GUIDE-HF
Hemodynamic-GUIDEd Management of Heart Failure (GUIDE-HF) NCT03387813
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Clinical Investigation Plan (CIP)

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1 Introduction

This document is a clinical investigation plan (CIP) for the Hemodynamic-GUIDEd Management of Heart Failure (GUIDE-HF) clinical trial. This clinical trial is intended to demonstrate the effectiveness of the CardioMEMS™ HF System in patients with New York Heart Association (NYHA) Class II, III, or IV Heart Failure (HF) who have an elevated N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) (or an elevated Brain Natriuretic Peptide (BNP)) and/or a prior HF Hospitalization (HFH). This clinical trial will be conducted under an investigational device exemption (IDE) and is intended to support an expanded indication for the CardioMEMS™ HF System. This clinical trial is sponsored by Abbott.

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

2 Background and Justification for Clinical Trial

HF affects over six million Americans, with 960,000 new cases diagnosed each year. The syndrome tends to be progressive and is associated with severe morbidity and high mortality. HF costs the United States healthcare system over $30 billion annually (1), with the largest cost component associated with over 1.2 million annual hospitalizations required to provide rescue therapy during acute decompensation of the chronic condition. HF is a growing pandemic with estimates from the American Heart Association (AHA) predicting the prevalence of HF in the United States to approach nine million patients by 2030, with an associated increase to three million hospitalizations yearly. Innovative approaches focusing on decreasing decompensation events are needed to not only improve patient quality of life and survival, but also reduce the overall cost of delivering healthcare to HF patients (1-3). Implantable hemodynamic monitoring systems are one such innovative approach that have been proven effective in maintaining stability in selected HF patients by providing a novel clinical disease management strategy that proactively avoids decompensation, replacing the traditional reactive rescue approach to treat acute decompensation. Remote pulmonary artery (PA) pressure monitoring provides clinical providers with actionable data to guide patient-centric individualized medication dosing and adjustments with the goal of preventing HFHs or other decompensation events (4-7). The CardioMEMS™ HF System is currently the only FDA approved system indicated for previously hospitalized NYHA Class III HF patients, regardless of left ventricular ejection fraction (LVEF), with the goal of reducing HFHs. The system is comprised of a lead-less, battery-less pressure sensor permanently implanted in the PA, which remotely transmits PA pressure measurements from the patient's home to a secure website. Healthcare professionals are able to access these measurements and associated waveforms to remotely guide individualization of medical management for their patients with chronic HF. The purpose of the GUIDE-HF clinical trial is to discover whether hemodynamic-guided HF management is applicable to a larger group of at-risk HF patients and whether maintaining hemodynamic stability improves overall survival and quality-of-life in such HF patients.

2.1.1 CardioMEMS™ Clinical Experience

The safety and effectiveness of the CardioMEMS™ HF System was evaluated in the CHAMPION (**C**ardioMEMS™ **H**F Sensor **A**llows **M**onitoring of **P**ressures to **I**mprove **O**utcomes in **N**YHA Functional Class III HF Patients) trial (ClinicalTrials.gov Identifier: NCT00531661). CHAMPION was a prospective, multi-center, randomized, controlled trial, which demonstrated a significant reduction in HFHs when PA pressure measured by the CardioMEMS™ PA Sensor was used by clinicians to guide HF patient management (Treatment Group), compared to patients managed without clinician knowledge of PA pressure information (Control Group) (5, 8). This included the first treatment strategy to successfully improve outcomes in HF patients with a preserved ejection fraction (EF) (HFpEF) (9). Additionally, hemodynamic-guided HF care in patients with reduced HF (HFrEF) augmented the survival benefit of guideline directed medical therapy (GDMT) (10, 11). Results of the CHAMPION trial led to the Food and Drug Administration (FDA) approval of the CardioMEMS™ HF System for wirelessly measuring PA

pressure to guide HF management in NYHA Class III HF patients who experienced a HFH in the previous year.

Early experience with the CardioMEMS™ HF System in a post-FDA approval, real-world environment continues to support the utility of hemodynamic-guided HF management for this population. In particular, PA pressure-guided HF management using the implantable CardioMEMS™ PA Sensor in large real-world cohorts demonstrated reduced HFHs (12), along with a concomitant reduction in PA pressure (13). Real-world reductions in HFHs were associated with significant cost savings based on Medicare claims data. Additional clinical evidence on post-market experience with CardioMEMS™ in this population is currently being generated in a post-approval registry study (PAS, NCT02279888) in 1,200 patients followed for two years. Enrollment in this registry was completed earlier than expected and is currently in the long-term follow-up phase. Preliminary results in the first 300 patients followed for at least six months found a lower HFH rate compared to the CHAMPION Trial Treatment Group, despite the fact that the PAS population is older with more advanced HF syndromes (14, 15).

2.1.2 Patient Selection for CardioMEMS™ Therapy

The CardioMEMS™ HF System is currently indicated for use in NYHA Class III HF patients, who have a documented HFH in the prior year. However, determination of these prerequisite conditions for patient selection can be challenging. The NYHA classification of HF symptoms is designed to subjectively quantify an individual's burden of congestive symptoms in order to provide specific medical and device interventions appropriate for the patient's condition. Accurate assessment of NYHA Class is limited by several important factors including the tendency for patients to accommodate chronic symptoms and variability in healthcare providers' diligence in historical assessment. These limitations may lead to misclassification of HF patient status, leading to a missed opportunity for preventive care. Biomarker assessment of HF patient status, particularly utilizing B-Type Natriuretic Proteins (NT-proBNP or BNP) may provide a superior means to determine the presence of subclinical congestion, thus providing a better prognostic assessment of the patient's subsequent risk for decompensation than NYHA class. Furthermore, it is now clear that United States clinical management trends have shifted away from hospitalization to treat acutely decompensated HF (ADHF) to increased reliance on outpatient intravenous medication intervention. However, regardless of the venue, decompensation requiring rescue therapy is associated with increased long-term mortality risk. Therefore, it is plausible to hypothesize that hemodynamic-guided care may be appropriate for patients whose clinical congestion status is determined by NT-proBNP (or BNP) even when clinical symptoms are assessed as NYHA Class II, III, or IV HF. Given the prognostic value of elevated NT-proBNP (or BNP), patients without history of a previous HFH may also benefit from hemodynamic-guided HF management strategies.

2.1.3 Natriuretic Peptides in HF

Natriuretic peptides, specifically NT-proBNP and BNP, are released into the circulation directly from the myocardium due to increased end-diastolic wall stress as a result of increased end diastolic volume and pressure (16). Natriuretic peptides are most commonly used to support the diagnosis of HF in patients with dyspnea, and numerous studies have demonstrated that NT-proBNP and BNP are strong independent predictors of adverse clinical outcome in HF patients (17). In the Breathing Not Properly study, a BNP threshold of 100 pg/ml accurately diagnosed acute HF with a sensitivity of 90% and a specificity of 76% (18). In the COMET study, a progressively increasing risk for mortality was observed with every 10% increase in NT-proBNP (19). The Agency for Healthcare Research and Quality of the Department of Health and Human Services in 2006 assessed 58 studies where NT-proBNP or BNP were evaluated in predicting cardiac events in primarily NYHA Class II, III or IV HF patients (20). A majority of the studies found baseline NT-proBNP or BNP to be independent predictors of mortality. This makes NT-proBNP and/or BNP assessments a promising alternative to prior HFHs for objectively identifying patients who are at high risk for HFHs and mortality, and who may derive clinical benefits from PA pressure-guided HF management (for more details see *Appendix D*). These data have supported a Class I recommendation for measurement of NT-proBNP or BNP to establish prognosis or disease severity in

chronic HF (21) and have resulted in NT-proBNP and BNP assessment being included as an entry criterion for numerous clinical trials in HF such as LAPTOP-HF (trial of a device for hemodynamic monitoring, NCT01121107 (7)), PARADIGM-HF and PARAGON-HF (trials of sacubitril-valsartan in HFrEF and HFpEF patients, NCT01035255 (22, 23), NCT01920711 (24)), and COAPT (trial of MitraClip percutaneous repair for functional mitral regurgitation, NCT01626079).

2.1.4 Clinical Trial Rationale

These data support the hypothesis that hemodynamic-guided HF management using the CardioMEMS™ HF System may be effective in a NYHA Class II, III, or IV HF patient population with elevated NT-proBNP (or BNP). Furthermore, the utility of elevated NT-proBNP (or BNP) and its equivalence to a history of previous HFHs for appropriate selection of HF patients for CardioMEMS™ implantation is plausible, but currently unknown. Hence, the rationale for conducting this clinical trial is two-fold:

- To generate scientific evidence supporting the clinical benefit of PA pressure-guided HF management in a broad range of HF patients (NYHA Class II, III, or IV), reflecting contemporary methods of patient selection (elevated NT-proBNP (or BNP))
- To demonstrate the equivalence of elevated NT-proBNP (or BNP) to prior HFHs for selecting the appropriate candidates who will clinically benefit from PA pressure-guided HF management, and to allow for the expansion of the current label to include NYHA Class III HF patients with elevated NT-proBNP (or BNP)

This clinical trial proposes to build on the clinical experience gained from the CHAMPION trial and attempts to fill an important clinical evidence gap in the management of eligible HF patients (including Medicare beneficiaries). The Sponsor is proposing to conduct an IDE trial to obtain pre-market approval (PMA) of the CardioMEMS™ HF System for NYHA Class II, III, or IV HF patients who have experienced either a HFH within the last 12 months (“prior HFH”) or have elevated NT-proBNP (defined as ≥ 1000 pg/mL for LVEF ≤ 40% or ≥ 700 pg/mL for LVEF > 40%) (or elevated BNP, defined as ≥ 250 pg/mL for LVEF ≤ 40% or ≥175 pg/mL for LVEF > 40%) within the last 30 days. Thresholds for NT-proBNP and BNP (for both LVEF ≤ 40% and LVEF > 40%) will be corrected for body mass index (BMI) using a 4% reduction per BMI unit over 25 kg/m^2 (23), see *Appendix G* for NT-proBNP (and BNP) thresholds according to BMI.

3 Device(s) Under Investigation

3.1 Identification and Description of the Devices under Investigation

3.1.1 Identification

Table 1 details the devices to be used in this trial. Although market released, the CardioMEMS™ HF System is not FDA approved for the proposed clinical trial population (NYHA Class II, III, or IV HF patients with elevated NT-proBNP (or BNP)).

Table 1: Identification of Devices under Investigation

Device name	Model/Type	Manufacturer	Region/ Country	Investigational or Market Released
CardioMEMS™ PA Sensor and Delivery Catheter	[redacted]	Abbott/SJM	United States	Market Released, but Investigational for this Indication
CardioMEMS™ Hospital Electronic Unit	[redacted]	Abbott/SJM	United States	Market Released, but Investigational for this Indication
CardioMEMS™ Patient Electronic Unit	[redacted]	Abbott/SJM	United States	Market Released, but Investigational for this Indication
Merlin.net™	[redacted]	Abbott/SJM	United States	Market Released

3.1.2 Device Description and Intended Purpose

The CardioMEMS™ HF System is currently indicated for wirelessly measuring PA pressure and heart rate to guide HF management in NYHA Class III HF patients who have been hospitalized for HF in the previous year. The resultant hemodynamic data are used by clinicians for HF management with the goal of reducing HFHs. The CardioMEMS™ HF System received FDA approval for that indication on May 28, 2014. The GUIDE-HF trial will evaluate the use of the CardioMEMS™ HF System for wirelessly measuring PA pressure to guide HF management in NYHA Class II, III, or IV HF patients who have been hospitalized for HF or who have elevated NT-proBNP (or BNP).

The CardioMEMS™ HF System provides PA hemodynamic data to monitor and manage HF patients. The CardioMEMS™ HF System measures PA pressure which clinicians use to initiate or modify HF treatment.

