.

12.1.3 Patient Data Transmission Success at 12 Months

Patient data transmission success is defined as percentage of successful transmissions among attempted transmissions.

Subject Group
All subjects who are consented and implanted with a pressure sensor regardless of study completion status will be included in the analysis.

Analysis
All attempted data transmissions through the 12-month visit or death or withdrawal will be included in the analysis. For each subject, the patient data transmission success rate (% of successful transmission) will be calculated as total number of successful transmissions divided by total attempted transmissions within 12 months. The per-subject patient data transmission success rate will be summarized as mean, standard deviation and the 95% confidence interval.

12.1.4 Secondary Endpoint

The secondary endpoint will compare the annualized HF hospitalization rate (including recurrent events) at 12 months post-implant with the rate (including recurrent events) in 12 months prior to implant, using a Cox proportional hazards regression with Anderson-Gill method for recurrent events and frailty to account for within-subject correlation. All follow-up through 12 months post-implant or until subject exits the study will be included in the analysis.

All subjects who are consented and successfully implanted with a pressure sensor, regardless of study completion status will be included in the analysis.

12.1.5 Additional Analyses:

12.1.5.1 HF hospitalization or all-cause death

The HF hospitalization or all-cause death rate at 12 months post-implant will be reported using the Kaplan-Meier method.

12.1.5.2 CardioMEMS Usage

For subjects who are successfully implanted, the ability for physicians and study site personnel to use the CardioMEMS HF System will be characterized by follow-up center types:

- Subject is followed by implanting center
- Subject is followed by a central follow up center
- Other type of follow-up

For subjects who are successfully implanted, the following device usage information will be summarized using descriptive statistics by follow-up center types:

- Annualized HF hospitalization rate (including recurrent events) at 12 months compared to the annualized HF hospitalization rate (including recurrent events) for 12 months prior implant
- Number of HF medication changes and reason for the change
- Patient compliance for taking pressure readings (total daily readings divided by total number possible for daily readings as well as total weekly readings divided by total possible weekly readings)
- HF care provider compliance for weekly readings (total weekly readings divided by the total number of possible weeks of readings)

12.1.5.3 Change in Quality of Life (QoL) between baseline and 12 months

Quality of life will be measured using the following questionnaires:

- EuroQOL Five Dimensions Questionnaire (EQ-5D)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Patient Health Questionnaire (PHQ-9)

12.1.6 Demographic and Baseline Information

The following variables will be collected at baseline to describe the subject population and verify that inclusion/exclusion criteria were met. Subject demographics, including age, gender, weight, height, BMI, NYHA Class, implanted device type (ICD, CRT-D or other), heart failure type (i.e., Ischemic Cardiomyopathy vs. Non-Ischemic Cardiomyopathy), and ejection fraction will be summarized using descriptive statistics. Comorbidities frequently associated with heart failure and baseline heart failure medication use will be reported.

12.1.7 Adverse Events

The frequency of the following events and the frequency and percentage of subjects experiencing the following events will be reported through 12 months: deaths, cardiovascular deaths, adverse device effect (ADEs), serious adverse device effect (SADEs), and serious adverse events (SAEs). Additionally, annualized rates of deaths, cardiovascular deaths, ADEs, SADEs and SAEs will be reported.

12.2 SAMPLE SIZE

The overall sample size of 230 subjects consented and implanted will provide at least 85% power to demonstrate that each primary safety endpoint is superior to its performance goal (refer to Appendix I for additional detail regarding sample size calculations).

12.3 PASS/FAIL CRITERIA TO BE APPLIED TO THE RESULTS OF THE CLINICAL STUDY

The study will be considered as successful if the primary safety endpoints are met.

12.4 THE PROVISION FOR AN INTERIM ANALYSIS

No interim analysis is planned for this study.

12.5 CRITERIA FOR THE TERMINATION OF THE CLINICAL STUDY ON STATISTICAL GROUNDS

No stopping rules are planned for this trial so there are no statistical grounds for study termination.

12.6 PROCEDURES FOR REPORTING ANY DEVIATION(S) FROM THE ORIGINAL STATISTICAL PLAN

Any deviations from the statistical plan within the protocol will be described in the result section of the clinical study report.

12.7 THE SPECIFICATION OF SUBGROUPS FOR ANALYSIS

No pre-specified sub-group analyses are planned for the trial. However, sub-group analyses may be performed to provide further support for benefit in important subgroups.

12.8 PROCEDURES THAT TAKE INTO ACCOUNT ALL THE DATA

The statistical procedures used to analyze the primary and secondary endpoints utilize all available data. No post-implant data will be excluded from the analyses.

12.9 THE TREATMENT OF MISSING, UNUSED, OR SPURIOUS DATA, INCLUDING DROP-OUTS AND WITHDRAWALS

The data distribution will be examined for potential outliers, spurious data and missing data. Analyses will utilize all available data from subjects, including those who withdraw prior to 1 year.

12.10 THE EXCLUSION OF PARTICULAR INFORMATION FOR THE TESTING OF THE HYPOTHESIS

No data will be excluded from the analyses to test the study hypotheses.

