Validation of CardioMEMS HF System Cardiac Output Algorithm IDE Clinical Investigation Plan

[redacted]

Val**I**dation of **C**ardioMEMS HF Sys**T**em Cardiac **O**utput Algo**R**ithm (VICTOR) IDE

NCT05428384

Version Number	B
Date	June 6, 2022
Planned Number of Sites and Region(s)	Up to 15 sites in the United States
Clinical Investigation Type	Prospective, single arm, multi-center, clinical investigation.
Abbott Medical Expert	[redacted]
Sponsor	St. Jude Medical (Abbott) [redacted]
Electronic Data Capture Software	[redacted]
Core Laboratories	[redacted]
CIP Author of Current Version	[redacted]

[redacted]

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

Site Principal Investigator

Printed name:
Signature:
Date:

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COMPLIANCE STATEMENT:
This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, and the applicable regulatory requirements (such as, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, 21 CFR Part 54, and 21 CFR Part 11). The conduct of the clinical investigation will be approved by the Food and Drug Administration (FDA) and the appropriate Institutional Review Board (IRB) of the respective investigational site.

1.0 INTRODUCTION

This document is a clinical investigation plan (CIP) for the **V**al**I**dation of **C**ardioMEMS HF Sys**T**em Cardiac **O**utput Algo**R**ithm (VICTOR) IDE study. The investigation will enroll subjects who have been previously implanted with the CardioMEMS™ PA Sensor. This clinical investigation is twofold; in the first phase (development phase) data collected will be used to complete development of an algorithm that can estimate cardiac output (CO) from CardioMEMS™ HF System readings. The second phase (validation phase) of this clinical investigation is intended to compare the CO estimate from the CardioMEMS HF System to CO estimates from Cardiac MRI (reference standard). This clinical investigation will be conducted under an investigational device exemption (IDE) and is intended to support market approval of the CO feature in the United States. This clinical investigation is sponsored by Abbott.

This clinical investigation will be conducted in accordance with this CIP. All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

1.1 Background and Rationale

1.1.1 Background

Heart failure (HF) is a serious and pervasive disease affecting more than 64 million people worldwide and accounts for more than one million hospital admissions each year in the United States (US) and Europe alone[1]. By 2030, the prevalence of developing HF is expected to nearly double[2]. With symptoms including shortness of breath, excessive tiredness, and systemic swelling, HF patients typically suffer impairment in functional capacity and quality of life. Despite current recommendations for evaluation and management, HF related morbidity and mortality remain high. HF related hospitalization is the leading cause of hospitalization among adults > 65 years of age in the US. Particularly, admission rates following HF hospitalization remain high[3-4], with > 50% of patients readmitted to the hospital within 6 months of discharge[3-4]. Since reduction in readmission rates reduces health care costs and improves quality of care, public and private payers have increasingly targeted readmission as a focus of pay-for-performance initiatives[5-6].

The majority of HF disease management has focused on surveilling traditional signs and symptoms of HF such as weight and vital signs in order to detect decompensation in time to avoid hospitalization. However, even when great effort is put into enhancing surveillance of these precursors of decompensation using such strategies as telemonitoring, no incremental benefit over routine clinic-based care is observed[7]. Hemodynamic monitoring offers the opportunity to detect changes in pressure that occur weeks before the traditional signs and symptoms that prompt a heart failure hospitalization (HFH). Because of this, an implantable hemodynamic monitoring system, such as the CardioMEMS HF System, is a superior approach to the detection of impending congestion in advance of traditional signs of HF decompensation. Pulmonary artery pressure (PAP) information collected via the CardioMEMS HF

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System was used in the CHAMPION™ trial. Results from this pivotal trial demonstrate that patients managed with PAP data provided by the CardioMEMS HF System along with standard of care, experienced a 28% reduction in hospitalizations compared to the patients who were managed based on standard of care alone[8]. Such benefit was sustained with a 33% reduction in heart failure hospitalizations over the full randomized study duration[9]. Further evidence from the MEMS-HF study conducted in Europe and long-term data collected during the CardioMEMS US Post-Approval Study (PAS) have shown continued safety, large longitudinal reductions in HFH, and improvements in quality of life[1,7]. Most recently, the GUIDE-HF trial demonstrated the benefits of hemodynamic guided management in an expanded population of NYHA class II and NYHA class III subjects with a recent HF hospitalization or elevated natriuretic peptides[10]. Prior to the COVID-19 pandemic, management utilizing PA pressure data from the CardioMEMS PA Sensor was shown to reduce a composite of HF hospitalizations, urgent HF visits, and all-cause mortality in the GUIDE-HF patient population.

1.1.2 Rationale for Conducting this Clinical Investigation

[redacted] CO is an important parameter that can be used to gain a greater understanding of the hemodynamic pathophysiology in patients with HF. As HF advances, CO becomes too low to meet the metabolic demands of the body[2,11]. When CO is reduced, the body tries to compensate for this reduction and maintain normal arterial pressures by activating neurohormonal pathways that increase fluid retention and vessel constriction. If not treated appropriately, the result of this process is acute heart failure decompensation.

Currently, the most commonly used methods employed to determine CO, such as thermodilution and the Fick method, are invasive and are inextricably linked to the non-physiological, laboratory environment in which they take place[12]. In this environment, patients have often undergone at least mild sedation and CO measurements taken during this time can only provide information from this one imposed state[12]. In addition to risks associated with these common methods to measure CO, there are also additional costs. The additional costs are not limited to methods that employ invasive means of measuring CO; additional costs are also associated with less invasive means of measurement. CO monitoring using the CardioMEMS HF System may overcome these obstacles and provide information to manage patients with HF. In order to validate that the CO derived from the CardioMEMS HF System is comparable to CO obtained from the reference method, a clinical study in which the CO values from the CardioMEMS HF System are compared against the CO values from cardiac Magnetic Resonance Imaging (cMRI) is being proposed.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

2.1.1 Primary Objectives

There are two primary objectives of this clinical investigation. The first objective is to finalize development of the algorithm estimating CO from CardioMEMS HF System readings by collecting paired cMRI measurements of CO, as well as other parameters of heart function, and CardioMEMS HF System readings in the same subject. The second objective of this clinical investigation is to use data collected during the validation phase, distinct from the subjects within the development phase, to evaluate the agreement between the CardioMEMS HF System-derived CO and the CO values from cMRI in patients previously implanted with the commercially available CardioMEMS HF System.

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2.2 Devices Used in the Clinical Investigation

2.2.1 Name of the Devices Under Investigation

Table 1 details the devices to be used in this study. The CardioMEMS HF System is currently approved by FDA in the US (P100045) and available for market release. The algorithm/software used to estimate CO will be considered investigational in this study.

Table 1: Identification of Devices under Investigation

Device name	Model	Manufacturer	Region/ Country	Investigational or Market Released
CardioMEMS™ PA Sensor and Delivery System	CM2000	St. Jude Medical, an Abbott Company	United States	Market Released
CardioMEMS™ Hospital Electronics System	CM3000 CM3100	St. Jude Medical, an Abbott Company	United States	Market Released
Merlin™ Patient Care Network	CM6000	St. Jude Medical, an Abbott Company	United States	Market Released
CardioMEMS Backend WebApp	CM4000	St. Jude Medical, an Abbott Company	United States	Market Released

2.2.2 Indication for Use

The CardioMEMS HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides. The hemodynamic data are used by physicians for heart failure management with the goal of controlling pulmonary artery pressures and reducing heart failure hospitalizations.

2.2.3 Description of the Devices Under Investigation

The CardioMEMS HF System provides pulmonary artery (PA) hemodynamic data used for monitoring and management of HF patients. The system measures PA pressure and heart rate, which clinicians use to modify and manage HF treatment. The CardioMEMS HF System consists of an implantable PA Pressure Sensor with Delivery System and the Patient and Hospital Electronics Systems, which are designed to read the hemodynamic data from the implanted PA Sensor and transmit the data to a secure website.