The CardioMEMS™ HF System includes the following components:

- CardioMEMS™ PA Sensor and Delivery Catheter
- CardioMEMS™ Hospital Electronic Unit
- CardioMEMS™ Patient Electronic Unit
- Merlin.net™ (patient database website)

The implantable CardioMEMS™ PA Sensor measures PA pressure using Micro-ElectroMechanical System (MEMS) technology, which enables powering of the implanted sensor via external interrogation thus removing the need for batteries or leads. It is fabricated using silicon wafers and measures 15 mm in length, 3.4 mm in width and 2 mm in thickness.

The CardioMEMS™ PA Sensor is permanently implanted in the left or right distal PA using trans-catheter techniques in the catheterization laboratory, and the sensor baseline is calibrated to the mean PA pressure as measured from the PA catheter. To facilitate implantation, the CardioMEMS™ PA Sensor is tethered to an over-the-wire delivery catheter. A right heart catheterization (RHC) is performed using either the femoral or right internal jugular veins, and a hand-injected selective pulmonary angiogram is performed via a balloon-tipped PA catheter to define the distal PA branch anatomy. A 0.018" guidewire is then advanced through the balloon-tipped PA catheter into the target distal PA branch. The PA catheter is then removed, and the delivery catheter is advanced over the guidewire. Once it is optimally positioned, the CardioMEMS™ PA Sensor is separated from the delivery catheter by removing the tether wire. The delivery catheter is then carefully removed from the body. The balloon-tipped PA catheter is then re-inserted into the PA and the CardioMEMS™ PA Sensor baseline is calibrated using the CardioMEMS™

Hospital Electronic Unit during simultaneous PA pressure measurements from the PA catheter and the sensor. The CardioMEMS™ Hospital Electronic Unit uses an antenna to transmit low power pulses of radiofrequency energy to power and communicate with the CardioMEMS™ PA Sensor.

After implantation, the CardioMEMS™ HF System is interrogated daily by the patient from their home environment to provide clinicians with the patient's systolic, diastolic, and mean PA pressures, the current PA pressure waveforms, and heart rate. Home readings are acquired using the CardioMEMS™ Patient Electronic Unit, which consists of an antenna placed in a pillow and a handheld remote screen that guides the patient through the PA pressure measurement process. Body position is standardized by requiring patients to lie supine on the pillow to interrogate the implanted CardioMEMS™ PA Sensor. The hemodynamic data are encrypted and transmitted by the CardioMEMS™ Patient Electronic Unit to the Merlin.net™ website, which provides a secure interface for clinicians to review PA pressure data.

3.1.3 Intended Purpose within the Clinical Trial

The CardioMEMS™ HF System will be used in this clinical trial to assess the effectiveness of PA pressure-guided HF management in a patient population that is not currently indicated but are at risk for future HF events (HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy) or mortality.

3.1.4 Device Handling and Storage

The CardioMEMS™ HF System is market approved and commercially available in the United States but is investigational for the indications evaluated in this trial. The commercial product will be used in this IDE trial. However, the CardioMEMS™ HF System and the Merlin.net™ website manuals will have a supplement page stating that the product used in this trial is the same as the commercially available product, but is being used outside of the current indication, and therefore considered investigational for this trial. All product utilization within the trial will be tracked and reported.

4 Clinical Trial Design

The GUIDE-HF IDE trial consists of two arms: a Randomized Arm and a Single Arm. Sites will be instructed to offer their subjects participation in the Randomized Arm first. [redacted]

4.1.1 Clinical Trial Duration

[redacted]

4.1.2 GUIDE-HF Randomized Arm

The GUIDE-HF Randomized Arm is a prospective, multi-center, randomized, controlled, single-blind clinical trial of the CardioMEMS™ HF System in NYHA Class II, III, or IV HF patients with either elevated NT-proBNP (or BNP) and/or a prior HFH. The trial will be conducted in 140 sites across North America. After screening procedures and signing the Informed Consent Form, subjects will complete baseline assessments. Within 60 days of consent, subjects will receive a CardioMEMS™ HF System and, within 24 hours of implantation, be randomized in a 1:1 ratio into one of two groups:

- **Treatment Group:** Management of subjects based on PA pressure information derived from the CardioMEMS™ HF System
- **Control Group**: Management of subjects per standard of care (signs, symptoms, weight etc.) without knowledge of PA pressure information derived from the CardioMEMS™ HF System

Subjects will be considered enrolled in the Randomized Arm once all entry criteria are met, informed consent is provided, and implantation of the CardioMEMS™ PA Sensor is attempted. Safety information and adverse events (AEs) will be reported (per section 8.2) for all enrolled subjects. However, subjects will only contribute towards the sample size and primary, secondary effectiveness, and descriptive endpoint analyses following successful implantation and randomization. [redacted]

No subject in the trial, regardless of treatment group, will have direct access to their uploaded PA pressure information. Investigators and clinical trial personnel will not have access to uploaded pressure information for subjects in the Control Group. Efforts will be made to ensure that subjects in the Treatment and Control Groups of the Randomized Arm will have communications with the sites at a similar frequency, using only a pre-specified telephone script. Both Treatment and Control Group subjects will be contacted at least once every two weeks for the first three months post-implantation, and at least monthly from three months until the 12 month follow-up visit. [redacted]

The GUIDE-HF Randomized Arm will include approximately 1000 subjects (following successful implantation and randomization, 500 per group) at approximately 140 sites. Each subject will be followed for 12 months, with follow-up visits at 6 and 12 months.

4.1.3 GUIDE-HF Single Arm

The GUIDE-HF Single Arm is a prospective, multi-center, single-arm clinical trial of the CardioMEMS™ HF System in North America in NYHA Class III HF patients, with either elevated NT-proBNP (or BNP) and/or a prior HFH. After screening procedures and signing the Informed Consent Form, subjects will

[redacted]

complete baseline assessments. Within 60 days of consent, subjects will receive a CardioMEMS™ HF System. Subjects will be considered enrolled in the Single Arm once all entry criteria are met, informed consent is provided, and implantation of the CardioMEMS™ PA Sensor is attempted. Safety information and adverse events (AEs) will be reported (per section 8.2) for all enrolled subjects. However, subjects will only contribute towards the sample size and primary, secondary effectiveness, and descriptive endpoint analyses following successful implantation. Subjects will upload PA pressure information daily, and receive HF management guided by PA pressure information.

The GUIDE-HF Single Arm will include approximately 2600 subjects (following successful implantation) at approximately 140 sites. Each subject will be followed for 12 months, with follow-up visits at 6 and 12 months.

4.2 Objectives

GUIDE-HF Randomized Arm: The objective of the GUIDE-HF Randomized Arm is to determine if PA pressure-guided HF management using CardioMEMS™ improves health outcomes in NYHA Class II, III, or IV HF patients with either elevated NT-proBNP (or BNP) and/or a prior HFH.

GUIDE-HF Single Arm: The objective of the GUIDE-HF Single Arm is to demonstrate the equivalence of the effect of PA pressure-guided HF management on health outcomes between NYHA Class III HF patients with elevated NT-proBNP (or BNP) only and those with a prior HFH only.

4.3 Endpoints

Refer to *Appendix C* for event definitions used for the trial endpoints.

4.3.1 GUIDE-HF Randomized Arm

The GUIDE-HF Randomized Arm will evaluate one primary endpoint, several secondary endpoints, and several descriptive endpoints. All endpoints will be compared between the Treatment and Control Groups unless otherwise noted.

4.3.1.1 Primary Endpoint

The primary endpoint is a composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy or all-cause mortality at 12 months post-implantation (referred to as the Composite Endpoint). Emergency department visits and hospital outpatient observation visits involving intravenous diuretics, along with HFHs, are included in the primary endpoint, as the duration of hospitalization can vary, and decompensation events requiring intravenous diuretic therapy impact subject quality-of-life and mortality, regardless of form (inpatient or outpatient). The following events will be included in the composite: 1) hospitalization (≥ 24 hours) with the primary reason for admission being acute decompensated HF and intravenous administration of diuretic therapy; 2) an unscheduled or unplanned admission to the emergency department, hospital outpatient observation visit, or hospital inpatient visit and intravenous administration of diuretic therapy; 3) all-cause mortality. All events contributing to the primary endpoint will be adjudicated by an independent Clinical Events Committee (CEC) (see section 5.10.4 for details). In rare instances, CEC discretion may be used to determine whether additional criteria would identify a decompensation event that could represent a valid contribution to the primary endpoint (e.g., ultra-filtration in lieu of diuretics).

4.3.1.2 Secondary Endpoints

The secondary effectiveness endpoints are:

- Composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy
- Health status at baseline, 6, and 12 months post-implantation as assessed by the EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire

- Health status at baseline, 6, and 12 months post-implantation as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ-12)
- Six Minute Hall Walk (6MHW) test at baseline, 6, and 12 months post-implantation
- In addition, the individual components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints:
    - HFHs at 12 months post-implantation
    - Emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation
    - All-cause mortality at 12 months post-implantation

The secondary safety endpoint is freedom from device/system related complications (DSRCs) at 12 months post-implantation. The secondary safety endpoint will be evaluated for all subjects enrolled in the Randomized Arm (i.e. with an attempted implant, whether successful or unsuccessful) and reported for the entire subject cohort and by subject group.

4.3.1.3 Descriptive Endpoints

Descriptive endpoints are reported using only summary statistics and no hypothesis tests will be performed. All mortality- and hospitalization-related components of the primary endpoints will be adjudicated by the CEC. The following additional data will be collected and reported:

- Cardiovascular mortality at 12 months post-implantation
- All-cause hospitalizations at 12 months post-implantation
- Frequency of subject PA pressure uploads through 12 months
- HF medication changes through 12 months
- PA pressure measurements from baseline through 12 months
- NT-proBNP (or BNP) at baseline, 6, and 12 months
- HFHs at 12 months post-implantation compared to HFHs in the 12 months prior to implantation

4.3.2 GUIDE-HF Single Arm

The GUIDE-HF Single Arm will evaluate one primary endpoint, several secondary endpoints, and several descriptive endpoints.

4.3.2.1 Primary Endpoint

The primary endpoint is a composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy or all-cause mortality at 12 months post-implantation (same as for the Randomized Arm), to be compared between subjects with an elevated NT-proBNP (or BNP) only and subjects with a prior HFH only. Subjects who have both elevated NT-proBNP (or BNP) and a prior HFH will not be included in the analysis for the primary endpoint. All events contributing to the primary endpoint will be adjudicated by the CEC (see section 5.10.4 for details). In rare instances, CEC discretion may be used to determine whether additional criteria would identify a decompensation event that could represent a valid contribution to the primary endpoint (e.g., ultra-filtration in lieu of diuretics).

4.3.2.2 Secondary Endpoints

The secondary effectiveness endpoints are:

- Composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation
- HFHs at 12 months post-implantation compared to HFHs in the 12 months prior to implantation. All subjects who receive a CardioMEMS™ PA Sensor implant will be included in the analysis of this endpoint.
- In addition, the individual components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints:
    - HFHs at 12 months post-implantation

[redacted]

- Emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation
- All-cause mortality at 12 months post-implantation

The secondary safety endpoint is freedom from DSRCs at 12 months post-implantation. The secondary safety endpoint will be evaluated for all subjects enrolled in the Single Arm (i.e. with an attempted implant, whether successful or unsuccessful) and reported for the entire subject cohort and by subject group.

4.3.2.3 Descriptive Endpoints

Descriptive endpoints are reported using only summary statistics and no hypothesis tests will be performed. All mortality- and hospitalization-related components of the primary endpoints will be adjudicated by the CEC. The following additional data will be collected and analyzed. The EQ-5D-5L, KCCQ-12, and 6MHW test will be collected and reported only for the first 1000 subjects enrolled and successfully implanted in the Single Arm.