12.11 IN MULTI-CENTER STUDIES, THE MINIMUM AND MAXIMUM NUMBER OF SUBJECTS TO BE INCLUDED FOR EACH CENTER

This study will attempt to have no more than 15% of subjects at any one center. No minimum number of subjects is required for each center.

13.0 DOCUMENT RETENTION

The principal investigator (PI) will maintain all clinical study documents from prior, during and (as specified) after the clinical study on file at the site for a minimum of 15 years after the termination of this study, or longer as per local laws, or when it is no longer needed to support a marketing application, whichever is later.

The PI must contact the sponsor prior to destroying or archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on-site.

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

All data and documents will be made available on request of the relevant authorities in case of an audit.

The sponsor will archive and retain all essential clinical study documents from prior, during and (as specified) after the clinical study as per requirements.

14.0 AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Study related documents such as, the CIP, CRFs, Informed Consent form and other subject information, or other clinical study documents will be amended as needed throughout the clinical study, and a justification statement will be included with each amended section of a document. Proposed amendments to the CIP will be agreed upon between the sponsor and the coordinating investigator (if applicable).

The amendments to the CIP and the subject's Informed Consent will be notified to, or approved by, the EC and CA, if required. The version number and date of amendments will be documented.

The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

Any amendment affecting the subject requires that the subject be informed of the changes and a new consent be signed and dated by the investigator at the subject's next follow up.

Changes to, or formal clarifications of, the CIP will be documented in writing and provided to the investigators. This information will be incorporated when an amendment occurs.

15.0 STUDY COMMITTEES

15.1 STEERING COMMITTEE (SC)

The composition and function of the SC is described in detail in the SC charter.

16.0 INVESTIGATION SUSPENSION OR TERMINATION

16.1 PREMATURE TERMINATION OF THE WHOLE CLINICAL STUDY OR OF THE CLINICAL STUDY IN ONE OR MORE INVESTIGATIONAL SITES

The sponsor reserves the right to stop the study at any stage, with appropriate written notice to the investigator.

Possible reasons for early termination of the study by the sponsor, either at local, national or international level, may include, but are not limited to:

- The device / therapy fails to perform as intended
- Sponsor's decision
- Request from Regulatory bodies
- Request of Ethics Committee(s)
- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Repeated non-compliance with this CIP or the Clinical Trial Agreement
- Inability to successfully implement this CIP
- Violation of the Declaration of Helsinki (refer to Appendix C)
- Violation of applicable national or local laws and regulations

- Falsification of data, or any other breach of ethics or scientific principles
- Loss of or unaccounted use of investigational device inventory

The study will be terminated according to applicable regulations.

The investigator may also discontinue participation in the clinical study with appropriate written notice to the sponsor.

Should either of these events occur, the investigator will return all documents to the sponsor; provide a written statement as to why the premature termination has taken place and notify the EC and/or the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per CIP requirements.

A Principal Investigator, EC or CA may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical study or when so instructed by the EC or CA, St. Jude Medical may suspend the clinical study as appropriate while the risk is assessed. St. Jude Medical will terminate the clinical study if an unacceptable risk is confirmed.

St. Jude Medical will consider terminating or suspending the participation of a particular investigational site or investigator in the clinical study if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party will justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and St. Jude Medical will keep each other informed of any communication received from EC or CA.

If for any reason St. Jude Medical suspends or prematurely terminates the study at an individual investigational site, St. Jude Medical will inform the responsible regulatory authority, as appropriate, and ensure that the EC are notified, either by the Principal Investigator or by St. Jude Medical. If the suspension or premature termination was in the interest of safety, St. Jude Medical will inform all other Principal Investigators.

If suspension or premature termination occurs, St. Jude Medical will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical study, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

16.2 RESUMING THE STUDY AFTER TEMPORARY SUSPENSION

When St. Jude Medical concludes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, St. Jude Medical will inform the Principal Investigators, EC, or CA, where appropriate, of the rationale, providing them with the relevant data supporting this decision.

Concurrence will be obtained before the clinical study resumes from the EC or CA where appropriate.

If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

16.3 STUDY CONCLUSION

The study will be concluded when:

- All sites are closed AND
- The final report generated by St. Jude Medical has been provided to sites or St. Jude Medical has provided formal documentation of study closure.

17.0 PUBLICATION POLICY

The results of the clinical study will be submitted, whether positive or negative for publication.

A 'Publication Agreement' will be signed between the Principal Investigator and the sponsor either as a separate Publication Agreement or within the Clinical Trial Agreement.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

18.0 BIBLIOGRAPHY

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Appendix A: Abbreviations

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
DD	Device Deficiency
DMP	Data Management Plan
DSRC	Device/System-Related Complications
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D	EuroQOL Five Dimensions Questionnaire
GDMT	Guideline Directed Medical Therapy
GP	General practitioner
HF	Heart Failure
ICD	Implantable Cardiac Device
IPG	Implantable Pulse Generator
ISO	International Organization for Standardization
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IV	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular Ejection Fraction
MEMS	Micro-ElectroMechanical System
NYHA	New York Heart Association
PA/PAP	Pulmonary Artery/ Pulmonary Artery Pressure
PD	Protocol Deviation
PHQ	Patient Health Questionnaire
PI	Principal Investigator
RHC	Right Heart Catheterization
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SJM	St. Jude Medical
WMA	World Medical Association