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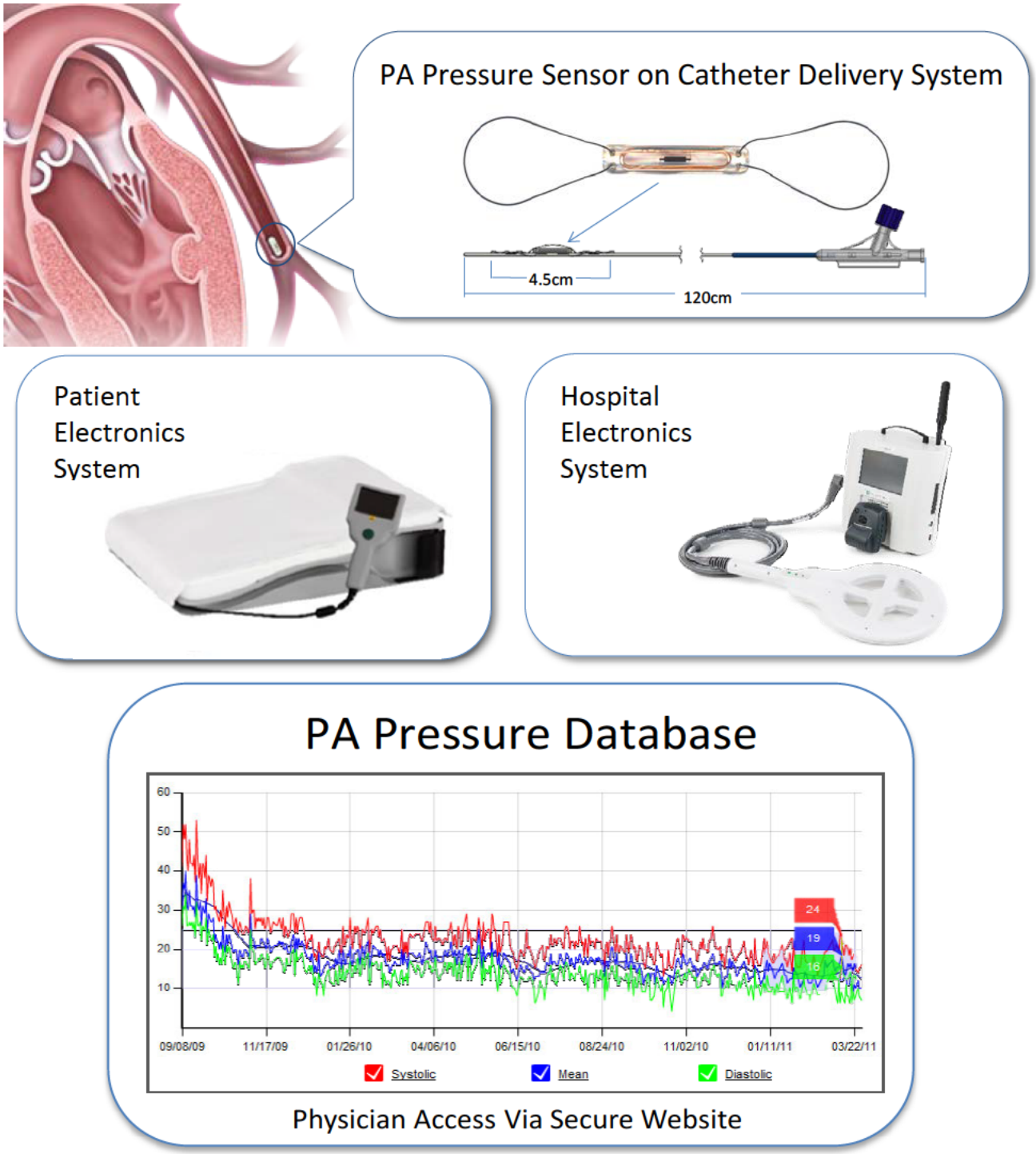
Figure 1. CardioMEMS HF System



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The CardioMEMS PA Sensor and Delivery System features a wireless PA Pressure Sensor mounted to a multi-lumen endovascular delivery catheter used by the clinician to introduce and deploy the PA Sensor in the target implant location within the distal pulmonary artery to achieve the desired therapeutic benefit. Once inserted, the PA Sensor can provide non-invasive diagnostic information regarding a patient's hemodynamic health. Patients can obtain pressure measurements at home or in a clinical setting, which are then transmitted to a secure database for clinician use. The clinician can then access and evaluate the patient's transmitted data, develop tailored treatments, and remotely manage the patient.

Implantable Sensor (CardioMEMS PA Sensor)
The CardioMEMS PA Sensor is a passive implant that is placed in a descending branch of the left or right pulmonary artery to allow wireless measurement and monitoring of hemodynamic parameters in the pulmonary artery. The Sensor housing is fused silica and is encapsulated with silicone. Two platinum/iridium marker bands at each end of the Sensor (total of four marker bands) allow the device to be visualized under fluoroscopy during the implant procedure (and on imaging/x-ray during follow-up visits) and indicate the position of the sensor.

CardioMEMS 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. 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 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 the delivery system is then removed.

Hospital Electronics System and Patient System
The CardioMEMS HF System includes the Hospital Electronics System (CM3000) or Hospital System (CM3100) which is used by clinicians in the hospital or clinic, and the Patient Electronics System (CM1100) which is used for home patient monitoring. The hospital and patient systems are similar except for greater functionality in the hospital system, including display and printing (CM3000 only) of the pressure data. The Hospital Electronics System (CM3000 and CM3100) can be attached to a pole cart and the system software allows pressure measurements to be visualized on the touch screen with systolic, diastolic, and mean PA pressures, as well as a waveform. The software on the Patient Electronics System prompts and guides the patient to make a PA pressure measurement and automatically uploads the information to the website.

Merlin.net Website
The physician accesses data for each of their patients via a secure website that allows the physician to utilize PA pressure measurements in the management of heart failure. When the patient is hospitalized or returns to the clinic/office setting, the Hospital Electronics System can be used to obtain PA pressure measurements and allows the physician to see not only the pressure data, but also the waveform. When the patient returns home the Patient Electronics System can be used to obtain and transmit PA pressure measurements to the website for physician access.

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.

[redacted]

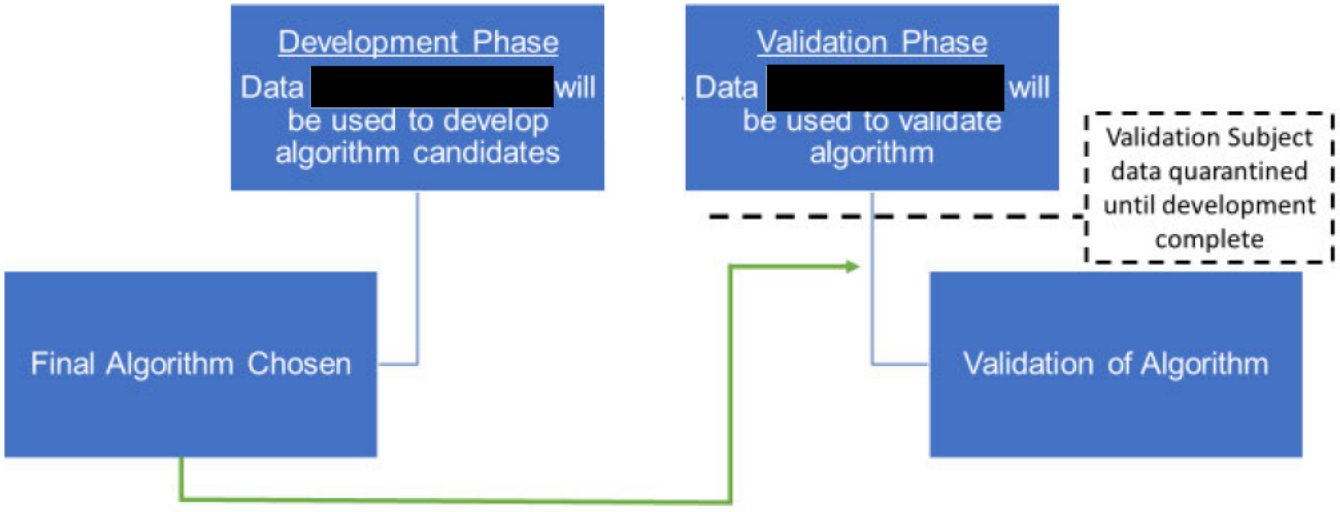
2.2.4 Device Accountability

Device accountability is not required for this study as the study will only enroll patients previously implanted with the CardioMEMS PA Sensor and thus, no implants will be performed as part of the study.