- Health status at baseline, 6, and 12 months post-implantation as assessed by EQ-5D-5L
- Health status at baseline, 6, and 12 months post-implantation as assessed by the KCCQ-12
- 6MHW test at baseline, 6, and 12 months post-implantation
- Cardiovascular mortality at 12 months post-implantation
- All-cause hospitalizations at 12 months post-implantation
- Frequency of subject PA pressure uploads through 12 months
- HF medication changes through 12 months
- PA pressure measurements from baseline through 12 months
- NT-proBNP (or BNP) at baseline, 6 months, and 12 months

4.4 Clinical Trial Population

The intended population for this clinical trial includes patients over the age of 18 years with symptomatic NYHA class II, III, or IV HF and either a prior HFH within the past 12 months and/or elevated NT-proBNP (or BNP) within 30 days prior to consent, that meet the trial entry criteria defined below. Refer to *Appendix C* for NYHA class definitions.

4.4.1 Inclusion Criteria

To participate in this clinical trial and receive a CardioMEMS™ HF System implant, subjects must meet all of the following inclusion criteria:

1. Diagnosis and treatment for HF (regardless of LVEF) for > 90 days prior to the date of consent:
    a. Subjects should be on stable, optimally titrated medical therapy for at least 30 days, as recommended according to current AHA/American College of Cardiology (ACC) guidelines as standard-of-care for HF therapy in the United States, with any intolerance documented.
2. **GUIDE-HF Randomized Arm Only**: NYHA Class II, III or IV HF symptoms documented within 30 days prior to consent.
3. **GUIDE-HF Single Arm Only**: NYHA Class III HF symptoms documented within 30 days prior to consent.
4. HFH within 12 months prior to consent and/or elevated NT-proBNP (or BNP) within 30 days prior to consent defined as:
    a. Subjects with LVEF ≤ 40%: NT-proBNP ≥ 1000 pg/mL (or BNP ≥ 250 pg/mL).
    b. Subjects with LVEF > 40%: NT-proBNP ≥ 700 pg/mL (or BNP ≥ 175 pg/mL).
    c. Thresholds for NT-proBNP and BNP (for both LVEF ≤ 40% and LVEF > 40%) will be corrected for BMI using a 4% reduction per BMI unit over 25 kg/m^2
5. ≥ 18 years of age
6. Chest circumference of < 65 inches, if BMI is > 35 kg/m^2
7. Written informed consent obtained from subject

8. Willing and able to upload PA pressure information and comply with the follow-up requirements

4.4.2 Exclusion Criteria

Subjects who meet any of the following criteria must be excluded from the clinical trial:

1. Intolerance to all neuro-hormonal antagonists (i.e., intolerance to angiotensin converting enzyme-inhibitors (ACE-I), angiotensin receptor blockers (ARB), angiotensin-neprilysin inhibitors (ARNi), hydralazine/isosorbide dinitrate ***and*** beta-blockers)
2. ACC/AHA Stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)
3. Received or are likely to receive an advanced therapy (e.g., mechanical circulatory support or cardiac transplant) in the next 12 months
4. NYHA Class IV HF patients with:
    a. Continuous or chronic use of scheduled intermittent inotropic therapy for HF and an INTERMACS level of ≤ 4, OR
    b. Persistence of fluid overload with maximum (or dose equivalent) diuretic intervention
5. Glomerular Filtration Rate (eGFR) < 25 mL/min/1.73m^2 and non-responsive to diuretic therapy, or receiving chronic dialysis
6. Inability to tolerate or receive dual antiplatelet therapy or anticoagulation therapy for one month post-implantation
7. Significant congenital heart disease that has not been repaired and would prevent implantation of the CardioMEMS™ PA Sensor
8. Implanted with mechanical right heart valve(s)
9. Unrepaired severe valvular disease
10. Pregnant or planning to become pregnant in the next 12 months
11. 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).
12. History of current or recurrent (≥ 2 episodes within 5 years prior to consent) pulmonary emboli and/or deep vein thromboses
13. Major cardiovascular event (e.g., unstable angina, myocardial infarction, percutaneous coronary intervention, open heart surgery, or stroke, etc.) within 90 days prior to consent
14. Implanted with Cardiac Resynchronization Therapy (CRT)-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) for less than 90 days prior to consent
15. Enrollment into another trial with an active treatment arm
16. Anticipated life expectancy of < 12 months
17. 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 CardioMEMS™ PA Sensor implantation

4.4.3 Enrollment of Medicare Beneficiaries

This clinical trial will enroll appropriate Medicare beneficiaries that qualify based on the inclusion and exclusion criteria set forth in the trial. This IDE clinical trial adheres to all standards of Medicare coverage requirements set forth by the IDE and clinical trial coverage policies of the Center for Medicare and Medicare Services (CMS). Section 7, Risks and Benefits, describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the CardioMEMS™ HF System under investigation.

Subjects enrolled in the clinical trial are expected to be consistent with the Medicare population based on demographic characteristics and cardiovascular risk factors; therefore, the clinical trial results are expected to be generalizable to the Medicare population.

4.4.4 Historically Underrepresented Demographic Subgroups

The Sponsor intends to implement FDA's guidance on sex-specific data in medical device clinical studies to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical trial.

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

- 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
- The Sponsor will regularly review withdrawal rates for under-represented subgroups and compare these rates with that in the overall clinical trial population
- As appropriate and necessary, the Sponsor will retrain sites on the importance of recruiting and retaining subjects in the clinical trial
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups
- The Sponsor will have the Informed Consent Forms in alternative languages and will work with sites and IRBs/ECs on recruitment materials

5 Clinical Trial Procedures

All parties involved in the conduct of this clinical trial will be qualified by education, training, or experience to perform their tasks, and this training will be documented appropriately. The investigation will not commence until the Sponsor receives written approval from the Institutional Review Board (IRB)/Ethics Committee (EC) and relevant regulatory authorities, and all required documents have been collected from the investigational site(s). All trial staff will be required to undergo training prior to performing any trial-related activities. Approval from the Sponsor must be received prior to initiating clinical trial procedures.

An overview of the study procedures is shown in Figure 1. Following consent, confirmation of eligibility, and baseline assessments, subjects will undergo a procedure to implant the CardioMEMS™ PA Sensor. After discharge from hospitalization post-procedure, subjects will have phone contact and follow-up visits at 6 and 12 months. If any CardioMEMS™ PA Sensor inaccuracy is suspected at any point, contact Sponsor's technical support for instructions to re-calibrate the CardioMEMS™ PA Sensor baseline. Upon completion of the 12 month follow-up visit, subjects will have completed the follow-up requirements of this clinical trial. The Principal Investigator should arrange for appropriate care of subjects following trial completion. After completing the 12 month visit, at the discretion of the clinician, Control Group subjects in the Randomized Arm may be treated with clinician knowledge of their PA pressure. The Sponsor must be notified if a site intends to view PA pressure data for a Control Group subject following the 12 month follow-up visit. [redacted]

The following sections provide a detailed description of procedures required by this CIP.

[redacted]

5.1 Clinical Trial Flow Chart

The Flow Chart (Figure 1) and Table 2 below summarize the subject flow and requirements of this clinical trial.

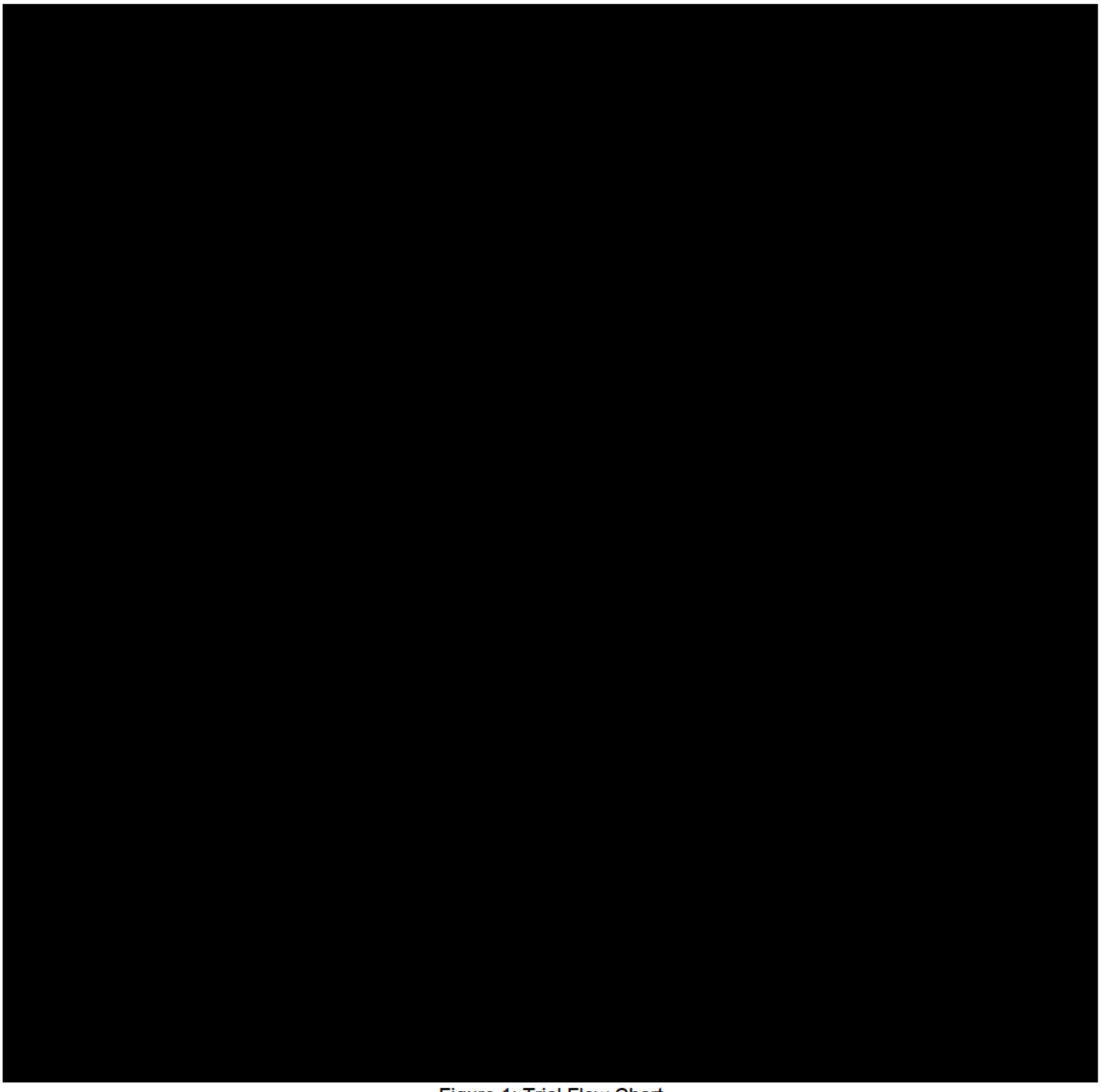


Figure 1: Trial Flow Chart

Table 2: List of all clinical trial tests and procedures

Visit Trial Activity	Baseline (up to -60 days)	Implant (time zero)	Prior to Discharge	Phone Contact[1] (Randomized Arm Only)	6 Months (+/-14 days)	12 Months (+/-30 days)
Informed Consent Process	X					
Assessment of Inclusion/Exclusion Criteria	X[2]					
Demographic Information	X					
Cardiovascular History	X					
BMI (and Chest Circumference if BMI > 35kg/m^2)	X					
Limited Echo for EF (if no EF documented)	(X)					
EQ-5D-5L and KCCQ-12 Administration[3]	X				X	X
Creatinine and Calculation of eGFR	X				X	X
NT-proBNP (or BNP)	X				X	X
Medication Review and Documentation	X		X		X	X
HF Exam (Including NYHA Assessment)	X				X	X
6MHW Test[3]	X				X	X
CardioMEMS™ HF System Information		X				
Catheterization Laboratory PA Pressure Measurements		X				
Randomization (Randomized Arm Only[4])			X			
Subject Teaching / Compliance Assessment			X	X	X	X
Subject Contact Worksheet				X		
Medication Update Documentation		(X)	(X)	(X)	(X)	(X)
Reportable AEs	(X)	(X)	(X)	(X)	(X)	(X)
Protocol Deviation	(X)	(X)	(X)	(X)	(X)	(X)
Non-AE Device Issues		(X)	(X)	(X)	(X)	(X)
Death	(X)	(X)	(X)	(X)	(X)	(X)

(X) If applicable/as it occurs

[redacted]

5.2 Subject Recruitment

For the recruitment of subjects, sites will screen charts from their own HF patient population and/or reach out to clinicians within their referral base. Any subject-facing recruitment materials or advertisements will require both Sponsor and IRB approval prior to use.