Appendix B: CIP Revision History

Revision History				
Amendment Number	Version	Date	Rationale	Details
Not Applicable	VA	15DEC2015	First release of CIP	NA
1	VB	28OCT2016	Clarification of eligibility criteria	Protocol-specific definition of HF hospitalization revised to add to the current definition the use of treatments other than IV medications and to specify an overnight stay
2	VB	28OCT2016	Extended follow up at the request of BSI for collection of longer term safety information	Subject follow up changed from follow up is completed following their 12 month visit to all patients will be followed until the last subject completes their 12 follow up visit. Updated study duration, study flow diagram, Adverse Events section in Statistical Considerations, and Patient Consent Form to reflect this change
1	VC	19SEP2017	Guidelines for standardized pre- and post-discharge HF care, the recommended use of the Subject Contact Log and the Structured Interview, and the need to document screening failures added. Clarifications added where needed.	Guidelines for standardized pre- and post-discharge HF care added (optimization of HF therapy prior to discharge; patient education and patient self-monitoring). The Subject Contact Log should be used each time a subject is contacted by a member of the study site.

Appendix C: Declaration of Helsinki

The most current version of the document will be followed.

Appendix D: 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. For baseline, the clinical assessment of NYHA Class should incorporate the predominant symptoms over the previous 30 days of the patient's life prior to study enrolment:

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 E: 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 normal ranges, which should be the goal of therapy if possible. The physician can adjust the thresholds specifically for each patient. These threshold notifications are intended to guide the physician to review the CardioMEMS HF 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 only require a weekly review. All patients should be reviewed at least weekly. The physician or designee has unlimited access to the CardioMEMS HF 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). 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 latest ESC Guidelines on Acute and Chronic Heart Failure (Reference European Heart Journal (2012) 33, 1787–1847).

The hypothesis of this study is that treating heart failure patients using frequently assessed PA pressures is superior to standard follow-up methods. The PA pressure readings should be used to guide medical therapy, particularly diuretics, but should be used in the context of the overall patient condition. It is important to make medication changes based on review of the PA pressures trends. 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
- 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

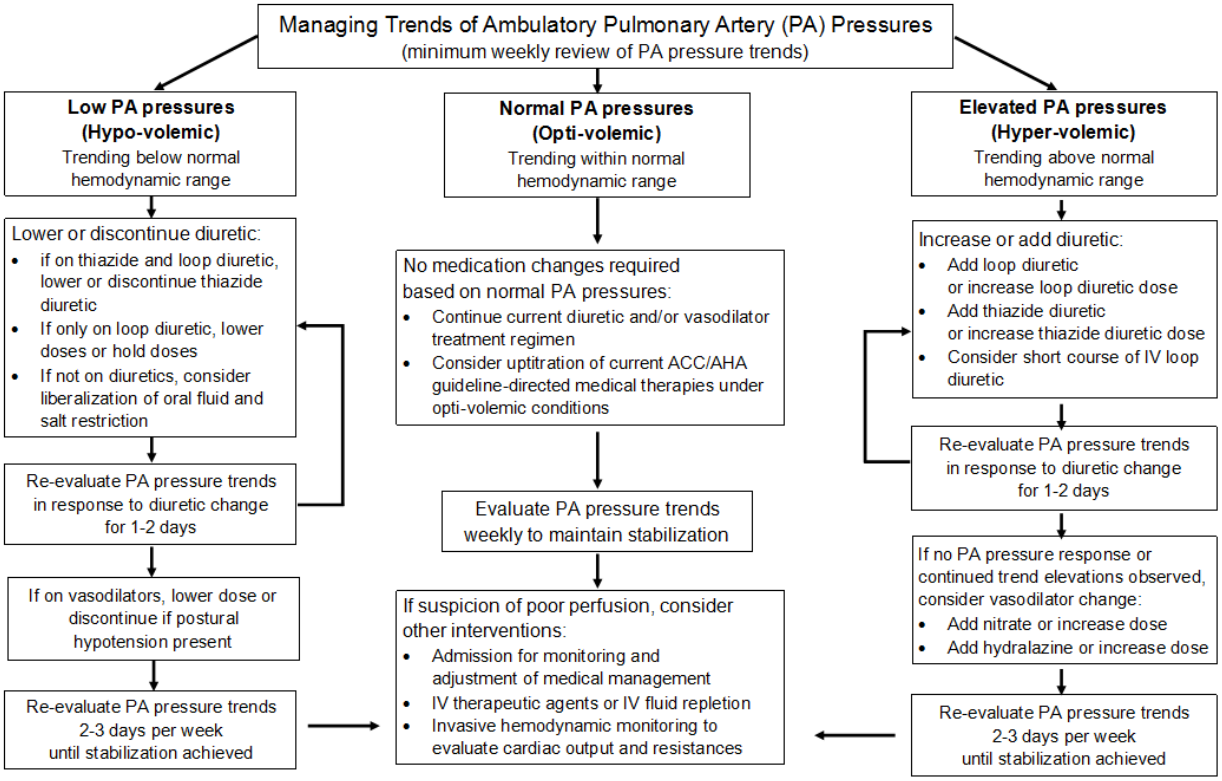
Treatment Recommendations

- 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 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

Costanzo et al, J Am Coll Cardiol HF 2015; Adamson et al, J Card Fail 2011;17:3-10.