3.0 CLINICAL INVESTIGATION DESIGN

This is a prospective, multi-center, clinical study of patients previously implanted with the commercially available CardioMEMS PA Sensor. The clinical study will be conducted in up to 15 centers in the US. [redacted] Each subject will have [redacted] CardioMEMS HF System readings paired with [redacted] cMRI scans at each study visit (baseline and 3 months) and measurements completed for each subject will be under nominally the same conditions. The measurements will be taken in patients who already have the CardioMEMS PA Sensor implanted and subject data will be collected in two, sequential phases, (Figure 2): 1) Data used to develop an algorithm to estimate CO, termed the development phase; and 2) Data used to validate the CO algorithm, termed the validation phase. [redacted] During the development phase potential algorithms will be assessed to determine the optimal algorithm for estimating CO. Once identified, the selected algorithm will then undergo validation, [redacted]. These subjects will be in addition to and separate from the initial [redacted] subjects enrolled in the development phase. Additional subjects may be added to both the development and validation cohorts based on development needs, [redacted]

Figure 2: Clinical Investigation Design



During validation, measurement data from a distinct subject cohort to subjects included in the development phase will be used to determine if the chosen algorithm meets the validation criteria.

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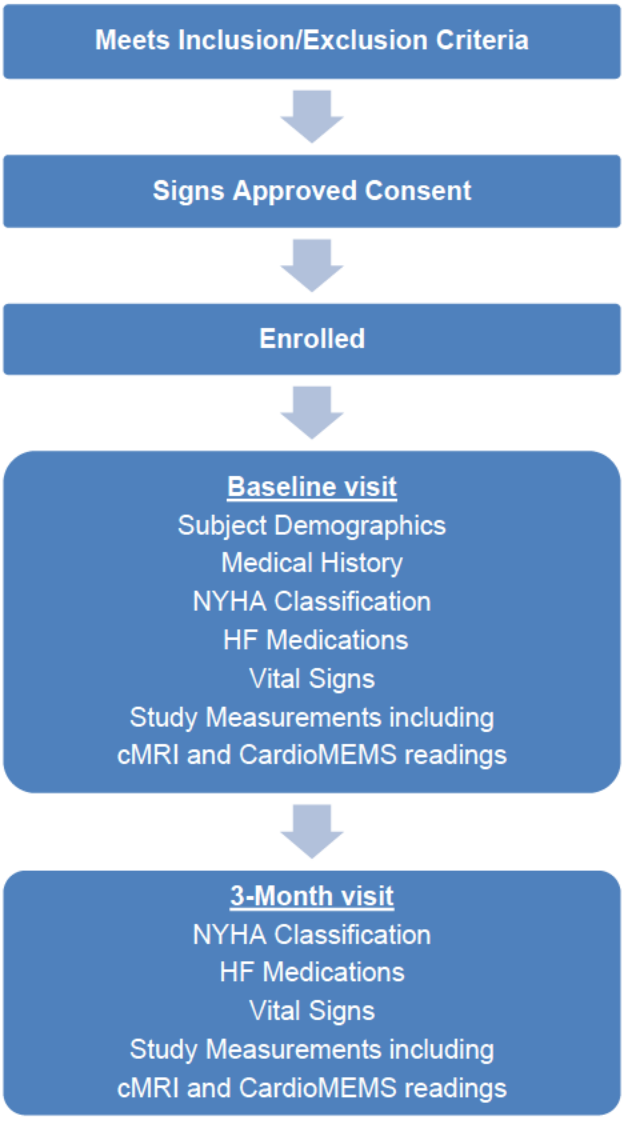
[redacted]

he Sponsor has designed this clinical investigation to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risk Analysis in Section 15.0 of this clinical investigation plan for details.

3.1 Clinical Investigation Procedures and Follow-up Schedule

The flowchart and the follow-up requirements of this clinical investigation are described below.

Figure 3: Clinical Investigation Flowchart



[redacted]

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Clinical sites will follow each subject until they complete their 3-month visit or withdraw from the study. Clinical investigation visits will occur at Baseline and 3 months. Visits will include demographics (baseline), medical history (baseline), adverse event information, NYHA classification, vital signs, and study measurements including, but not limited to, cMRI and CardioMEMS HF System readings.

3.2 Measures Taken to Avoid and Minimize Bias

In order to minimize bias, a core lab will be employed to train sites on the collection of cMRI images and associated data, collect images and imaging data, and review images and imaging data independently.

3.3 Site Selection Criteria

In addition to standard site selection criteria, sites in this study will also be selected based on additional pre-defined criteria. These additional criteria will be defined in advance of site nomination and will be based on the sites ability to perform the imaging assessments required for this trial. In part, the criteria to fulfil these assessments will be based on the technical requirements and training outlined in the protocol provided from the imaging vendor.

3.4 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects
- Further product development is cancelled

Should the Sponsor discontinue the clinical investigation, sites will follow subjects per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The investigator shall return all clinical investigation materials (including devices) to the Sponsor and provide a written statement to the IRB (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in Section 11.5 of the CIP.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators. If suspension or premature termination occurs, the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, if appropriate, and return patients to their standard medical treatment. A Principal Investigator, IRB, or regulatory authority may also suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

4.0 ENDPOINTS

4.1 Primary Endpoint and Rationale

The primary endpoint of this clinical investigation is to estimate CO from CardioMEMS HF System data. The estimated CO will be evaluated for agreement between the CardioMEMS HF System-derived CO and the CO values from cMRI in patients with the CardioMEMS HF System. [redacted]

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[redacted]

4.2 Descriptive Endpoints

[redacted]

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll subjects of all genders who are ≥ 18 years of age from the CardioMEMS HF System patient population. The patient population for this clinical trial consists of potential subjects who have had a CardioMEMS PA Sensor previously implanted for a minimum of 3 [redacted]

months at time of consent. Patients must meet all general eligibility criteria and provide written informed consent prior to sites conducting any investigation-specific procedures not considered standard of care.

5.2 Subject Recruitment/Screening and Informed Consent

5.2.1 Subject Recruitment and Screening

The following assessments are performed as part of the subject recruitment process prior to obtaining informed consent:

- Confirmation of prior CardioMEMS PA Sensor implantation.

A member of the site's clinical investigation team previously trained to the CIP must evaluate patients for the general clinical investigation eligibility criteria, and if applicable, will enter the patients into a site-specific recruitment/screening log. A patient who does not satisfy all general eligibility criteria prior to informed consent is considered a recruitment failure and should not be enrolled in the clinical investigation.

Sites will ask patients meeting general inclusion criteria and no general exclusion criteria to sign an Informed Consent form following the established Informed Consent process (described in Section 5.2.2) if they wish to participate in the clinical investigation. Sites will enter these patients into the recruitment/screening log. Once a duly dated and signed Informed Consent form is obtained, sites will confirm patients meet all eligibility criteria.

Only subjects who meet all inclusion and no exclusion criteria and have consented to the study are considered enrolled in the study. All other subjects should be considered screen failures. The Principal Investigator or the delegated clinical investigation personnel will record the screen failure in the hospital records and on a recruitment/screening log as required.

5.2.2 Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's IRB. This process will include a verbal discussion with the patient on all aspects of the clinical investigation that are relevant to the patient's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Sites must inform patients about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty, or loss of benefits to which the patient is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the patient and will respect patient's legal rights. Financial incentives will not be given to patients. Patients may be compensated for time and travel directly related to their participation in the clinical investigation. The site shall provide the patient with the Informed Consent form written in a language that is understandable to the patient and that has been approved by the center's IRB. The patient shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the patient understands the information provided. If the patient agrees to participate, they must sign and date the Informed Consent form, along with the person obtaining the consent prior to any clinical investigation-specific procedures.