5.3 Point of Enrollment

In both the Randomized Arm and Single Arm, subjects will be considered enrolled once all entry criteria are met, informed consent is provided, and implantation of the CardioMEMS™ PA Sensor is attempted. Safety information and adverse events (AEs) will be reported (per section 8.2) for all enrolled subjects. However, subjects will only contribute towards the sample size and all other endpoint analyses following successful implantation and randomization (Randomized Arm) or following successful implantation (Single Arm). See *Appendix L* for a flow chart reflecting trial enrollment procedures. Subjects who provide written informed consent, but fail to meet entry criteria (or choose to no longer participate) prior to an attempted implantation will be considered screening failures. Subjects with an attempted, but unsuccessful, implant will be followed for 30 days post-implantation attempt for safety and/or will undergo a re-attempted implantation procedure (see section 5.4.4.1 for details).

The Principal Investigator or delegated trial personnel will record enrollment information (including, but not limited to the date of implant (Single Arm), date of consent, and inclusion/exclusion information) in the subject records and complete and submit the applicable CRFs. Notification of enrollment to the Sponsor is considered to have occurred when the Sponsor has received documentation of the enrollment information via the applicable CRFs.

5.4 Scheduled Procedures

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, implant training and proctoring for implantations for sites using the CardioMEMS™ HF System for the first time.

5.4.1 Screening Procedures

The following information will be evaluated from medical records and documented, to ensure each subject meets entry criteria prior to consent. Subjects are required to have either a HFH within the previous 12 months or a documented elevated NT-proBNP (or BNP) within the previous 30 days (outside of clinical trial procedures per standard-of-care). Documentation of a prior HFH and/or elevated NT-proBNP (or BNP) is required for verification of inclusion and exclusion criteria. If necessary, screening procedures to address other entry criteria (such as EF and eGFR, if not previously documented) can be evaluated during the baseline visit following consent.

- Duration of HF from first diagnosis
- NYHA class evaluation within the previous 30 days
- All HFHs within the previous one year, as provided by the subject's cardiologist, internist, or referring physicians including gathering of source documentation of hospitalizations
- Laboratory analyses for qualifying NT-proBNP (or BNP) within the previous 30 days for inclusion verification (outside of clinical trial procedures)
- EF within six months prior to the consent date (can be from echo, nuclear testing, angiography, CT, MRI). If no documentation exists in the required timeframe, a limited echo to document EF only will be required during the baseline visit.

- Calculation of BMI using subject height and weight (see *Appendix H*) and calculation of chest circumference measurement if BMI > 35kg/m^2
- Age
- Cardiovascular history including:
  - previous cardiac procedures and CRT device information
  - relevant co-morbidities
- HF medication review with documentation

5.4.2 Informed Consent

As this IDE trial has two distinctly unique arms (Randomized Arm and Single Arm), one of two Informed Consent Forms will be utilized detailing requirements and considerations in each arm. The Principal Investigator or his/her authorized designee will conduct the informed consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the subject on all aspects of the clinical trial that are relevant to the subject's decision to participate such as details of the procedures, anticipated benefits, and potential risks of clinical trial participation. During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect the subject's legal rights. The subject shall be provided with the Informed Consent Form (for the applicable trial arm) written in a language that is understandable to the subject and has been approved by the center's IRB/EC. The subject shall have adequate time to review, ask questions and consider participation.

If the subject agrees to participate, the Informed Consent Form for the applicable trial arm must be signed and dated by the subject and by the person obtaining the consent. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

The Principal Investigator or his/her authorized designee will document the informed consent process in the subject's hospital and/or research charts. The date of signature will be entered on the applicable CRF.

Failure to obtain informed consent from a subject prior to clinical trial enrollment should be reported to Sponsor within five working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

If, during the clinical trial, new information becomes available that can significantly affect a subject's health and medical care, the Principal Investigator or his/her authorized designee will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

5.4.3 Baseline Procedures

The following assessments and information will be collected during the baseline visit prior to implant (see Table 2 for additional details). The Quality of Life assessments (KCCQ-12 and EQ-5D-5L) should be administered prior to all other baseline procedures.

- KCCQ-12 Quality of Life assessment (see *Appendix I* for details)
- EQ-5D-5L Quality of Life assessment (see *Appendix I* for details)
- Verification of inclusion and exclusion criteria (as necessary from the screening procedures)
- Documentation of key demographic information such as ethnicity, gender and age
- Cardiovascular history including:
  - previous cardiac procedures and CRT device information
  - relevant co-morbidities
- HF assessment including NYHA class evaluation
- HF medication review with documentation
- Laboratory analyses for baseline NT-proBNP (or BNP)

- NT-proBNP is preferred, however laboratory analyses conducted must be consistent with that of the screening procedures (e.g., if BNP was collected from medical records during screening procedures, BNP must be collected at baseline and follow-up visits). If both (or neither) NT-proBNP and BNP were collected from screening procedures, NT-proBNP should be collected at baseline and follow-up visits if possible.

- Limited echo to document EF (if necessary due to lack of documentation in the required timeframe)
- Laboratory analyses for creatinine with eGFR calculation (see *Appendix J*).
- 6MHW Test (see *Appendix K*)

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.

5.4.3.1 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 an attempted implantation, the subject must be also documented as a screening failure.

5.4.4 Implant Procedure

Once the subject has been determined to meet all eligibility criteria and provided informed consent, the subject will be scheduled for the implant/RHC procedure within 60 days of consent. Institutional standards should be followed for preoperative requirements. Implantation and baseline calibration of the CardioMEMS™ PA Sensor should be performed according to the CardioMEMS™ HF System user manual. The CardioMEMS™ HF System is considered investigational in this trial; however all other aspects of the IFU apply and should be followed. In the event that an alternative implantation approach is pursued, the alternative implantation approach and associated justification must be reported as a protocol deviation.

[redacted]

All enrolled subjects will be provided with trial ID cards instructing non-trial

[redacted]

providers to notify the trial research team upon presentation or admission to a hospital. Following randomization, data for subjects within the Randomized Arm are no longer to be viewed on the CardioMEMS™ Hospital Electronic Unit, so as to prevent Investigator access to PA pressure. Cards for Randomized Arm subjects will additionally specify to non-trial providers not to use the Hospital Electronic Unit. [redacted]

5.4.4.1 Unsuccessful implant

If an implant is attempted, but is unsuccessful, the subject should not be randomized, and associated information must be documented on the applicable CRF. If a reattempt is medically appropriate and planned, and there is no change in the subject's eligibility status, the implant can be rescheduled within 30 days. If clinically appropriate, the subject can be rescreened at a later date. Subjects with an attempted, but unsuccessful, implant, with no plan to be re-attempted, will be followed for 30 days post-implantation attempt, to document CardioMEMS™ PA Sensor/implant-related AEs. After 30 days, the subject will no longer participate in the trial and the applicable CRF must be completed. The 30 day follow-up may be conducted remotely.

5.4.5 Randomization

[redacted]

5.4.6 Prior to Discharge

Prior to discharge, subjects will be provided with a CardioMEMS™ Patient Electronic Unit and instructed in the use and importance of transmitting data daily to the website. The home measurements should be taken at the same time each day with the subject in the same position (e.g., supine, sitting or reclined) for each measurement. It is recommended that subjects obtain home measurements in a supine position. However, if the subject is unable to lie flat, measurements can be obtained in a sitting or reclined position. Refer to subject's CardioMEMS™ HF System Guide for more detailed information. Note that the CardioMEMS™ Patient Electronic Unit provides no PA pressure information to subjects, but only to the sites through the Merlin.net™ website. [redacted] However, subjects will also be informed that should they have symptoms, questions or concerns, they can contact the applicable site personnel. The site should provide the subjects with the time and date for their first trial follow-up visit and applicable site contact information.

5.4.7 Hemodynamic Management of HF – Treatment Guidance

Investigators are encouraged to follow the current GDMT with consideration of available PA pressure information for all subjects within both the Randomized Arm and Single Arm and to reevaluate the appropriate use of GDMT in each clinical encounter with subjects. This evaluation should include assessing the choice of appropriate agents and ensuring appropriate target dosing as outlined in *Appendix E* and in the AHA/ACC/HFSA Guidelines.

[redacted]

Subjects in the Control Group of the Randomized Arm are to be managed with standard of care procedures per GDMT, and per treatment guidelines outlined in *Appendix E* with respect to available PA pressure information (from any right heart catheterization procedures).

Subjects in the Treatment Group of the Randomized Arm and the Single Arm are to be managed using PA pressure readings per the treatment guidelines (see *Appendix E*). [redacted]

PA pressure data from Merlin.net™ will be reviewed and monitored by the clinician as frequently as is clinically indicated, but at a minimum weekly. Additionally, failure to maintain the subject in the targeted range or selection of a PA pressure goal outside of the target ranges will be documented, along with the reason for nonconformance.

5.4.8 Patient database (Merlin.net™)

[redacted]

5.4.9 PA Pressure Readings in the Hospital

If a randomized subject is admitted to the hospital, the Hospital Electronic Unit cannot be used to collect PA pressure data for subjects within the Randomized Arm, and PA pressure data may only be accessed through the Merlin.net™ website as collected from the CardioMEMS™ Patient Electronic Unit. The **only** exception, in which use of the Hospital Electronic Unit would be allowed, would be for the review of PA pressure during a clinically-warranted repeat RHC procedure for a subject in the Treatment Group of the Randomized Arm. The clinician may utilize data from the CardioMEMS™ Hospital Electronic Unit **ONLY** during the RHC procedure since the data are comparable to those typically obtained during a standard-of-care RHC. The PA pressure data obtained during the RHC can be used, if required, to re-calibrate the baseline of the CardioMEMS™ PA Sensor as appropriate.

[redacted]

Following CardioMEMS™ PA Sensor implant, subsequent clinically-warranted RHC procedures or PA catheter insertions in either the Treatment Group or Control Group must be performed under fluoroscopic guidance to avoid dislodgement or damage to the CardioMEMS™ PA Sensor. Repeat RHC procedures are not a requirement of this trial, and should only be performed if clinically necessary.

5.4.10 Post-Discharge Subject Phone Contact Requirements

Subjects will be instructed to take and upload their PA pressure measurements daily. Subjects will also be notified that their compliance with taking daily PA measurements will be reviewed and that, as part of the trial, the site will be in contact with the subject on a regular basis.

No contact will be initiated by the Sponsor Representative or Steering Committee to the Investigator or site regarding subject-specific PA pressure measurements or medication adjustments.

Randomized Arm:

[redacted]

[redacted]

Single Arm:

[redacted]

5.4.11 Scheduled Follow- ups

Follow-up visits are scheduled at 6 (± 14 days) and 12 months (± 30 days) post-implantation. The scheduled visit windows are calculated from the successful implant date (time zero). Sponsor Representatives will be available to provide support if needed during the follow-up procedures.

5.4.11.1 6 and 12 Month Follow-up Visits

The following assessments and information will be collected during the 6 and 12 month follow-up visits (see Table 2 for additional details). The Quality of Life assessments (KCCQ-12 and EQ-5D-5L) should be administered prior to all other procedures.