Appendix F: List of clinical investigation sites and EC

A list of Clinical Investigational sites and EC will be kept under a separate cover and is available upon request.

Appendix G: Sample Informed Consent

STUDY TITLE AND NUMBER	**CardioMEMS European Monitoring Study for Heart Failure**
SPONSOR	**St. Jude Medical, Inc.**
PRINCIPAL INVESTIGATOR	**Name of principal investigator** **Address**
SITE NAME	**Institution/Site Name** **Address**

Introduction

You are being asked to take part in a research study which consists in an observational study evaluating the CardioMEMS HF System because your doctor has determined that this technology could be beneficial to you in improving the treatment of your heart failure disease.

Heart failure (HF) is a disorder resulting from damage to the heart. High blood pressure (hypertension) or narrowed or blocked blood vessels to the heart (coronary artery disease) are the most common causes of heart failure. This damage makes it difficult for the heart to pump enough blood to meet the demands of the body. Heart failure is a progressive disease that often gets worse over time and may necessitate frequent hospitalizations.

This form explains why this observational study is being done and what your role will be if you decide to participate. This form also talks about the possible risks that may happen if you take part in this study. The study is sponsored by St. Jude Medical (SJM). This company manufactures medical devices intended to treat various medical conditions.

Please read this form, and ask your study doctor any questions you may have about the observational study so that your questions may be answered before you decide if you want to take part in the study. This form may contain some words that you do not understand, please ask the study doctor or the study staff to explain any words or information that you do not understand. Please take your time and talk about this information with your family, friends, or family doctor.

If you decide you want to take part in the observational study, you will be asked to sign the consent section before any study-related activities are performed. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the observational study
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

Taking part in this observational study is entirely voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part in the study. Refusing participation will not involve any penalty or loss of benefit.

What is the purpose of this study?

The CardioMEMS HF System is commercially approved in the United States since May 2014. The approval was granted based on the results of a clinical study (CHAMPION Trial) in which the system was proven to reduce hospitalizations related to heart failure. The purpose of this observational study (CardioMEMS European Monitoring Study for Heart Failure) is to demonstrate that the use of the CardioMEMS HF System will have comparable benefits for patients with heart failure living in Europe, and in other regions. The CardioMEMS HF

system is market-released in Europe and Australia and participation in this observational study does not increase your health risks.

In order to evaluate if the CardioMEMS-HF System is effective in reducing hospitalizations related to heart failure, the study team will collect information on your hospitalizations before and after you receive the CardioMEMS HF system. To do so you will come for visits with your doctor which are part of your normal care and would be done even if you were not in the study. In addition to the assessments that are considered to be part of your normal care, you will be asked to answer three questionnaires on how you are feeling; these questionnaires are called Quality of Life questionnaires.

What is the device being tested?

Typically, physicians who treat patients with heart failure rely on signs and symptoms (such as weight increase and lab values) to adapt their therapy (essentially medications) in order to reduce the patient's symptoms or to control the worsening of symptoms.

The CardioMEMS HF System is a novel technology that provides daily measurement of the patient's pulmonary artery (PA) pressure which is a good indicator of the 'state' of heart failure. The PA pressure information is transmitted to a secure website, remotely accessible by the physician who is able to adjust your treatment (usually changes in medications) before the symptoms get too serious. This system has obtained appropriate approvals to be market release within Europe.

The CardioMEMS HF System consists of 3 components:

- The *wireless sensor* (about the size of a paperclip) is permanently implanted in your pulmonary artery (a vessel close to the heart) and measures your pulmonary artery (PA) pressure.
- The *patient unit* is used at home by you to record your own PA pressure, as measured by the sensor, and to transmit the information to the website. You need to lie on a special pillow containing an antenna for few minutes in order to record the PA pressure. The transmission to the website is done automatically by the unit.
- The *hospital unit* is used by the physician to record your PA pressure while in the clinic or hospital using a similar antenna as the one used at home.

What will be requested from you if you take part in this observational study?

Enrollment and Baseline visit

During this visit, the study will be thoroughly explained and the study staff will evaluate whether you can participate in the study. Before any study-related procedures are performed, you will be asked to carefully read this patient information sheet and sign the informed consent form at the end of this document to confirm your wish to participate.

If your doctor determines that you cannot take part in this study or that you do not need the sensor implant or that another type of heart failure treatment would be better for you, your participation will end.