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The site will file the signed original in the patient's hospital or research charts and provide a copy to the patient.

Sites should report any failure to obtain informed consent from a patient to the Sponsor within 5 working days and to the reviewing center's IRB according to the IRB's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, sites will ask the subject to confirm their continuing informed consent in writing.

5.2.2.1 Special Circumstances for Informed Consent
This clinical investigation excludes individuals unable to make the decision to participate in a clinical investigation on their own or who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits, or fear of retaliatory response. This clinical investigation excludes individuals under the age of 18 or age of legal consent from the clinical investigation population.

Sites may enroll individuals unable to read or write in this clinical investigation. Sites will obtain informed consent through a supervised oral process. An independent witness will be present throughout the Informed Consent process. A member of the site's clinical investigation team previously trained to the CIP will read the written Informed Consent form and any other information aloud and explain to the prospective subject and will sign and personally date the Informed Consent form. The witness will also sign and personally date the Informed Consent form attesting that the information was accurately explained, and that informed consent was freely given. In addition, no incentives or financial inducements will be provided to these patients for their participation in the clinical investigation. The clinical investigation excludes pregnant women. All other aspects of the Informed Consent process will follow Section 5.2.2.

In addition, sites must obtain an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), from the subject.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. Patients must meet ALL general inclusion criteria to participate in the clinical investigation. If ANY general exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled (recruitment or screen failure depending on whether or not the patient has signed the Informed consent [screen failure]).

If any clinical and/or laboratory tests are required for patient screening and are not included in a site's standard tests, they must be completed after written informed consent is obtained.

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5.3.2 Inclusion Criteria

1. Subject is willing and able to provide written informed consent prior to any clinical investigation-related procedure.
2. Subject is implanted with the CardioMEMS PA Sensor for a minimum of 3 months at time of consent.
3. Subject is ≥ 18 years of age.
4. Subject is willing and able to undergo several cardiac MRI scans. This is including but not limited to:
    - Subject must have all MRI compatible devices
    - Subject must be able to hold their breath during imaging
    - Subject must be free of all metal bodies, fragments, or implants that would prohibit MRI imaging
5. Subject is willing and able to upload PA pressure information (i.e., take daily CardioMEMS readings and have their hemodynamic information collected at study visits) and comply with the follow-up requirements.

5.3.3 Exclusion Criteria

1. Subject will receive or is likely to receive an advanced therapy (e.g., mechanical circulatory support or cardiac transplant) in the next 6 months.
2. Subject was implanted with Cardiac Resynchronization Therapy (CRT)-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) for less than 90 days prior to consent.
3. Subject is pregnant or planning to become pregnant in the next 6 months.
4. Subject is enrolled into another trial with an active treatment arm.
5. Subject has significant congenital heart disease that has not been repaired.
6. Subject is implanted with mechanical right heart valve(s).
7. Subject has unrepaired severe valvular disease.
8. Subject has an anticipated life expectancy of < 6 months.
9. Subject has an active, ongoing infection, defined as being febrile, an elevated white blood cell count, on intravenous antibiotics, and/or positive cultures (blood, sputum, or urine).
10. Subject has had a major cardiovascular event (e.g., unstable angina, myocardial infarction, percutaneous coronary intervention, open heart surgery, or stroke, etc.) within 90 days prior to consent.
11. Subject has any condition that, in the opinion of the Investigator, would not allow for utilization of the CardioMEMS HF System to manage the subject using information gained from hemodynamic measurements to adjust medications, including the presence of unexpectedly severe pulmonary hypertension (e.g., trans-pulmonary gradient >15) at implant RHC, a history of non-compliance, or any condition that would preclude ability to obtain CardioMEMS PA Sensor readings and paired cardiac MRI data from being collected.
12. Subjects who, in the opinion of the investigator, are at-risk for serious adverse reaction to Dobutamine (ex. subjects with idiopathic hypertrophic subaortic stenosis and subjects who have shown previous manifestations of hypersensitivity to Dobutamine) should be excluded from the study.

Sites should instruct female patients of childbearing potential to use safe contraception (e.g., hormonal contraceptives: contraceptive pills, implants, transdermal patches hormonal vaginal devices, injections with prolonged release.) It is accepted, in certain cases, to include subjects having a sterilized regular

partner or subjects using a double barrier contraceptive method. However, this should be explicitly justified in special circumstances arising from the clinical investigation design, product characteristics and/or clinical investigation population.

5.4 Subject Enrollment

A patient is considered enrolled in the clinical investigation only when they have met all inclusion and no exclusion criteria and have provided written informed consent. If subjects enter the study without meeting all the items listed above, they should complete all follow-up requirements. These subjects are considered CIP deviations.

5.4.1 Enrollment of Medicare Beneficiaries

This clinical investigation will enroll Medicare beneficiaries and therefore conforms to all standards of Medicare coverage requirements. The Risks and Benefits section describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation. Subjects enrolled in the clinical investigation are expected to be consistent with the Medicare population based on age and as such, the clinical investigation results are expected to be generalizable to the Medicare population.

5.4.2 Historically Under-Represented Demographic Subgroups

The Sponsor intends to implement FDA's guidance on sex-specific data in medical device clinical investigations to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical investigation. As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical investigations have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the clinical investigation population may unintentionally exclude specific subgroups
- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Avoidance of specific subgroups by investigators and Sponsor due to the perception that it takes more time and resources to recruit them
- Fear of fetal consequences (for female participants)
- Family responsibilities limiting women's ability to commit time for follow-up requirements

The Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- The Sponsor will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups
- The Sponsor will regularly review enrollment data to investigate whether there is under-representation of these demographic subgroups
- As appropriate and necessary, the Sponsor will retrain sites on the importance of recruiting and retaining subjects in the clinical investigation
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups

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5.5 Subject Withdrawal and Discontinuation

Each subject meeting all general and screening eligibility criteria shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated due to subject non-compliance.

Sites must notify the Sponsor of the reason(s) for subject discontinuation. Investigators must also report this to their respective IRB as defined by their institution's procedure(s).

No additional follow-up is required, or data recorded from subjects once withdrawn from the clinical investigation, except for the status (deceased/alive).

However, if a subject withdraws from the investigation due to problems related to the safety or performance of the device under investigation, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

In case of subject withdrawal of consent, the site should make attempts to schedule the subject for a final clinical investigation visit. At this final follow-up visit, the following will be recorded, with the subject's permission:

• Subject status (deceased/alive)
• Any adverse event details prior to withdrawal of consent

<u>Lost-to-Follow-up</u>

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time, and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, the site should send a letter (certified if applicable) to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Telephone contact with General Practitioner, non-clinical investigation cardiologist, or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

5.6 Number of Subjects

[redacted]

5.7 Total Expected Duration of the Clinical Investigation

[redacted] The expected duration of each subject's participation is 3 months, including the scheduled visits and data collection for this clinical investigation that will occur at baseline and 3 months. Subjects will exit the trial at the end of their 3-month follow-up visit. [redacted]

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

The Principal Investigator is responsible for ensuring all clinical trial data are collected as required per this CIP. Trained Sponsor personnel may provide technical expertise and technical guidance on the use of the CardioMEMS HF System, including the Merlin.net website.

6.1 Screening Procedures

The following information will be evaluated from medical records and documented, to ensure each subject meets entry criteria.

- Subject is implanted with the CardioMEMS PA Sensor for a minimum of 3 months at time of consent.
- Age ≥ 18 years
- Subject has not been implanted with Cardiac Resynchronization Therapy (CRT)-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) for less than 90 days prior to consent
- Subject has not had a major cardiovascular event (e.g., unstable angina, myocardial infarction, percutaneous coronary intervention, open heart surgery, or stroke, etc.) within 90 days prior to consent
- Cardiovascular history including:
  - previous cardiac procedures and CRT device information
  - relevant co-morbidities

  to ensure subjects will meet imaging inclusion and exclusion criteria.
- [redacted]

Enrollment Assessments

The following assessments and information will be collected during the Enrollment visit:

[redacted]

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- Patient & Investigator signed Informed Consent
- Verification of inclusion and exclusion criteria (as necessary from the screening procedures).