- KCCQ-12 Quality of Life Assessment (see *Appendix I* for details)
- EQ-5D-5L Quality of Life Assessment (see *Appendix I* for details)
- HF Exam Assessment including NYHA Class evaluation
- HF medication review with documentation (including any changes in HF medications) and reevaluation of the appropriate use of GDMT
- Laboratory analyses for baseline NT-proBNP (or BNP)
    - NT-proBNP is preferred; however laboratory analyses conducted must be consistent with that of the prior clinical trial procedures (e.g., if BNP was collected during screening and baseline procedures, BNP must be collected at follow-up visits).
- Laboratory analyses for creatinine with eGFR calculation (see *Appendix J*)
- 6MHW test (see *Appendix K*)
- Review and report of Serious Adverse Events (SAEs), Adverse Device Effects (ADEs), Serious Adverse Device Effects (SADEs), Unanticipated Adverse Device Events (UADEs), non-AE device issues, emergency department visits or hospitalizations which occurred since last trial visit not yet reported
- Troubleshoot and re-educate, for any transmission or non-compliance issues

5.4.12 Data Viewing After 12 Months

Subjects in the Randomized Arm are required to remain in their assigned treatment group until they complete their 12 month visit. After the 12 month visit has been completed, at the clinicians' discretion, PA pressure readings for Control Group subjects can be made visible to the site through the Merlin.net™ website. To view data after the 12 month visit, contact the clinical technical support team who will arrange access to the data on the Merlin.net™ website and will review the waveforms to evaluate accuracy of the signal for any signs of drift. Upon initiating contact with clinical technical support, sites will be instructed to allow three working days for review.

5.5 Unscheduled Visits

Clinicians may follow standard of care for frequency of follow-up outside of the trial required visits. Routine office visits which are not required by the protocol, do not require reporting. However, all

[redacted]

reportable events (e.g., SAEs, ADEs, SADEs, UADEs, and non-AE device issues, see section 8.2) identified during an unscheduled visit are required to be reported and documented by completing the applicable CRF. Medication changes will be captured as they occur on the applicable CRF. For Randomized Arm subjects, the CardioMEMS™ Hospital Electronic Unit cannot be used during follow-up visits and PA pressure data can only be viewed on the Merlin.net™ website.

5.6 Healthcare Economic Data Collection

[redacted]

5.7 Description of Activities Performed by Sponsor Representatives

Trained Sponsor personnel will provide technical expertise and technical guidance to the site on the use of the CardioMEMS™ PA Sensor, including proctored case support, training on the protocol, use of Merlin.net™ website, and data collection requirements. The Sponsor will not advise on individual subject management but will provide clear training in the protocol expectations and best practices concerning hemodynamic-guided HF management. This educational process will be provided at initiation of the site for the trial but will neither be specific to individual subjects or ongoing during the trial. The Sponsor will provide re-training to sites only as necessary (see section 11.3 for detail). Educational material will be provided by the Sponsor to the site personnel that represent the current protocol guidelines of best practices. While Sponsor representatives may support some of these activities, the PI remains responsible for providing trial data and ensuring all clinical trial data are collected as required per CIP.

5.8 Subject Clinical Trial Completion

Subject participation in the clinical trial will conclude upon completion of the 12 month visit. Following trial completion, subjects should continue to be followed per standard-of-care, reporting any CardioMEMS™ HF System issues or deaths through the standard medical device reporting channels.

5.9 Subject Withdrawal

Subjects must be informed about their right to withdraw from the clinical trial at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical trial will not jeopardize their future medical care or relationship with the Investigator. Subjects will be requested to specify the reason for the request to withdraw. The Investigator must make all reasonable efforts to retain the subject in the clinical trial until completion of the trial.

A subject will be considered 'Lost to Follow-up' after two missed visit(s) and a minimum of two unsuccessful phone calls from investigational site personnel to the subject or subject's contact to schedule the next follow-up visit. These two phone calls must be documented in the subject's hospital records. If the subject is deemed lost to follow-up a letter should be sent to the subject's last known address or to the subject's general practitioner and a copy of the letter must be maintained in the subject's hospital records.

If the subject requests to withdraw from the trial, the site should make attempts to schedule the subject for a final trial visit. If the subject agrees, then at this final trial visit, the subject will undergo the following assessments:

- Collect all reportable event information (see section 8.2.1) since the prior visit

[redacted]

- Medication review and documentation

5.10 Clinical Trial Committees

5.10.1 Steering Committee

A Steering Committee has been formed to advise the Sponsor on key aspects related to the development, execution, analysis and reporting, and overall conduct of the clinical trial. The primary function, responsibilities and membership of the Steering Committee will be described in detail in a Steering Committee charter.

5.10.2 Publication Committee

A Publication Committee shall be established to oversee trial publications, including publication planning and authorship determinations. Publication Committee membership may include members of the Steering Committee, Principal Investigators, a representative of the Sponsor and a statistician. The primary function, responsibilities and membership of the Publication Committee, as well as rules to define authorship, will be described in detail in a Publication Committee charter.

5.10.3 Data Safety Monitoring Board (DSMB)

An independent DSMB will review on a regular basis accumulating data from the clinical trial and will advise the Sponsor regarding the continuing safety of subjects and those yet to be recruited, as well as the continuing validity and scientific merit of the clinical trial. However, analysis of efficacy will not be used by the DSMB to consider continuance of the trial. DSMB members will not be Investigators in the clinical trial. At any time during the investigation, the DSMB may offer opinions or provide formal recommendations concerning aspects of the trial that impact subject safety (e.g. safety-related protocol changes or input regarding CardioMEMS™ HF System-related AE rates). The function, responsibilities and membership of the DSMB will be described in detail in a DSMB charter.

5.10.4 CEC

A CEC will be responsible for providing an independent review and adjudication of the following data:

- Events that could contribute to primary endpoints for either trial arm, to determine which events meet primary endpoint qualification, including:
  - All cardiovascular hospitalizations, cardiovascular emergency department visits, and cardiovascular hospital outpatient visits, all defined as a hospital visit with the primary cause being cardiovascular in nature, as reported by the Investigator
  - All deaths
  - Any hospitalizations which, when reviewed by the Sponsor, could potentially meet endpoint qualification
- HFHs that occurred within 12 months prior to baseline
- All events that could contribute to the secondary safety endpoint for either trial arm including ADEs, SADEs, and UADEs

All attempts will be made to blind the CEC to the treatment group assignment. The function, responsibilities and membership of the CEC will be described in greater detail in a CEC charter.

6 Statistical Considerations

The following section describes the statistical methods for the clinical trial and justification of the design. Additional details on statistical analyses, including sensitivity analyses, poolability analyses, subgroup analyses and analysis of descriptive endpoint(s) will be described in a separate Statistical Analysis Plan (SAP). Hypothesis tests will be 1-sided and conducted at a significance level of 2.5% unless stated otherwise.

6.1 GUIDE-HF Randomized Arm

6.1.1 Primary Endpoint

The primary endpoint is a composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy or all-cause mortality (referred to as Composite Endpoint) at 12 months post-implantation. [redacted] The analysis population will include subjects enrolled in the Randomized Arm, successfully implanted, and randomized to either Treatment or Control Groups.

To demonstrate effectiveness of PA pressure-guided HF management compared to standard-of-care-guided HF management, the following hypothesis will be tested:

H_0: HR for the Composite Endpoint at 12 months (Treatment to Control) ≥ 1
H_1: HR for the Composite Endpoint at 12 months (Treatment to Control) < 1

6.1.1.1 Analysis Methods

[redacted]

6.1.1.2 Sample Size

[redacted]

6.1.1.3 Criteria for Success

The primary endpoint must be met in order for the GUIDE-HF Randomized Arm to be considered successful. Primary and secondary endpoints will be used to support label claims.

6.1.1.4 Missing Data

[redacted]

6.1.2 Secondary Endpoints

The secondary effectiveness endpoints of the GUIDE-HF Randomized Arm include the composite of HFH and emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation (i.e., HFH + HFH Equivalents) as well as health status, as assessed by the EQ-5D-5L Questionnaire and the KCCQ-12, and the 6MHW test at baseline, 6, and 12 months post-implantation. In addition, the individual components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints: HFH at 12 months post-implantation, emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation, and all-cause mortality at 12 months post-implantation. [redacted] The analysis population for the secondary effectiveness endpoints will include subjects enrolled in the Randomized Arm, successfully implanted, and randomized to either Treatment or Control Groups.

[redacted]

The secondary safety endpoint of the GUIDE-HF Randomized Arm is freedom from DSRCs at 12 months post-implantation. The analysis population for the secondary safety endpoint will include subjects enrolled in the Randomized Arm (i.e. with an attempted implant, whether successful or unsuccessful).

6.1.2.1 HFH + HFH Equivalents at 12 Months Post-Implantation

To demonstrate effectiveness of PAP-guided HF management compared to standard-of-care-guided HF management with respect to HFH + HFH Equivalents, the following hypothesis will be tested:

H_0: HR for HFH + HFH Equivalents at 12 months (Treatment to Control) ≥ 1
H_1: HR for HFH + HFH Equivalents at 12 months (Treatment to Control) < 1

6.1.2.1.1 Analysis Methods

[redacted]

6.1.2.2 EQ-5D-5L at 6 and 12 Months Post-Implantation

To demonstrate effectiveness of PA pressure-guided HF management compared to standard-of-care-guided HF management with respect to the EQ-5D-5L, the following hypothesis will be tested for the EQ-5D-5L visual analogue scale (VAS):

H_0: Treatment effect$_{\text{EQ-5D-5L VAS}} \leq 0$
H_1: Treatment effect$_{\text{EQ-5D-5L VAS}} > 0$

6.1.2.2.1 Analysis Methods

[redacted] he null hypothesis will be rejected if the [redacted] show benefit of Treatment over Control and the p-value is less than 2.5% using a one-sided test.

6.1.2.3 KCCQ-12 at 6 and 12 Months

To demonstrate effectiveness of PA pressure-guided HF management compared to standard-of-care-guided HF management with respect to the KCCQ-12, the following hypothesis will be tested:

H_0: Treatment effect$_{\text{KCCQ-12 Overall Summary Score}} \leq 0$
H_1: Treatment effect$_{\text{KCCQ-12 Overall Summary Score}} > 0$

6.1.2.3.1 Analysis Methods

The hypothesis will be evaluated using a mixed linear model with repeated measures. Treatment [redacted] The null hypothesis will be rejected if the [redacted] show benefit of Treatment over Control and the p-value is less than 2.5% using a one-sided test.

6.1.2.4 6MHW Test at 6 and 12 Months Post-Implantation

To demonstrate effectiveness of PA pressure-guided HF management compared to standard-of-care-guided HF management with respect to the 6MHW test, the following hypothesis will be tested:

[redacted]

H_0: Treatment effect$_{6MHW} \leq 0$
H_1: Treatment effect$_{6MHW} > 0$

6.1.2.4.1 Analysis Methods

[redacted] The null hypothesis will be rejected if the [redacted] show benefit of Treatment over Control and the p-value is less than 2.5% using a one-sided test.

6.1.2.5 Individual Components of the Primary Endpoint

6.1.2.5.1 HFH at 12 months post-implantation

[redacted]

6.1.2.5.2 HFH Equivalents at 12 months post-implantation

[redacted]

6.1.2.5.3 All-Cause Mortality at 12 months post-Implantation

[redacted]

6.1.2.6 Secondary Safety Endpoint: Freedom from DSRCs over 12 Months Post-Implantation

[redacted]

6.2 GUIDE-HF Single Arm

6.2.1 Primary Endpoint

The primary endpoint is a composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy or all-cause mortality at 12 months post-implantation (identical to the Randomized Arm primary endpoint). The two subject groups to be compared are a) subjects having elevated NT-proBNP (or BNP) but without having a HFH in the year prior (i.e., **elevated NT-proBNP (or BNP) only subjects**) and b) subjects having a HFH in the year prior but without elevated NT-proBNP (or BNP) (i.e., **prior HFH only subjects**). The analysis population of the GUIDE-HF Single Arm primary endpoint will include subjects enrolled into the Single Arm and successfully implanted with either elevated NT-proBNP (or BNP) **only** or a prior HFH **only**. Subjects with both elevated NT-proBNP (or BNP) and a prior HFH will not be included in the analysis for the primary endpoint.