Your doctor or other study personnel will conduct the following assessments and reviews:

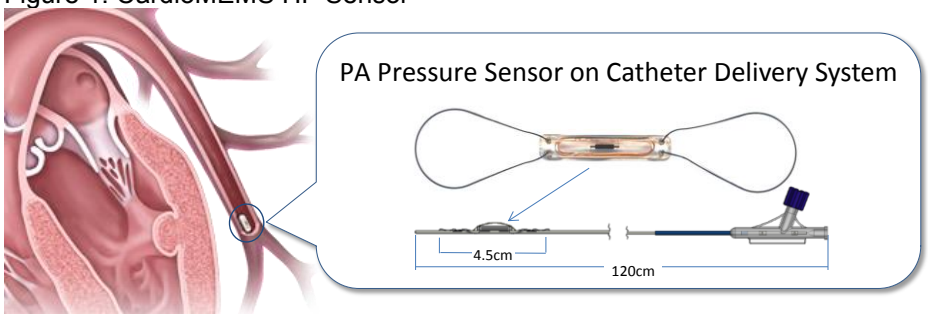
- Demographics information (gender, age)
- Physical examination including vital signs (heart rate and blood pressure), weight, height.
- Classification of the severity of your heart failure
- Review of your medical, surgical and cardiac device (if applicable to you) history
- Review of your heart failure medications
- Review of your heart failure hospitalizations in the 12 months prior to the implant
- You will be asked to answer three quality of life questionnaires

Your doctor will make arrangements to schedule your sensor implant procedure.

Sensor implant procedure (Standard of Care for this type of device).

The sensor is about the size of a paper clip and has a thin curved wire at each end. It is placed inside your pulmonary artery with a special delivery catheter. The sensor will be implanted during a heart catheterization procedure which is a standard hospital practice for collecting pressure information in patients suffering from heart failure. The procedure may last up to one hour.

Figure 1. CardioMEMS HF Sensor



After the procedure is completed, your will be taken care of as per your hospital practice. This might consists of the use of a heart failure information booklet and a booklet that will help you recording your heart failure signs and symptoms. You might be called by your doctor on a regular basis depending on the severity of your symptoms to check how you are feeling about your heart failure.
Your doctor or nurse will instruct you how take PA pressure readings from your home using the patient unit. The home readings typically take less than one minute to complete. It is important that you are comfortable with setting up your patient unit and that you understand how to take a reading. You will be asked to take your reading once a day. Should you need assistance with the System when you get home, you may call the St. Jude Medical helpline at *[insert toll-free/local number]*.

Your doctor will have access to your PA pressure information through the secure website allowing him/her to make adjustments to your heart failure treatment (usually changes in medications). As a result, you will be contacted by your doctor or his/her staff periodically during the study when these adjustments are necessary. It is important that you follow all the instructions from your doctor, including taking PA pressure readings and going to all of the scheduled follow-up visits. You should feel free to contact your doctor or his/her staff as you would normally do and it is important that you notify your doctor immediately if you have any worsening symptoms of heart failure.

Follow-Up Visits
Following your sensor implant, you will return to see your doctor for follow up visits at 6 months and 12 months and every 6 months until the study is complete. This visits are part of you routine clinical Follow up after Sensor Implant. Your involvement in the study will last up to a maximum of 36 months.

During the study visits, the following assessments will be conducted:

- Classification of the severity of your Heart Failure (6 months and 12 months visits)
- Physical examination including vital signs (heart rate and blood pressure) and weight (6 months and 12 months visits)
- Review of your heart failure medication
- Review of adverse events, if any, that have occurred since your last visit
- Review of hospitalizations, if any, that have occurred since your last visit
- You will be asked to answer three quality of life questionnaires (6 months and 12 months visits)
- Your doctor may obtain PA pressure measurements during the visit
- You will be reminded to take your PA pressure readings on a daily basis.

How long will the study last?

If you agree to take part in the observational study, your involvement is expected to last up to a maximum of 36 months. You will be asked to return to the clinic a minimum of 2 times. Each visit will take approximately 45 minutes.

It is anticipated that about 230 people will take part in this observational study at about 35 centers in Europe.

What are the possible risks and discomforts?

There are risks, discomforts, and inconveniences associated with any observational study to you (or to an embryo, unborn child or nursing infant if you become pregnant). These deserve careful thought.

The risks and complications associated to the study device have been assessed in 567 patients in the United States in the CHAMPION trial. There were no reports of failures of the sensor and no unanticipated complications.

Your study doctor will inform you about the risks and complication that are related to the heart catheterization and/or drugs associated with the procedure. These risks are expected to be similar to those related to any standard heart catheterization. You should talk with your study doctor if you have any questions.

Potential adverse events associated with the implantation procedure include, but are not limited to the following:

- Air embolism
- Allergic reaction
- Abnormal heart rate or rhythm
- Bleeding
- Bruising
- Chest pain
- Nausea
- Stroke
- Infection
- Sepsis
- Delayed wound healing
- Atrial dysrhythmia
- Thrombus formation
- Hematoma
- Venous trauma
- Valve damage
- Pulmonary infarct
- Pulmonary embolism
- Heart attack (myocardial infarction)
- Death
- Hemoptysis
- Sensor does not detach from delivery system

At implant, your sensor is set up to measure the pressures in your heart. In rare cases, it may be necessary to repeat this set up so that it can measure your heart pressures correctly. This would require that you undergo an echocardiogram or an equivalent procedure as the one needed for the initial implant (heart catheterization procedure) and would include the risks associated with those procedures.

There may be other risks or discomforts to you (or to an embryo, unborn child or nursing infant if you become pregnant) that are not known at this time. If important information is learned during the course of this observational study, your doctor will be notified by St. Jude Medical. Your doctor will discuss with you important new information that is learned during the course of this study that may affect your condition or willingness to continue to take part in this observational study.