Once a duly dated and signed Informed Consent form is obtained, sites will confirm the patient meets all inclusion criteria and does not meet any of the exclusion criteria. A patient is considered enrolled in the clinical investigation only when they have met all inclusion and no exclusion criteria and have provided written informed consent.

6.1.1 Screening Failure

If a **consented** subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure. The Principal Investigator or the delegated trial personnel will record the screening failure in the subject's records and on a screening log as required. To assist the Sponsor in understanding reasons for screening failure, a screening log must be maintained and submitted to the Sponsor on a regular basis. If appropriate, subjects who fail screening may be rescreened at a later date. If any subject discontinues participation after informed consent has been obtained, but prior to any study visit procedures are conducted, the subject must be also documented as a screening failure.

6.1.2 Baseline Assessments

The following assessments and information will be collected during the baseline visit prior to imaging (see Table 2 for additional details).

- Documentation of key demographic information such as ethnicity, sex at birth, and age
- Subject medical history and co-morbidities
- Physical exam including vital signs
- Cardiovascular history including:
  - previous cardiac procedures and CRT device information
  - relevant co-morbidities
- HF assessment including NYHA class evaluation
- HF medication review with documentation
- Limited echo to document EF
- NYHA class evaluation within the previous 30 days
- Calculation of BMI using subject height and weight (see Appendix III) and calculation of chest circumference measurement if BMI > 35kg/m^2

It is strongly recommended that the site obtain alternate contact information for the subject in the event the subject cannot be reached or does not attend follow-up visits. Sites will be encouraged to include the subject's family or significant others in the consent process as well as trial education efforts. This information should be maintained in the subject's research chart.

6.1.3 Baseline Imaging Assessments

[redacted]

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[redacted]

6.1.4 Baseline CIP-Required Medication

[redacted]

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[redacted]

6.2 Blinding

Investigators and subjects will not be blinded.

6.3 Follow-up Assessments

Subjects will have one follow-up visit at 3 months after the baseline visit has occurred.

The following assessments and information will be collected during the follow-up visit prior to imaging (see Table below for additional details).

- Physical exam including vital signs
- Changes to cardiovascular history including:
  - previous cardiac procedures and CRT device information
  - relevant co-morbidities
- HF assessment including NYHA class evaluation
- HF medication review with documentation
- Limited echo to document EF
- NYHA class evaluation within the previous 30 days
- Calculation of BMI using subject height and weight (see Appendix III) and calculation of chest circumference measurement if BMI > 35kg/m^2

6.3.1 Follow-up Imaging Assessments

[redacted]

6.3.2 Follow-up CIP-Required Medication

[redacted]

6.3.3 Schedule of Events

CIP Activity	Enrollment/ Baseline	3 Month ((± 7 days)
Informed Consent Process	X	
Demographics	X	
Physical Examination	X	X
Cardiovascular History	X	
Medical History	X	
Medication	X	X
EF Assessment (Echo)	X	X
NYHA Assessment	X	X
cMRI	X	X
CardioMEMS HF System Readings	X - - - - - - - - -	X
Adverse Event	As Occurs	As Occurs
Deviation	As Occurs	As Occurs
Non-AE Device Issue	As Occurs	As Occurs
Withdrawal	As Occurs	As Occurs
Death	As Occurs	As Occurs

6.4 Requirement for Clinical Laboratories

A core lab will be employed to train imaging personnel, collect images and imaging data, review and assess images and imaging data (via an independent reviewer), and store images and imaging data. [redacted]

7.0 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 Adverse Event

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

As part of ISO 14155 Section 3.2, the Adverse Event definition has the following notes:

[redacted]

Note 1: This definition includes events related to the medical device under investigation.
Note 2: This definition includes events related to the procedures involved.
Note 3: For users or other persons, this definition is restricted to events related to medical devices under investigation.

7.1.2 Serious Adverse Event

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

a) Led to a death,
b) Led to a serious deterioration in health of the subject, that either resulted in
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient hospitalization or prolongation of existing hospitalization, or
    4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
    5. chronic disease
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

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

7.1.3 Device Deficiency/Device Malfunction

Device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: performance specifications include all claims made in the labeling of the device.

A device malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended, when used in accordance with the instructions for use or CIP.

7.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate Case Report Form (CRF). Determination should be based on the assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.2.1 Unanticipated Adverse Device Effect [UADE]

Unanticipated adverse device effect (UADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

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7.3 Adverse Event and Device Deficiency/Device Malfunction Reporting

7.3.1 Adverse Event Reporting

General AE Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled and eligible for the study specific procedures in the clinical investigation. Adverse events will not be collected for screen failure subjects. Safety surveillance and reporting will continue until sites perform the last follow-up visit, the subject is deceased, the subject concludes participation in the clinical investigation, or the subject withdraws from the clinical investigation. Sites will collect all adverse event data, including deaths and device deficiency data, throughout the period defined above and will report these events to the Sponsor on a CRF. Sites should update additional information regarding an adverse event on the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

The Sponsor will provide an offline form to allow the investigator to report SAEs in the event the entry cannot be made in the Electronic Data Capture (EDC). This does not replace the EDC reporting system. Sites must still enter all information in the EDC system as soon as feasible.

SAE Reporting

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

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

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

7.3.2 Unanticipated Adverse Device Effect Reporting to Sponsor and IRB

The Sponsor requires the Investigator to report any UADE to the Sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB per IRB requirements.

7.3.3 Device Deficiency/Malfunction Reporting

Sites should report all device deficiencies/malfunctions on the appropriate CRF form.

The investigator must report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than outlined below.

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

Sites must report device deficiencies/malfunctions to the IRB per the investigative site's local requirements.

Sites should return any devices (ex., PES), if returned by or not remaining in the subject, to the Sponsor.

Sites will have access to an offline form to allow the investigator to report device deficiencies/malfunctions if sites cannot enter the information in the EDC system. This does not replace the EDC reporting system. Sites must still enter all information in the EDC system as soon as feasible.

In case a device deficiency/malfunction occurred before the subject ID has been assigned, sites should report the device deficiency to the Sponsor via the offline reporting form.

7.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

Note: Reportable device deficiencies/malfunctions include device deficiencies/malfunctions that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. A separate Statistical Analysis Plan will provide additional details on statistical analyses, including justification of clinical investigation design, sensitivity analyses, poolability analyses, subgroup analyses, and analysis of descriptive endpoints, if applicable.

8.1 Analysis Populations

8.1.1 Enrolled Population

The Enrolled population includes all enrolled subjects (development phase and validation phase),

- Informed Consent obtained
- Inclusion/Exclusion criteria satisfied

8.1.2 Per-Protocol (PP) Population

[redacted]

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8.2 Statistical Analyses

8.2.1 Primary Endpoint Analyses

[redacted]

8.2.2 Descriptive Endpoint Analyses

[redacted]

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[redacted]

8.3 Sample Size Calculation

[redacted]

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[redacted]

[redacted]

8.4 Timing of Analysis

[redacted]

8.5 Subgroup Analysis

No subgroup analyses are planned for this clinical investigation.

8.6 Planned Interim Analysis

No interim analyses are planned for this study.

8.7 Success Criteria

[redacted]

8.8 Deviations from Statistical Plan

The Sponsor will document any major changes to the statistical plan in an amendment to the statistical plan and any less significant changes to the planned analyses in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for performing clinical investigation-related monitoring, audits, IRB review, and regulatory inspections.

[redacted]

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Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities, including foreign countries, to review in confidence any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the subject's personal and private information.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

10.2 CIP Amendments

The Sponsor will provide approved CIP amendments to the Investigators prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Sites must document in writing acknowledgement/approval of the CIP amendment by the IRB prior to implementation of the CIP amendment. Sites must also provide copies of this documentation to the Sponsor.