To demonstrate equivalence of outcomes between subjects with elevated NT-proBNP (or BNP) only and those with prior HFH only, the following hypothesis will be tested:

H_{0a}: ln[HR for Composite Endpoint (Elevated NT-proBNP (or BNP) Only vs. Prior HFH Only)] $\leq$ -0.2877
H_{0b}: ln[HR for Composite Endpoint (Elevated NT-proBNP (or BNP) Only vs. Prior HFH Only)] $\geq$ 0.2877
H_1: -0.2877 < ln[HR for Composite Endpoint (Elevated NT-proBNP (or BNP) Only vs. Prior HFH Only)] < 0.2877
Where ln is the natural log

[redacted]

6.2.1.1 *Analysis Methods*

The hypothesis will be tested at the 5% significance level. [redacted] The test will be successful and equivalence will be established only if both null hypotheses are rejected.

6.2.1.2 *Sample Size*

[redacted]

6.2.1.3 *Criteria for Success*

The primary endpoint must be met in order for the GUIDE-HF Single Arm to be considered successful. The primary and secondary endpoints will be used to support label claims.

6.2.2 Secondary Endpoints

The secondary effectiveness endpoints of the GUIDE-HF Single Arm include the composite of HFH and emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation (i.e., HFH + HFH Equivalents) as well as the comparison of the annualized rate of recurrent HFHs at 12 months post-implantation to the annualized rate of recurrent HFHs in the 12 months prior to implantation. In addition, the individual components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints: HFH at 12 months post-implantation, emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation, and all-cause mortality at 12 months post-implantation. [redacted]

The secondary safety endpoint of the GUIDE-HF Single Arm is freedom from DSRCs at 12 months post-implantation. The analysis population for the secondary safety endpoint will include subjects enrolled in the Single Arm (i.e. with an attempted implant, whether successful or unsuccessful).

6.2.2.1 *HFH + HFH Equivalents at 12 Months Post-Implantation*

To demonstrate equivalence of HFH + HFH Equivalents between elevated NT-proBNP (or BNP) only subjects and prior HFH only subjects, the following hypothesis will be tested for HFH + HFH Equivalents at 12 months:

H_{0a}: ln[HR for HFH+HFH Equivalents (Elevated NT-proBNP Only vs. Prior HFH Only)] ≤ -0.2877
H_{0b}: ln[HR for HFH+HFH Equivalents (Elevated NT-proBNP Only vs. Prior HFH Only)] ≥ 0.2877
H_1: -0.2877 < ln[HR for HFH+HFH Equivalents (Elevated NT-proBNP Only vs. Prior HFH Only)] < 0.2877
Where ln is the natural log

[redacted]

6.2.2.1.1 Analysis Methods

[redacted]

6.2.2.2 HFHs at 12 Months Post- vs. Pre-Implantation

To demonstrate effectiveness of PA pressure-guided HF management with respect to the goal of reducing HFHs, the following hypothesis will be tested:

H_0: HR for annualized HFHs at 12 months (Rate at 1 year post-implant to Rate at 1 year pre-implant) ≥ 1
H_1: HR for annualized HFHs at 12 months (Rate at 1 year post-implant to Rate at 1 year pre-implant) < 1

6.2.2.2.1 Analysis Methods

The hypothesis will be tested at the 2.5% significance level. [redacted] The null hypothesis will be rejected if the upper limit of the 1-sided, 97.5% CI for the HR of Post-Implant to Pre-Implant is less than 1.

6.2.2.3 Individual Components of the Primary Endpoint

6.2.2.3.1 HFH at 12 months Post-Implantation

[redacted]

6.2.2.3.2 HFH Equivalents at 12 months Post-Implantation

[redacted]

6.2.2.3.3 All-Cause Mortality at 12 months Post-Implantation

[redacted]

6.2.2.4 Secondary Safety Endpoint: Freedom from DSRCs over 12 Months Post-Implantation

[redacted]

6.3 Justification of Clinical Trial Design

The Randomized Arm will evaluate the effectiveness of HF management using the CardioMEMS™ HF System by comparing outcomes against HF management on the basis of standard of care alone. The Randomized Arm is a prospective, randomized, controlled, single-blind investigation, providing the highest level of evidence (26, 27) to expand the indication for the CardioMEMS™ HF system to patients with elevated NT-proBNP (or BNP) or NYHA Class II or Class IV. [redacted]

[redacted]

The Single Arm is a prospective, multi-center, clinical trial of the CardioMEMS™ HF System in NYHA Class III HF patients with either elevated NT-proBNP (or BNP) levels and/or a prior HFH. It will be used to demonstrate equivalence of clinical outcomes between NYHA Class III subjects with an elevated NT-proBNP (or BNP) only and those with a prior HFH only. Results of this clinical trial will be used to support an expanded indication to subjects with elevated NT-proBNP (or BNP) for NYHA Class III patients.

The primary effectiveness endpoint of both the Randomized Arm and Single Arm, the composite of HF events and mortality, is a clinically relevant endpoint for HF patients, and has been used in previous IDE trials (6, 8) and was recommended for use in future clinical trials by consensus among HF experts (28).

The secondary effectiveness endpoints of the Randomized Arm (not including the individual components of the primary endpoint) were selected for the following reasons:

- Change in EQ5D-5L – Use of EQ5D in cardiovascular studies has increased in recent years and published studies provide evidence of its validity and reliability (29). The EQ5D-5L was shown to have better measurement properties than the original EQ5D (30).
- Change in KCCQ-12 – This instrument has been shown to be a valid, reliable, responsive, and prognostically important measure of health status for HF patients (31).
- Improvement in 6MHW test – In congestive HF patients, the 6MHW test provides an objective assessment of exercise capacity that supplements clinical information obtained from medical history and physical examination (32).

The secondary endpoint of the Single Arm (not including the individual components of the primary endpoint), the comparison of HFH in the 12 months prior compared to the 12 months post-implantation, was selected as it provides an objective measure of whether individual hospitalizations have decreased compared to pre-implantation and has been used in prior retrospective analyses in similar patient populations (12).

The secondary safety endpoint for both the Randomized Arm and Single Arm were selected as it has been used in previous IDE and post-approval trials for implantable hemodynamic monitoring devices, including the CardioMEMS™ HF System.

6.4 Multiplicity

[redacted]

6.5 Overall Sample Size

The overall sample size required for evaluation of the Randomized Arm and Single Arm primary endpoints is approximately 3600 (1000 (successfully implanted and randomized) for the Randomized Arm and 2600 (successfully implanted) for the Single Arm). [redacted]

6.6 Statistical Criteria for Termination

There are no statistical criteria for termination of this trial.

6.7 Deviations from Statistical Plan

If any deviations from the original statistical plan occur, such deviations will be documented in the clinical trial report or statistical report containing the analysis results.

7 Risks and Benefits

The risks associated with the CardioMEMS™ HF System can be found in the CardioMEMS™ System User Manual. The trial does not require any additional procedures or assessments over the standard of care being used in the currently indicated population. Although this trial will evaluate the CardioMEMS™ HF System in a patient population that is different than the currently indicated population, there are no anticipated additional risks introduced to trial subjects.

7.1 Risks Associated with the Device under Investigation

The following list of anticipated AEs is outlined in the CardioMEMS™ IFU from past clinical experience. In addition, the list includes the most common events observed and/or documented in the literature associated with HF and CardioMEMS™ HF System implant and exposure.

7.1.1 Anticipated AEs

Events associated with the CardioMEMS™ PA Sensor or the implant procedure (in conjunction with RHC) or post-implantation complications are considered anticipated and include the following:

- Infection
  - Upper respiratory infection
  - Bronchitis
  - Pneumonia
  - Acute Bronchitis
  - Groin abscess
  - Methicillin-resistant staphylococcal aureus infection
  - Pulmonary Infiltration
  - Sepsis
- Arrhythmias
  - Ventricular tachycardia
  - Atrial fibrillation
  - Ventricular arrhythmia
  - Ventricular fibrillation
  - Atrial fibrillation with rapid ventricular response
  - Atrial flutter
  - Cardiac dysrhythmias
  - Tachycardia
  - Wide complex tachycardia

[redacted]

- Bleeding
  - Epistaxis
  - Hemoptysis
  - GI bleed
  - Bleeding
  - Blood in stool
  - Catheter site bleeding
  - Catheter site ecchymosis
  - Hematuria
  - Nose bleeds
- Hematoma
  - Hematoma
  - Catheter site hematoma
  - Vessel puncture site hematoma
- Thrombus
  - Arterial thrombosis (limbs)
  - Blood clot
- Myocardial infarction
- Transient ischemic attack
- Stroke
- Death
- Sensor embolization
- Pulmonary artery perforation

Refer to the CardioMEMS™ PA Sensor and Delivery Catheter, Model CM2000 User Manual for more information. If there are any questions regarding whether an event meets the associated definition (see *Appendix C*), the in-house Sponsor contact should be consulted.

7.1.2 Anticipated ADEs/SADEs

The following is a list of possible anticipated ADEs/SADEs:

- Hemoptysis
- Sensor not deploying
- Transient ischemic attack
- Atypical chest pain
- Sepsis leading to death
- Atrial arrhythmia leading to death
- Arterial embolism (upper extremity)
- PA (in-situ) thrombus
- Catheter site bleeding
- Catheter site ecchymosis
- Catheter site hematoma
- Vessel puncture site pain
- Cardiac monitoring abnormal
- Heart rate irregular
- Serum creatinine increased
- Dyspnea
- Congestive HF
- Ventricular tachycardia
- Dizziness
- Vessel perforation
- Sensor failure/malfunction
- Sensor migration

- System not transmitting

7.1.3 Non-AE Device Issue

To adequately capture non-AE device issues, any device issues that fall outside of the AE definition (see *Appendix C*), a separate form will be used to capture such instances when the device fails to perform or does not function properly without an associated an adverse clinical outcome.

7.2 Risk Control Measures

Every possible effort will be taken to minimize the risks, including:

- Careful selection of experienced Investigators for the clinical trial
- Early (within 60 days of the first enrollment) 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/EC or applicable regulatory authorities where the clinical trial is performed
- Preparation of the CardioMEMS™ PA Sensor and performance of the implantation procedure in accordance with the IFUs
- Training of Investigators both on the CIP and the CardioMEMS™ PA Sensor implantation procedure
- Securing compliance of non-compliant sites (see section 11.3)
- Assessment of continuing safety of subjects in the clinical trial by a DSMB

7.3 Possible interactions with concomitant treatments

The CardioMEMS™ PA Sensor is implanted in the PA via entry through the right side of the heart. If other device right heart leads are previously implanted, it is possible to cause dislodgement. Care should be taken to perform the implant procedure under fluoroscopy.

7.4 Anticipated Benefits

The benefit of hemodynamic-guided HF management in this population is unknown and information will be learned from this trial. Subjects with NYHA Class III HF and a prior HFH studied in the Treatment Group of the CHAMPION™ trial experienced a reduction in HF admissions. However, there is no guarantee that a similar benefit will occur in this slightly different population of NYHA Class II, III, or IV HF patients with a prior HFH and/or elevated NT-proBNP (or BNP). The information gathered will provide additional evidence regarding hemodynamic-guided HF management in at-risk NYHA Class II, III, or IV HF patients.

7.5 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. Treating with the knowledge of PA pressures may extend benefit to this at-risk population of HF patients with the goal of reducing decompensation events that result in HFHs or emergency department/hospital outpatient visits requiring intravenous diuretic therapy. The trial is designed to demonstrate this benefit to an expanded patient population.

7.6 History of Device Modifications or Recall

There have been no modifications or recall in relation to safety and clinical performance of the CardioMEMS™ HF System under investigation.

8 Requirements for Investigator Records and Reports

8.1 Deviations from CIP

A deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the CIP. The Investigator should make every effort not to deviate from the CIP, and all deviations must be reported.

If a subject is successfully implanted and/or randomized, but later found to not meet all inclusion/exclusion criteria, the subject will remain enrolled and a protocol deviation must be submitted.