What are the possible benefits to you or others?
If you decide to take part in this observational study, you may expect a reduction in hospitalizations related to heart failure, but there is no guarantee that this will happen. The information gathered in this study may also add to the understanding of treatment options for other patients with heart failure.

If you do not want to take part in this observational study, what other options are available to you?
An alternative is not to participate in this study and continue with your current care.
There is no other similar approved therapy to the CardioMEMS HF System. Currently, heart failure patients can be followed up remotely by means of telephone or internet systems used for the monitoring of worsening heart failure symptoms and/or weight. Your study doctor will discuss other options available to you.

If you choose to take part in this study, what are the costs?
Any tests or examinations that are not part of your routine care and that are required as a consequence of your participation in this study will be free of charge. There will be no cost associated with the use of the patient unit at your home.

[Any country specific additional requirements should be added here.]

Will you receive payment for taking part in this observational study?
No payment will be made to you for taking part in this observational study.

Who is organizing and funding the observational study?
This observational study is being sponsored and funded in *[insert country]* by St Jude Medical. St Jude Medical may benefit financially from this observational study if, for example, the project assists St Jude Medical to obtain approval for a new device.

In addition, if knowledge acquired through this observational study leads to discoveries that are of commercial value to St Jude Medical, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

[Name of institution] will be compensated by St Jude Medical for undertaking this research study. No member of the research study team will receive a personal financial benefit from your involvement in this research study (other than their ordinary wages).

What if you are injured because of this study?
If you suffer any injuries, illnesses, or complications as a direct result of participation in this study, medical treatment will be available to you. You or your insurance company will be responsible for all costs resulting from such treatment. No other arrangement has been made for other compensation (such as lost wages, lost time or discomfort) with respect to such injuries. However, signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities.

During the study, if you experience any injuries, illnesses, or complications from taking part in this observational study, please contact *Dr.* _____ *at* ___-___-_____.

[Any country specific additional requirements regarding insurance should be added here.]

What are your rights if you decide to take part in this observational study?
Your signature on this consent form means that you have received information about this observational study and that you agree to be a part of the observational study.

You may stop taking part in the observational study at any time without penalty or loss of benefits to which you are otherwise entitled. If you wish to stop taking part in this observational study for any reason, you should contact your study doctor. If you withdraw your consent during the study, the study doctor and study staff will not collect

additional personal information from you, although personal information already collected will be retained. You should be aware that data collected by the sponsor up to the time you withdraw will be part of the study results.

Your doctor or designee will discuss with you what follow-up is required if you decide to withdraw, or are withdrawn from the observational study before the study is finished.

Your doctor or the sponsor of the study may also stop your participation in the observational study at any time, without your consent for any reason.

Role of the sponsor representative

The role of the sponsor representative in this study is to provide training and technical support. A representative of the sponsor may be present during the sensor implant procedure. The sponsor's representative may assist your doctor to make sure your CardioMEMS HF System is working as expected. The representative will work under the direction of your doctor and may be aware of your medical history but will in no way compromise your confidentiality.

How will your information be kept confidential?

To help keep your medical file and personal information confidential, only certain authorized people will have access to your records. These include the researchers in your hospital who are part of this study, the sponsor, its affiliates and representatives of SJM that perform study-related services in the United States (U.S.), Europe and other countries, the regulatory authorities and/or the ethical committees, insofar as this relates to this study. The goal of this access is to follow-up on the study progress, to verify the study data and procedures, and to ensure that the information collected for this study is accurate. Your study doctor or one of his/her colleagues will supervise the access to your personal records.

Your personal data will be key-coded using a unique patient number before they are processed with the purpose not to permit your identification, except if necessary for the purpose of the trial or for regulatory obligations. Your coded study data will be processed manually as well as by computer and analyzed during and after the study.

Your coded personal data may be transferred outside of the European Economic Area, including to the U.S., for purposes that include, without limitation, processing, monitoring, auditing and control of the study or the conduct of inspections by the relevant authorities, medical product development, additional scientific analysis of the study data and obtaining approval to use and market medical products resulting from, or related to the study. Your coded study data may be transferred to other countries where data protection laws may not be as strict as in your own country. However, SJM has taken security measures to ensure your identity will not be disclosed.
You have a right to access your personal data and to have any justifiable corrections made. If you wish to do so, you should request this to your study doctor.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

By signing the Patient Informed Consent form, you authorize the sponsor to use the information obtained during the study for scientific communications and publications in medical journals without disclosing your name and any other information that could identify you. By signing, you also agree that your General Practitioner may be informed of your participation in this study unless you specifically request not to do so.

[Any country specific additional requirements regarding personal data protection should be added here.]

Who can you contact for study information?

If you have any questions or concerns about the study or taking part in this observational study or in the event of an injury, you should preferably contact Dr. _____ at ___-___-_____.

In addition, if you have any concerns, complaints or questions about your rights as a observational study patient or an injury that you believe is a study-related, you should preferably contact Dr. /Mr. /Mrs. _____ at -___-___-_____.

Consent and authorization for participation in this observational study

Taking part in this observational study is entirely voluntary. You are making a decision on whether or not to take part in the observational study. Your signature indicates that you have read the information in this document and have decided to take part in the observational study. You will be given a signed and dated copy of this form to keep.