10.3 Training

10.3.1 Site Training

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

10.3.2 Training Required for the Cardiac MRI Imaging

Sites and Investigators will be required to train with and follow imaging protocol provided by the Imaging Core Laboratory.

10.4 Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

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Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations and has signed the Investigator Agreement.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Sites must have source documentation (including original medical records) to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records and will maintain a monitoring visit sign-in log at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

10.5 Deviations from CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety, and well-being of the subject, or to eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

The Sponsor will not grant any waivers for CIP deviations. Sites must report all deviations to the Sponsor using the Deviation CRF. The Sponsor will monitor the occurrence of CIP for evaluation of investigator compliance to the CIP and regulatory requirements and handle according to written procedures. Investigators will inform their IRB or equivalent committee of all CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP, or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, the Sponsor may terminate the investigator's participation in the clinical investigation.

Deviations from the appropriate informed consent process; Imaging Assessment not obtained per protocol; and late SAE reporting are considered major.

10.6 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

If an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). The Sponsor may provide any needed assistance in responding to regulatory audits.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the EDC system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the end of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites, if requested.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records (if applicable), correspondence with the IRB and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a ‘need to know’ basis, including periodic review of access rights, and revocation of access when an individual’s employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to enter only pseudonymous Personal Information (key-coded) necessary to conduct the clinical investigation, such as the patient’s medical condition, treatment,

dates of treatment, etc., into Sponsor's data management systems. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring, and quality control purposes. All parties will observe confidentiality of Personal Information always throughout the clinical investigation. All reports and data publications will preserve the privacy of each subject and confidentiality of his/her information.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss, or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the Sponsor may update the DMP throughout the duration of the clinical investigation. The Sponsor will track and document control all revisions.

11.3 Source Documentation

Regulations and Good Clinical Practice (GCP) require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. To comply with these regulatory requirements/GCP, sites should include the following information in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number, and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- AEs reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports and assessments, reviewed and annotated for clinical significance of out of range results (if applicable).
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF

11.4 Case Report Form Completion

Site research personnel trained on the CIP and CRF completion will perform the primary data collection clearly and accurately based on source-documented hospital and/or clinic chart reviews. The investigator will ensure accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor on the

CRFs and in all required reports. Sites will collect data on all subjects who sign an informed consent form, including subjects who may not meet all inclusion/exclusion criteria during screening. Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. The Sponsor will use an electronic audit trail to track any subsequent changes of the entered data.

11.5 Record Retention

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

11.6 Investigational Devices Accountability

Device accountability is not required for this study as no patients will be implanted as part of the study.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board Review and Approval

The Principal Investigator at each investigational site will obtain IRB approval for the CIP and ICF/other written information provided to the patient prior to consenting and enrolling patients in this clinical investigation. The site must receive the approval letter prior to the start of this clinical investigation and provide a copy to the Sponsor.

Sites will submit any amendments to the CIP as well as associated ICF changes to the IRB and written approval obtained prior to implementation, according to each institution's IRB requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical investigation is completed, the Investigator will advise his/her IRB of the progress of this clinical investigation, per IRB requirements. Written approval must be obtained from the IRB yearly to continue the clinical investigation, or according to each institution's IRB requirements.

Sites will not perform any investigative procedures, other than those defined in this CIP, on the enrolled subjects without the written agreement of the IRB and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

14.0 PUBLICATION POLICY

[redacted]

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[redacted]

Upon receiving IDE approval from the FDA, the Sponsor will be responsible for registering this clinical investigation on ClinicalTrials.gov website, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. Sponsor shall be responsible for any such registration and results posting as required by the ClinicalTrials.gov website. Institution and/or Principal Investigator(s) shall not take any action to register the clinical investigation. A full report of the pre-specified outcomes, regardless of the results, will be made public through the ClinicalTrials.gov website no later than 12 months after clinical investigation completion, as required by section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

15.0 RISK ANALYSIS

The risks associated with the CardioMEMS HF System can be found in the CardioMEMS HF System User Manuals. This trial does not require implant of the CardioMEMS PA Sensor and will include the currently indicated population. As this trial will evaluate the CardioMEMS HF System in a patient population that has previously been implanted and all of the anticipated risks (listed in the CardioMEMS HF System's IFUs) would already apply to this population, no additional risks associated with the CardioMEMS HF System are expected to be introduced to trial subjects. As part of study participation, subjects will undergo a series of cMRI scans. As the CardioMEMS PA Sensor is non-ferrous and MRI conditional, there are no anticipated additional risks introduced to trial subjects due to cMRI scans.

[redacted]

15.1 Anticipated Clinical Benefits

CO is an important parameter that can be used to gain a greater understanding of the hemodynamic pathophysiology in patients with HF. The anticipated clinical benefits of providing CO as part of the CardioMEMS HF System are that physicians would be able to access this important hemodynamic measurement without additional risks to their CardioMEMS HF System patients associated with commonly employed invasive methods, or without additional costs for invasive CO measurement or non-invasive CO measurements. [redacted]

15.2 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Management Report / Risk Analysis Report

[redacted]

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[redacted] Based upon bench testing and prior Abbott sponsored clinical study data, all risks have been identified and mitigated as far as possible through application of appropriate controls and inspections and determined to be within acceptable levels.

Residual risks are likewise disclosed in the appropriate IFUs/User Guides in the form of clear instructions of what actions to take or to avoid, to avoid a hazardous situation of harm from occurring (contra-indications, warnings, and precautions). The anticipated AEs are disclosed in the IFUs and provide further information to enable the user, and potentially the patient, to make an informed decision that weighs the residual risk against the benefit of using the device.

15.3 Risks Associated with Participation in this Clinical Investigation

As part of study participation, subjects will undergo a series of cMRI scans. As the CardioMEMS PA Sensor is non-ferrous and MRI conditional, there are no anticipated additional risks introduced to trial subjects due to cMRI. All risk mitigations associated with MRI use in conjunction with the CardioMEMS HF System are included in the Sensor Design FMEA (Reference: TR-1002-70, Rev. AA). Subjects will also be administered a study medication at each of the two study visits in order to modulate cardiac output. Possible protocol administered medication interactions are described below in section 15.4.

15.4 Possible Interactions with Protocol-Required Concomitant Medication

[redacted]

15.5 Steps Taken to Control or Mitigate Risks

Every possible effort will be taken to minimize, control, or mitigate risks associated with the clinical investigation, including:

- Careful selection of experienced Investigators for the clinical trial
- Early and adequate monitoring for each clinical trial site per the trial monitoring plan
- Conducting the clinical trial in accordance with the CIP, all applicable laws and regulations and any conditions of approval imposed by the appropriate IRB or applicable regulatory authorities where the clinical trial is performed
- Training of investigators and all relevant site personnel on cMRI imaging procedures
- Training of Investigators both on the CIP and the CardioMEMS HF System use in the study and in conjunction with MRI imaging
- Securing compliance of non-compliant sites (see Section 10.5)
- Requiring medical supervision of study administered drugs by appropriate site personnel

The IFU also states that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean that the physician users are

expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.

Risks associated with the use of the device under investigation are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, study monitoring to ensure adherence to the protocol. Sites will report all adverse events and device deficiencies to the Sponsor and the Sponsor will monitor internally for safety surveillance purposes.