Additionally, in the event that the IFU is not followed and an alternative implantation approach is pursued, the alternative implantation approach and associated justification must be reported as a protocol deviation. The Sponsor will review and track deviation frequency and trends. All effort should be made to avoid deviations, and repeat offense will result in Sponsor intervention (see section 11.3). Deviations are expected to be infrequent.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects; such non-compliance exposes subjects to unreasonable risks. Examples include failure to comply with prescribed clinical trial procedures with respect to: obtaining ICF properly, performing assessments within the applicable time period, following the CardioMEMS™ PA Sensor implantation procedure, following treatment guidelines (without documentation of the reason), following subject contact procedures (for the Randomized Arm), adhering to the inclusion/exclusion criteria, and reporting device-related AEs. Investigators should seek to minimize such risks by adhering to the CIP.

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

The PI is required to adhere to local regulatory requirements for reporting deviations to IRB/EC.

An Investigator shall notify the Sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred. Except in such an emergency, prior approval by the Sponsor is required for changes in or deviations from the CIP, and if these changes or deviations may affect the scientific soundness of the CIP or the rights, safety, or welfare of human subjects, FDA and IRB/EC is also required.

8.2 Safety Reporting

Safety surveillance and the safety reporting by the Investigator starts as soon as the subject is enrolled (all entry criteria are met, informed consent is provided, and implantation of the CardioMEMS™ PA Sensor is attempted) in either the Randomized Arm or the Single Arm.

Safety surveillance and safety reporting will continue until the last investigational visit has been performed, the subject is deceased, the subject's participation in the clinical trial is concluded by the Investigator, or the subject withdraws from the clinical trial.

All reportable (per section 8.2.1) AE data including deaths will be collected throughout the clinical trial and will be reported to the Sponsor on the applicable CRFs.

Reportable AEs will be monitored until they are adequately resolved or the subject has ended his/her participation in the trial, whichever comes first. The status of the subject's condition will be documented at each visit.

See *Appendix C* for event definitions regarding safety reporting.

SAE Reporting

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

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

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

8.2.1 Criteria and Guidelines for Reportable Events

For the purposes of this clinical trial, the following events will be reported to the Sponsor for the duration of the trial:

- All hospital admissions, including:
  - All SAEs occurring during a hospital admission outside of the original indication for admission (e.g. stroke, myocardial infarction, etc.)
- Emergency department/hospital outpatient observation visits that are cardiovascular in nature
- All deaths
- HFHs that occurred within 12 months prior to baseline
- SAEs, ADEs, SADEs, and UADEs

Of the reportable events, the following events will be adjudicated by an independent CEC:

- Events that could contribute to primary endpoints for either trial arm, to determine which events meet primary endpoint qualification, including:
  - All cardiovascular hospitalizations, cardiovascular emergency department visits, and cardiovascular hospital outpatient visits, all defined as a hospital visit with the primary cause being cardiovascular in nature, as reported by the Investigator
  - All deaths
  - Any other hospitalizations which, when reviewed by the Sponsor, could potentially meet endpoint qualification
- HFHs that occurred within 12 months prior to baseline
- All events that could contribute to the secondary safety endpoint for either trial arm including ADEs, SADEs, and UADEs

A list of anticipated AEs is included in sections 7.1.1 and 7.1.2. The Sponsor will ensure that all applicable events are reported to the relevant authorities as per regulations. The sites should notify the Sponsor of reportable AEs by creating and saving the applicable CRFs within the electronic data capture (EDC) system. The description of the AE, date of the AE, treatment and resolution of the AEs will be reported, as applicable, to the relevant authorities per regulations. Additional information may be requested, when

required, by the Sponsor in order to support the reporting or adjudication of AEs. The Investigator must notify the IRB/EC, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the Sponsor.

8.2.2 Criteria and Guidelines for Non-Reportable Events

The following events are **not reportable** to the Sponsor:

- Non-serious AEs unrelated to the investigational device/procedure, including those occurring during the course of a hospitalization that are not the primary reason for the hospitalization
- Non-cardiovascular or trauma events unrelated to HF, not resulting in a hospital admission
- Minor outpatient non-cardiovascular procedures, such as colonoscopy or cataract surgery

8.2.3 Subject Death

Subject deaths will be documented and reported to the Sponsor as soon as possible after the site becomes aware of the event via the applicable CRF. If a subject death is not reported within the required time, it will be considered a protocol deviation.

The CEC will review and classify all subject deaths. Notification of death must include a detailed statement of the pertinent event and be submitted on the applicable CRF. It is the Investigator's responsibility to notify the IRB/EC per the IRB/EC policy. Details of death and the following information, if available, should be provided to the Sponsor:

- Date of death
- Primary/organ cause of death
- Any circumstances surrounding the death
- Approximate time interval to death from the initiating event.
- Autopsy report (if performed)
- Whether it was trial device- and/or procedure-related

8.2.4 UADEs

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/EC per IRB/EC requirements. The same reporting requirement applies to the investigational sites located in Canada.

In the case of a UADE reported to the Sponsor, the Sponsor will take any steps necessary to investigate the event, and, as appropriate, will be responsible for notifying the FDA, Health Canada, and all participating IRBs/ECs and Investigators within 10 working days.

Should the Sponsor determine, either through physician reports or in-house testing, that a UADE presents an unreasonable risk to participating patients, Sponsor will suspend the clinical investigation and notify the FDA, Health Canada, and all participating IRBs/ECs and Investigators.

8.3 Source records

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

Relevant source documents for all reportable events which will be adjudicated by the CEC (see section 8.2.1) must be provided. Sites are responsible to acquire, de-identify and label records with subject ID and submit them to the Sponsor in a timely manner.

8.4 Records Retention

The Sponsor and the Principal Investigators will maintain the clinical trial documents as required. Measures will be taken to prevent accidental or premature destruction of these documents. The Principal Investigator or the Sponsor may transfer custody of records to another person/party and document the transfer at the investigational site or the Sponsor's facility, as appropriate.

These documents must be retained by the investigational site for a period of two years after the conclusion of the clinical trial and made available for monitoring or auditing by the Sponsor's representative or representatives of the applicable regulatory agencies.

All original source documents must be stored for the maximum time required by the regulations at the hospital, research institute, or practice in question. If original source documents can no longer be maintained at the site, the Investigator will notify the Sponsor.

9 Clinical Data Handling

The Sponsor will be responsible for the handling of clinical data generated in this trial, submitted by the site or obtained from Merlin.net™. 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 worldwide and/or any other worldwide regulatory authority in support of a market-approval application.

9.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical trial. 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 trial. All data will be secured against unauthorized access.

9.2 Data Management Plan (DMP)

A DMP will describe procedures used for data review, database creation and cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the clinical trial duration. All revisions will be tracked and document controlled.

Subject data will be captured in a validated EDC system hosted by the Sponsor and compliant with FDA regulations.

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

9.3 Document and Data Control

9.3.1 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.

9.3.2 Recording Data

The CRFs will be reviewed by the authorized site personnel. An appropriate comment will be provided to explain changes to data reported on the CRFs.

10 Monitoring

It is the responsibility of the Sponsor to ensure the clinical trial is conducted, recorded and reported according to the approved CIP, subsequent amendment(s), applicable regulations and guidance documents.

Monitoring will be conducted according to the Sponsor's Clinical Monitoring work instruction. Prior to beginning the clinical trial, the Sponsor will contact the Investigator or designee to discuss the clinical trial and data requirements. The Investigator shall make subject and clinical trial records available to the clinical monitor for monitoring. A designated monitor will periodically review the subject records and associated source documents.

11 Compliance Statement

11.1 Statement of Compliance

In addition to applicable regional or local laws and regulations, this clinical trial will be conducted in compliance with the most current version of the World Medical Association (WMA) Declaration of Helsinki and 21 CFR Parts 50, 54, 56 and 812. In the event of any conflicts, local laws and regulations will have precedence and in such cases, good faith efforts will be made to adhere to the intent of the other documents.

The Investigator will sign a Clinical Trial Agreement and agrees to be compliant with it. The Investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining IRB/EC approval and relevant Regulatory Authority approval, if applicable, and authorization from the Sponsor in writing for the clinical trial. If additional requirements are imposed by the IRB/EC or relevant Regulatory Authority, those requirements will be followed. If any action is taken by an IRB/EC or a relevant Regulatory Authority with respect to the clinical trial, that information will be forwarded to the Sponsor.

The Sponsor has taken up general liability insurance in accordance with the requirements of the applicable local laws. An appropriate Sponsor's country representative will be utilized to understand the requirements for the type of insurance that will be provided for subjects, and such information will be incorporated into the site informed consent process, as applicable. If required, additional subject coverage or a clinical trial specific insurance will be provided by the Sponsor.

11.2 Quality Assurance Audits and Regulatory Inspections

The Investigator and/or delegate should contact the Sponsor immediately upon notification of a regulatory authority inspection at the site. A monitor or designee will assist the Investigator and/or delegate in preparing for the audit. The Sponsor may perform quality assurance audits, as required.

The Principal Investigator or institution will provide direct access to source and CRF data during and after the clinical trial for monitoring, audits, IRB/EC review and regulatory authority 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 trial.

11.3 Repeated and Serious Non-Compliance

The Sponsor will review compliance with the CIP and trends and deviations on a regular basis. In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a monitor or designee will attempt to secure compliance by one or more of the following actions and will document all attempts or actions:

- Retrain applicable site research staff
- Create a compliance plan

- Visit the Investigator,
- Contact the Investigator by telephone,
- Contact the Investigator in writing,
- Retrain 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 trial, the Sponsor will either secure compliance or, at its sole discretion, terminate the Investigator's participation in the clinical trial. In case of termination, the Sponsor will inform the responsible regulatory authority, as required, and ensure that the IRB/EC is notified, either by the Principal Investigator or by the Sponsor.

12 Suspension or Premature Termination of the Clinical Trial

The Sponsor reserves the right to terminate the clinical trial at any stage, with appropriate written notice to the Investigators, IRB/ECs and relevant Regulatory authorities, if required.

A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in a clinical trial at the investigational sites for which they are responsible. The Investigators will follow the requirements specified in the Clinical Trial Agreement.

If suspicion of an unacceptable risk to subjects arises during the clinical trial or when so instructed by the IRB/EC or regulatory authority, the Sponsor may suspend the clinical trial while the risk is assessed. The Sponsor will terminate the clinical trial if an unacceptable risk is confirmed. If the Sponsor completes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the Sponsor will inform the Principal Investigators, IRB/EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision. Approval from the IRB/EC or regulatory authority, where appropriate, will be obtained before the clinical trial resumes. If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

If the Sponsor suspends or prematurely terminates the clinical trial at an individual investigational site in the interest of safety, the Sponsor will inform all other Principal Investigators.

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

13 Clinical Trial Conclusion

The clinical trial 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 trial closure.