I have read all of the above information in this consent and authorization form. I have had the opportunity to ask questions and have received answers concerning areas I did not understand.

- I willingly give my consent to participate in this study and to comply with the procedures related to it.
- I confirm that my relevant coded personal data collected during the study will be used in the analysis and communicated in publications.
- I understand that I am free to refuse to participate in the proposed study, without giving any reason and without my medical care or legal rights being affected.
- I understand that I am free to withdraw from the proposed study at any time, without giving any reason, without my medical care or legal rights being affected.
- I give my permission to representatives from the sponsor, the ethics committee and the regulatory authorities to access my medical records.
- I understand that my personal physician may be informed of my participation in this observational study.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Person Obtaining Consent (please print) _____

Signature _____ Date _____

Appendix H: Case Report Forms

The Case Report Form will be kept under a separate cover and will be available upon request.

Appendix I. Additional detail regarding sample size calculations

Sample Size for Safety to Demonstrate Superiority to Performance Goal

Freedom from device / system-related complication (CHAMPION reported 0.986)

Numeric Results for testing H0: P = P0 versus H1: P > P0
Test Statistic: Exact Test

Power	N	Proportion Given H0 (P0)	Performance Goal Proportion Given H1 (P1)	Target Alpha	Actual Alpha	Beta	Reject H0 If R ≥ This
0.8631	230	0.8000	0.8700	0.0500	0.0385	0.1369	195
0.8745	235	0.8000	0.8700	0.0500	0.0402	0.1255	199
0.8850	240	0.8000	0.8700	0.0500	0.0419	0.1150	203

Freedom from Sensor Failure (CHAMPION reported 1.00)

Numeric Results for testing H0: P = P0 versus H1: P > P0
Test Statistic: Exact Test

Power	N	Proportion Given H0 (P0)	Performance Goal Proportion Given H1 (P1)	Target Alpha	Actual Alpha	Beta	Reject H0 If R ≥ This
0.8840	230	0.9000	0.9500	0.0500	0.0436	0.1160	215
0.8676	235	0.9000	0.9500	0.0500	0.0350	0.1324	220
0.9043	240	0.9000	0.9500	0.0500	0.0475	0.0957	224

Sample Size Calculations for Heart Failure Hospitalization Rate

The ESC-HF Pilot study showed 29.5% of previously hospitalized patients were re-hospitalized for HF by 1 year (see figure below). Since this study included NYHA I and II patients and 24% of the total number of re-hospitalizations were of unknown cause, the actual percent re-hospitalized for NYHA III-only patients is likely to be higher than 29.5%. The CHAMPION study in NYHA III-only patients found that 36.8% of Control patients were re-hospitalized for HF by 1 year. Thus the true re-hospitalization rate for European NYHA III patients is likely the same as observed in CHAMPION. Accordingly, the repeat HF hospitalization rate estimates from CHAMPION should serve as good estimates for European patients (Table B). The sample size was calculated using PASS v13.0.10.

Figure A. ESC-HF Pilot Study Results (A.P. Maggioni et al., 2013)

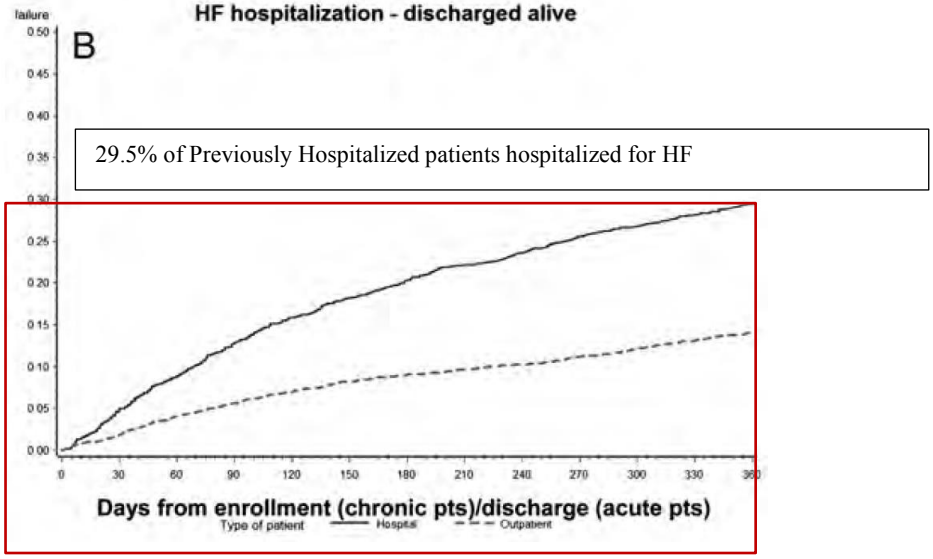


Table A. Proportion of CHAMPION Subjects Hospitalized for Heart Failure Up to 1 Year

	TREATMENT (270)	CONTROL (280)
12 Months	76 (28.2%)	103 (36.8%)

Table B. Sample Size for Effectiveness to Demonstrate Superiority of Treatment to Control Rate