15.6 Risk to Benefit Rationale

Congestive HF is a progressive disease and HF patients are generally symptomatic. Symptoms of dyspnea and fatigue increase with elevations of pressures within the heart and lungs, leading to instances of acute HF decompensation. The CardioMEMS HF System enables clinicians to medically manage HF patients by adjusting treatments to keep PA pressures within target ranges to prevent or reduce instances of acute HF decompensation. In doing so, the CHAMPION trial demonstrated a reduction in rates of HF decompensation resulting in an HFH, in NYHA Class III patients who had a HFH within the prior 12 months. In addition to pressure, CO is an important variable to describe hemodynamic pathophysiology in patients with HF. Deriving CO as part of remote monitoring with the CardioMEMS HF System is expected to produce an accurate assessment of CO without the associated risks and costs of traditional methods such as Fick and Thermodilution. CO monitoring using the CardioMEMS HF System can potentially provide important information to manage patients with HF. There are no new or additional risks related to the study device as part of the study protocol beyond the risks already incurred by the study subjects as they will already be implanted with the CardioMEMS PA Sensor and are currently using the CardioMEMS HF System. As part of study participation, subjects will undergo a series of cMRI scans. Since the CardioMEMS PA Sensor is non-ferrous and MRI conditional, there are no anticipated additional risks introduced to trial subjects due to cMRI. Subjects will also be administered a study medication to modulate CO. All precautions, including medical supervision during medication administration, will be taken to minimize any potential adverse effects from the medication administered per protocol. With the appropriate mitigations in place, the risks associated with participation in this study are outweighed by the potential benefit of providing CO via remote monitoring without the risks and costs associated with other CO assessments.

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16.0 APPENDIX I: ABBREVIATIONS AND ACRONYMS

ADE	Adverse Device Effect
ADHF	Acutely Decompensated Heart Failure
AE	Adverse Event
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
CHAMPION	CardioMEMS™ HF Sensor Allows Monitoring of Pressures to Improve Outcomes in NYHA Functional Class III HF Patients
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Form
CO	Cardiac Output
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy – Defibrillator
CRT-P	Cardiac Resynchronization Therapy – Pacemaker
DMP	Data Management Plan
DSRC	Device/System Related Complication
EDC	Electronic Data Capture
EF	Ejection Fraction
eGFR	Glomerular Filtration Rate
FDA	Food and Drug Administration
FMEA	Failure Mode Effect Analysis
GCP	Good Clinical Practice
GDMT	Guideline Directed Medical Therapy
HA	Hazard Analysis
HES	Hospital Electronic System
HF	Heart Failure
HFH	Heart Failure Hospitalization
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Heart Rate
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
LVEF	Left Ventricular Ejection Fraction
MEMS	Micro-ElectroMechanical Systems
MEMS-HF	CardioMEMS European Monitoring Study for Heart Failure
NT-proBNP	N-Terminal pro-Brain Natriuretic Peptide

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NYHA	New York Heart Association
PA	Pulmonary Artery
PAS	Post-Approval Study
PCWP	Pulmonary Catheter Wedge Pressure
PES	Patient Electronics System
PMA	Pre-Market Approval
RAP	Risk Analysis Plan
RHC	Right Heart Catheterization
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SV	Stroke Volume
UADE	Unanticipated Adverse Device Effect
VICTOR	ValIdation of CardioMEMS HF SysTem Cardiac Output AlgoRithm IDE

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17.0 APPENDIX II: DEFINITIONS

- **NYHA HF Classification:** The NYHA HF Classification provides a simple way of classifying the extent of HF. It places subjects in one of four categories, based on how much they are limited during physical activity:
  - ***Class I.*** Patients with HF, but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
  - ***Class II.*** Patients with HF resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea.
  - ***Class III.*** Patients with HF resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, or dyspnea.
  - ***Class IV.*** Patients with HF resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency, anginal syndrome, and dyspnea may be present even at rest. If any physical activity is undertaken, shortness of breath is increased.
- **Hospitalization:** Admission to hospital for at least 24 hours.
- **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 clinical investigation. This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved.
- **Serious AE (SAE)**: An AE 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 inpatient 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

  Note: A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered an SAE.
- **Adverse Device Effect (ADE)**: An AE related to the use of an investigational medical device. This definition includes AEs 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.
- **Serious Adverse Device Effect (SADE)**: ADE that has resulted in any of the consequences characteristic of a serious AE.
- **Unanticipated Adverse Device Effect (UADE)**: As defined in 21 CFR §812.3, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature,

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

- **Non-AE Device Issue**: any instance when the device fails to perform or does not function properly without an associated an adverse clinical outcome.
- **Device/System Related Complication (DSRC)**: An AE that is related or possible related to the system (CardioMEMS PA Sensor or other components of the CardioMEMS HF System) and has at least one of the following characteristics:
  - is treated with invasive means (other than intramuscular medication or a right heart catheterization which is used for diagnostic purposes)
  - resulted in the death of the subject
  - resulted in the explant of the device

18.0 APPENDIX III BODY MASS INDEX CALCULATOR

Subjects' BMI will be calculated using the website below:

https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm

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

Formulas used to calculate BMI:

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

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

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19.0 APPENDIX IV: CARDIAC MRI PROTOCOL SPECIFIC IMAGE ACQUISITION OUTLINE

[redacted]

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[redacted]

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Follow manufacturer [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Any Protocol deviation must be documented in the "comments" section of the transmittal form.

[redacted]

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[redacted]

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[redacted]

19.6 Acquisition Planning Guide

19.6.1 Localizer/Scout (SSFP)

[redacted]

[redacted]

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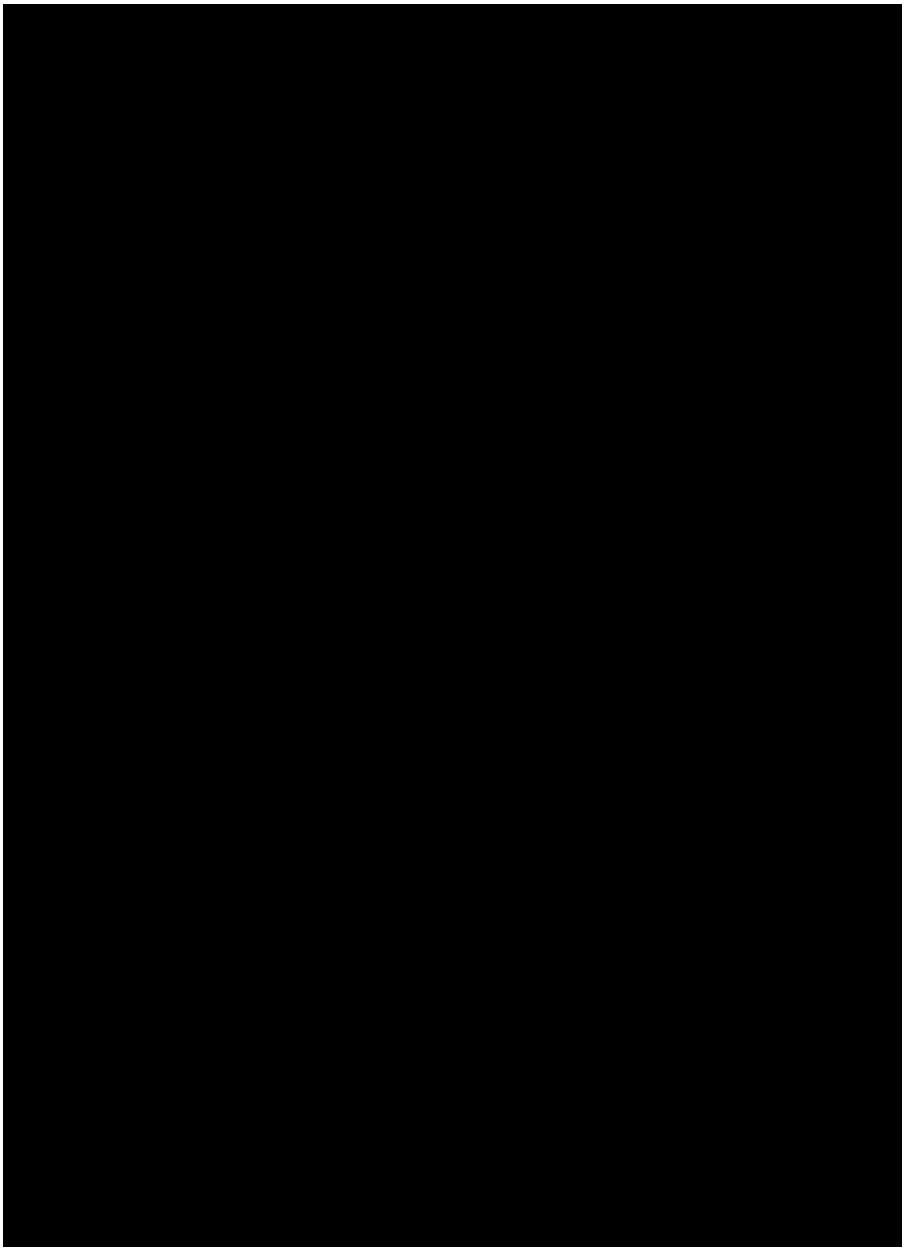

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19.6.3 [redacted]

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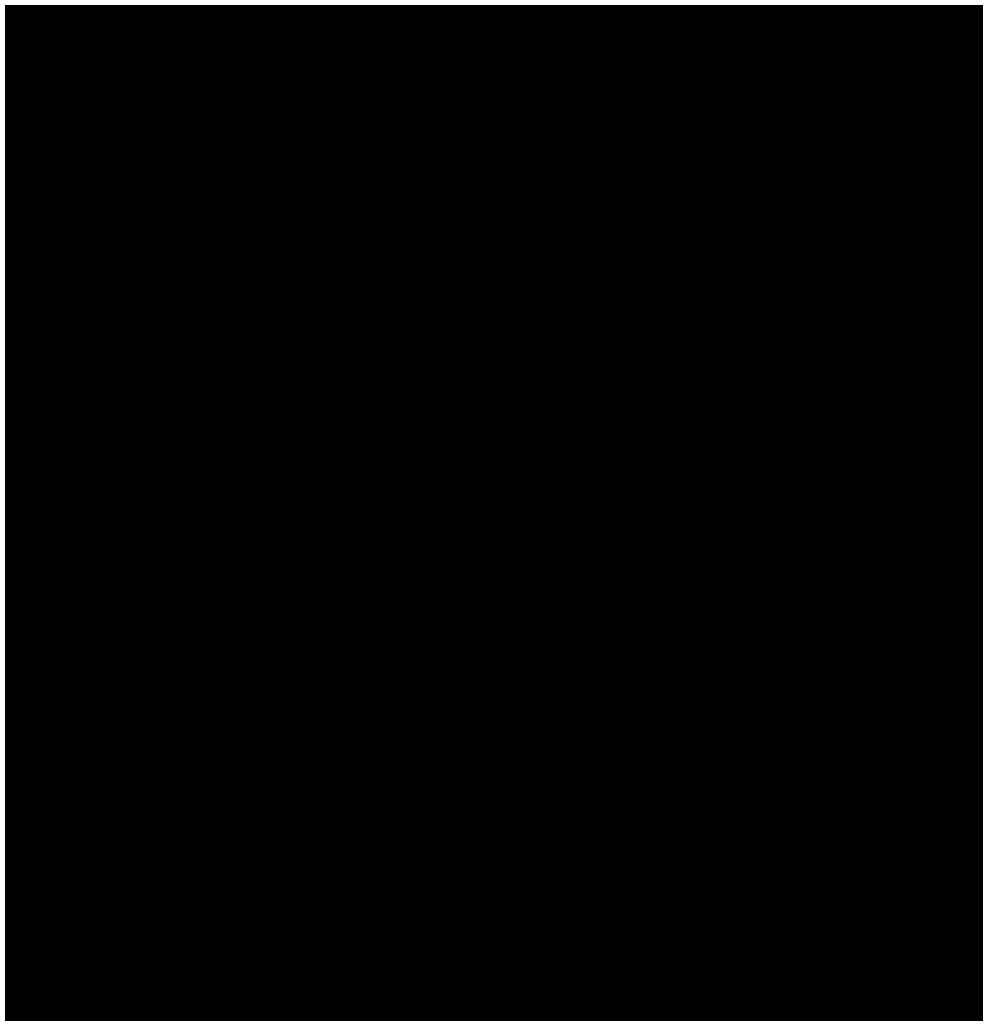

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20.0 APPENDIX V: REFERENCES

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21.0 APPENDIX VI: REVISION HISTORY

This CIP may be amended as appropriate by the Sponsor. Rationale will be included with each amended version in the revision history table below. The version number and date of amendments will be documented.

IRB and relevant Regulatory Authorities, if applicable, will be notified of amendments to the CIP.

Amendment Number	Version	Date	Details	Rationale
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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22.0 APPENDIX VII: CIP SUMMARY

Clinical Investigation Name and Number	VICTOR IDE (
Title	Validation of CardioMEMS HF SysTem Cardiac Output AlgoRithm IDE
Objectives	There are two primary objectives of this clinical investigation. The first objective is to finalize development of the algorithm estimating CO by collecting paired cMRI measurements of CO, as well as other parameters of heart function, and CardioMEMS HF System readings in the same subject. The second objective of this clinical investigation is to use data collected during the validation phase, distinct from the subjects within the development phase, to evaluate the agreement between the CardioMEMS HF System-derived CO and the CO values from cMRI in patients previously implanted with the commercially available CardioMEMS HF System.
Device Under Investigation	CardioMEMS HF System
Number of Subjects Required for Inclusion in Clinical Investigation	Up to 90 subjects will be enrolled
Clinical Investigation Design	This is a prospective, multi-center clinical study of patients previously implanted with the CardioMEMS PA Sensor. The clinical study will be conducted in up to 15 centers in the United States.
Primary Endpoint	The primary endpoint of this clinical investigation is to estimate CO from CardioMEMS HF System data. The estimated CO will be evaluated for agreement between the CardioMEMS HF System-derived CO and the CO values from cMRI in patients with the CardioMEMS HF System.
Subject Follow-up	• Clinical sites will follow each subject until they complete their 3-month visit or withdraw from the study. • Two in-person visits: Baseline and 3-month
Inclusion Criteria	1. Subject is willing and able to provide written informed consent prior to any clinical investigation-related procedure.

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	2. Subject is implanted with the CardioMEMS PA Sensor for a minimum of 3 months at time of consent. 3. Subject is ≥ 18 years of age. 4. Subject is willing and able to undergo several cardiac MRI scans. This is including but not limited to: • Subject must have all MRI compatible devices • Subject must be able to hold their breath during imaging • Subject must be free of all metal bodies, fragments, or implants that would prohibit MRI imaging 5. Subject is willing and able to upload PA pressure information (i.e., take daily CardioMEMS HF System readings and have their hemodynamic information collected at study visits) and comply with the follow-up requirements.
Exclusion Criteria	1. Subject will receive or is likely to receive an advanced therapy (e.g., mechanical circulatory support or cardiac transplant) in the next 6 months. 2. Subject was implanted with Cardiac Resynchronization Therapy (CRT)-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) for less than 90 days prior to consent. 3. Subject is pregnant or planning to become pregnant in the next 6 months 4. Subject is enrolled into another trial with an active treatment arm 5. Subject has significant congenital heart disease that has not been repaired 6. Subject is implanted with mechanical right heart valve(s) 7. Subject has unrepaired severe valvular disease 8. Subject has an anticipated life expectancy of < 6 months 9. Subject has an active, ongoing infection, defined as being febrile, an elevated white blood cell count, on intravenous antibiotics, and/or positive cultures (blood, sputum, or urine) 10. Subject has had a major cardiovascular event (e.g., unstable angina, myocardial infarction, percutaneous coronary intervention, open heart surgery, or stroke, etc.) within 90 days prior to consent 11. Subject has any condition that, in the opinion of the Investigator, would not allow for utilization of the CardioMEMS HF System to manage the subject using information gained from hemodynamic measurements to adjust medications, including the presence of unexpectedly severe pulmonary hypertension (e.g., trans-pulmonary gradient >15) at implant RHC, a history of non-compliance, or any condition that would preclude ability to obtain CardioMEMS PA Sensor readings and paired cardiac MRI data from being collected 12. Subjects who, in the opinion of the investigator, are at-risk for serious adverse reaction to Dobutamine (ex. subjects with idiopathic hypertrophic subaortic stenosis and subjects who have shown previous

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	manifestations of hypersensitivity to Dobutamine) should be excluded from the study