Power	CHAMPION Treatment Rate at 1 Year (Assumes same rate in EU Trial)	Control Rate at 1 year (Assumes same rate in EU Registry)	% RRR	Treatment Sample Size* **(+ 20% W/D)**
0.90	0.52	0.75	30.7%	130 (**156**)
Power	EU Treatment Rate at 1 Year (Assumes worse scenario)	Registry Rate at 1 year (Assumes worse scenario)		Sample Size*
0.90	0.55	0.72	23.6%	234 (**281**)

*Sample size required to show superiority of Treatment at 1 year in EU Trial to Control rate at 1 year in EU Registry using a 1-sample, 1-sided Poisson Test with α of 0.025. The Control rate is treated as a fixed value, similar to historical control comparison

Appendix J: Quality of life questionnaires

The EuroQOL Five Dimensions Questionnaire (EQ-5D), the Kansas City Cardiomyopathy Questionnaire (KCCQ), and the Patient Health Questionnaire (PHQ-9) will be kept under a separate cover and are available upon request.

Appendix K: Subject Contact Log

Abbott	MEMS-HF – SUBJECT CONTACT LOG	CENTER ID_____

SUBJECT STUDY ID _____

[1] Reason for call: PAP Low (L) / PAP High (H) / Transmission compliance (TC) / Reminders (R) / Patient's call (PC) (detail in comment section)/ Contact by email (C@)/ Other (detail in comment section) (OTH); standardized post-discharge HF care (PDHC)

DATE OF CALL	REASON OF CALL[1]	CALL SUCCESSFUL	NURSE/PHYSICAN NAME	CALL DUR. (MIN)	CALL OUTCOME (IF OTHER IS CHECKED, SPECIFY ACTION TAKEN UNDER "COMMENTS")	COMMENTS DOCUMENT EACH DRUG CHANGE IN THE CRF
___/____/_____		☐ YES ☐ NO			☐ New Drug given ☐ Drug Change ☐ Other	
___/____/_____		☐ YES ☐ NO			☐ New Drug given ☐ Drug Change ☐ Other	
___/____/_____		☐ YES ☐ NO			☐ New Drug given ☐ Drug Change ☐ Other	
___/____/_____		☐ YES ☐ NO			☐ New Drug given ☐ Drug Change ☐ Other	
___/____/_____		☐ YES ☐ NO			☐ New Drug given ☐ Drug Change ☐ Other	

Appendix L: Structured Interview

OPENING

Hello, we are calling you today to discuss the PA readings that you have been transmitting.

Do you remember that we had agreed on this telephone date?
This call will take about 15 minutes of your time. Is it okay to talk now?
Before we begin do you have questions regarding our last telephone call? Has anything been left unclear?

GENERAL HEALTH

1-How would you describe your general health?

1 Excellent ☐ 2 Very good ☐ 3 Good ☐ 4 Moderate ☐ 5 Bad ☐

2-Compared with your general health state at discharge from hospital / since our last telephone contact, how would you rate your general health now?

1 Much better ☐ 2 Somewhat better ☐ 3 Pretty similar ☐ 4 Somewhat worse ☐ 5 Much worse ☐

BODY WEIGHT

3-Have you measured your weight? _____kg Not measured ☐

4-Has your body weight increased over the last week(s)? No ☐ Yes ☐

BLOOD PRESSURE

5- Have you measured your resting blood pressure? ___/__mmHg Not measured ☐

HEART RATE

6- Have you measured your resting heart rate? ____beats/min Not measured ☐

7- Is your pulse regular? No ☐ Yes ☐

EDEMA

8- Have you noted swelling of your ankles or lower legs?

1 No ☐ 2 Slight ☐ (small dint, vanishing after a short while) 3 Considerable ☐ (deep dints, stay there for a longer time)

DYSPNEA / FATIGUE (NYHA CLASSIFICATION)

9- Do you experience dyspnea/breathlessness/fatigue with simple tasks during your normal life or at rest?

1 Never, no limitation ☐ 2 Minor compromise at light physical activity ☐ 3 Major compromise at physical activity ☐ 4 At rest or with any slight effort during everyday life ☐

FALLS

10- Did you experience any falls recently?	No ☐	Yes ☐

MOOD SCREENING		
11- How would you rate your mood/temper today on a scale of one (best) to six (worst)?		
You rated your mood (check last value) _____ during our last call. The value now is _____		
Do you think your mood has changed substantially since our last contact?	No ☐	Yes ☐

DAILY LIFE
12- How do you get on with your daily life?
How would you rate it on a scale of one (=best) to six (=worst)?

HOSPITALIZATIONS AND/OR VISITS TO THE SUBJECT GP OR SPECIALIST
13- Were you hospitalized and/or did you visit your GP or your Cardiologist since or last call?
If yes for hospitalization: document in detail on respective study CRF spreadsheet

MEDICATIONS		
14- Were there any changes in your medication (type and dose) since our last call? *If yes: document in detail on respective study CRF spreadsheet*	No ☐	Yes ☐

MEDICATIONS CHANGES DUE TO PAP CHANGES MADE DURING THIS CALL?	No ☐	Yes ☐
If yes, document in detail on respective study CRF spreadsheet		

SCHEDULING THE NEXT CALL (EXAMPLES)

I would like to contact you again in xx days' time in case further changes in your heart failure treatment are needed.

I suggest the following date: _____ at _____ o´clock.