14 Publication Policy

[redacted]

[redacted]

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

15 Reporting Results on ClincalTrials.gov Website

Upon receiving IDE approval from the FDA, this clinical trial will be registered on ClinicalTrials.gov. A full report of the pre-specified primary and secondary endpoint outcomes for both trial arms, regardless of the results, will be made public through the ClinicalTrials.gov website no later than 12 months after clinical trial completion, as required by section 801 of the FDA Amendments Act. If this clinical trial is terminated early for safety, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

[redacted]

Appendix A: CIP Revisions

[redacted]

Table A1: Revision History

Appendix B: Acronyms

6MHW	Six Minute Hall Walk
ACC	American College of Cardiology
ACE-I	Angiotensin Converting Enzyme-Inhibitor
ADE	Adverse Device Effect
ADHF	Acutely Decompensated Heart Failure
AE	Adverse Event
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
ARNi	Angiotensin-Neprilysin Inhibitor
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
CEC	Clinical Events Committee
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
CMS	Center for Medicare and Medicaid Services
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy – Defibrillator
CRT-P	Cardiac Resynchronization Therapy – Pacemaker
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
DSRC	Device/System Related Complication
EC	Ethics Committee
EDC	Electronic Data Capture
EF	Ejection Fraction
eGFR	Glomerular Filtration Rate
EQ-5D-5L	EuroQol 5-Dimension, 5-Level
FDA	Food and Drug Administration
GDMT	Guideline Directed Medical Therapy
GUIDE-HF	Hemodynamic-GUIDEd Management of Heart Failure
HF	Heart Failure
HFH	Heart Failure Hospitalization
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
KCCQ-12	Kansas City Cardiomyopathy Questionnaire

LSM	Least Squares Means
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
MAC	Medicare Administrative Contractor
MEMS	Micro-ElectroMechanical Systems
NT-proBNP	N-Terminal pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
PA	Pulmonary Artery
PAS	Post-Approval Study
PCWP	Pulmonary Catheter Wedge Pressure
PMA	Pre-Market Approval
RHC	Right Heart Catheterization
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TOST	Two, One-Sided Test
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analogue Scale
VRDC	Virtual Research Data Center
WMA	World Medical Association

Appendix C: 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.
- **HFH:** A hospitalization determined to be due to ADHF as the primary cause for the admission and requiring intravenous diuretics, as adjudicated by the CEC. [redacted]
- **Emergency department/hospital outpatient observation visits for intravenous diuretic therapy:** An unscheduled or unplanned admission to the emergency department (including freestanding or satellite emergency departments), hospital outpatient observation visit, or hospital inpatient visit (< 24 hours) determined to be due to ADHF at the primary cause for admission (as described in the HFH definition) and requiring intravenous diuretics, as adjudicated by the CEC. [redacted]
- **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

[redacted]

Note: A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered an SAE.

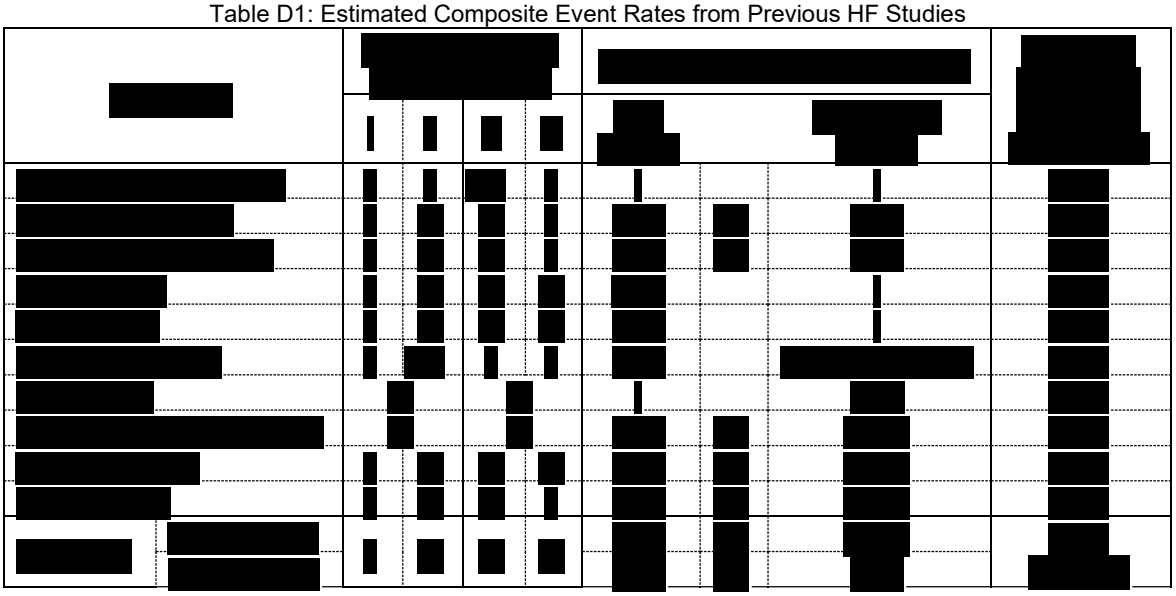
- **Adverse Device Effect (ADE)**: An AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. 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 possibly 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

Appendix D: Justification of NT-proBNP and BNP Thresholds

[redacted]

[redacted]

Table D1: Estimated Composite Event Rates from Previous HF Studies



Appendix E: Guidance for Management of Hemodynamic Parameters

Investigators are encouraged to follow the current GDMT with consideration of available PA pressure [redacted]

[redacted]

Appendix F: Measures to Ensure Enrollment into the Randomized Arm

[redacted]

Appendix G: NT-proBNP and BNP Thresholds According to BMI

Table G1: NT-proBNP and BNP Thresholds According to BMI

BMI (kg/m^2)	NT-proBNP Threshold (pg/mL)		BNP Threshold (pg/mL)	
	LVEF ≤ 40%	LVEF > 40%	LVEF ≤ 40%	LVEF > 40%
20	1000	700	250	175
21	1000	700	250	175
22	1000	700	250	175
23	1000	700	250	175
24	1000	700	250	175
25	1000	700	250	175
26	955	668	238	167
27	911	638	227	159
28	870	608	216	151
29	830	581	206	144
30	792	554	197	137
31	756	529	187	130
32	722	504	178	124
33	689	481	170	118
34	657	459	162	112
35	627	438	154	107
36	599	418	147	101
37	571	399	140	96
38	545	380	133	92
39	520	363	126	87
40	496	346	120	83
41	473	330	114	79
42	452	315	109	75
43	431	300	103	71
44	411	286	98	67
45	392	273	94	64
46	374	260	89	60
47	357	248	84	57
48	340	236	80	54
49	324	225	76	51
50	309	215	72	49

Thresholds for NT-proBNP and BNP (for both LVEF ≤ 40% and LVEF > 40%) were corrected for BMI using a 4% reduction per BMI unit over 25 kg/m^2 according to the Frankenstein equation (45).

Appendix H: Body Mass Index Calculator

[redacted]

Appendix I: Subject-Reported Outcome Measures

The Trial Coordinator or designee will administer subject-reported outcome questionnaires. It is important the subject understands the meaning of all words and instructions in the questionnaires. The subject should be instructed to ask any questions about the questionnaires if further explanation is needed. It is recommended that the subject-reported outcome measures are issued prior to all other procedures during each visit. Once the questionnaires are completed, the Trial Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

The following subject-reported outcome measures will be collected according to the trial requirements:

- EQ-5D-5L to be obtained at baseline, 6 months and 12 months
- KCCQ-12 to be obtained at baseline, 6 months and 12 months

EQ-5D-5L
The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. The questionnaire will take approximately two minutes to complete.

The EQ-5D-5L consists of two components – the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (VAS). For the descriptive system, five dimensions are measured (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has five levels: 1=none, 2=slight, 3=moderate, 4=severe, and 5=extreme. The respondent indicates his or her health state by ticking in the box against the most appropriate statement in each of the five dimensions. The VAS is scored from 0 (worst health) to 100 (best health).

KCCQ-12
The KCCQ-12 is a standardized, validated (53), and disease-specific health status measure for HF patients. It is a self-administered questionnaire that quantifies physical limitations, symptoms, self-efficacy, social interference and quality of life. It is shown to have high test-retest reliability and high responsiveness. It is prognostic of both clinical events and costs. The KCCQ-12 will be utilized as a performance measure of healthcare quality. It provides a reliable and effective tool to assess whether HF patients' conditions have changed over time. The questionnaire has twelve questions and takes approximately three minutes to complete.

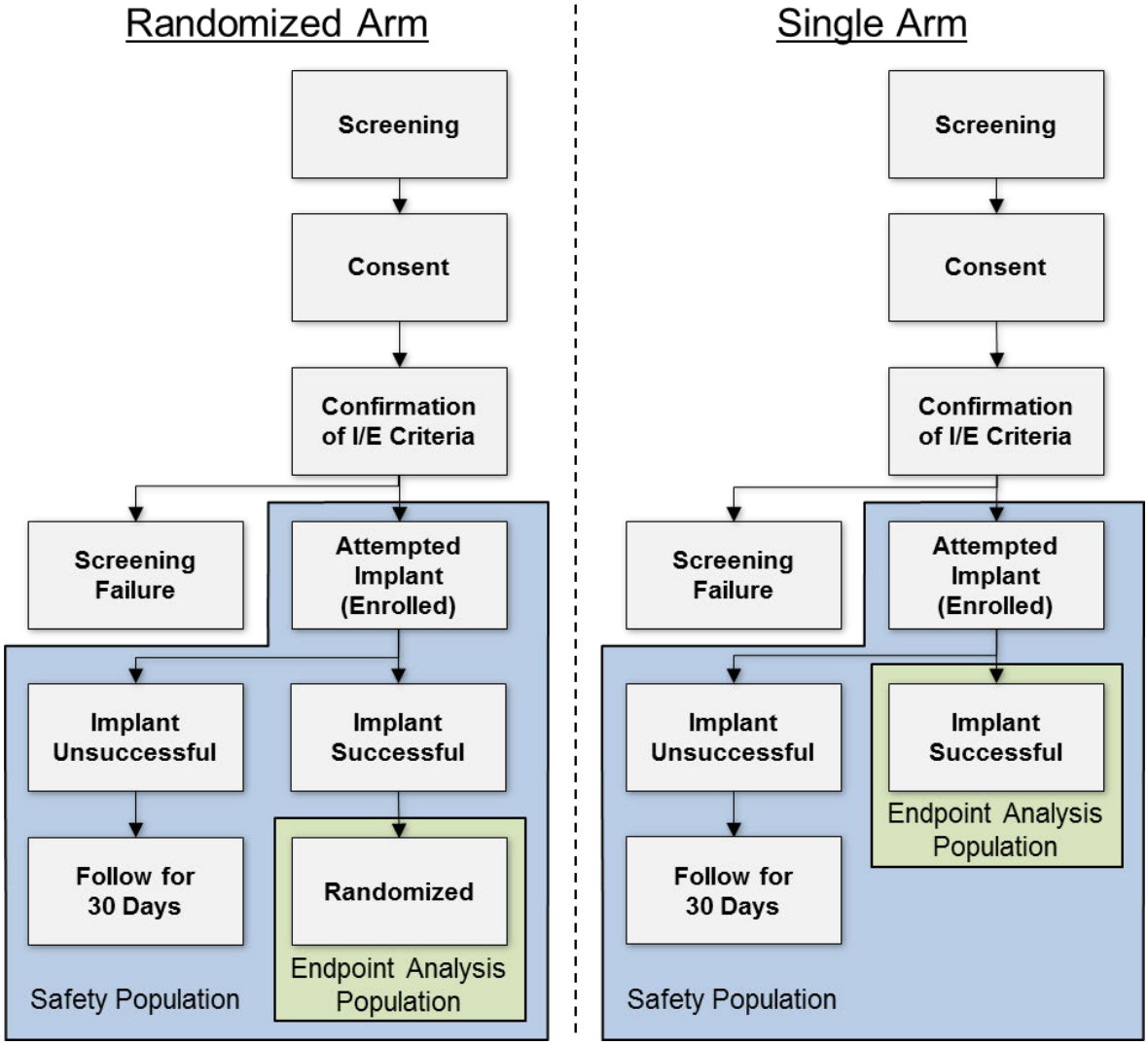
Appendix J: Calculation of Glomerular Filtration Rate

[redacted]

Appendix K: 6-Minute Hall Walk Test Instructions

[redacted]

Appendix L: Enrollment Flow Chart



Appendix M: Randomized Arm Subject Contact Worksheet

[redacted]

GUIDE-HF Randomized Arm Subject Contact Worksheet

[redacted]

Appendix N: Single Arm Echocardiogram and Quality-of-Life Sub-Study

[redacted]

Appendix O: CIP Summary

Clinical Investigation Name and Number	GUIDE-HF[redacted]
Title	Hemodynamic-**GUIDE**d Management of **H**eart **F**ailure (GUIDE-HF)
Objective(s)	The GUIDE-HF IDE trial consists of two arms: a Randomized Arm and a Single Arm. **GUIDE-HF Randomized Arm:** The objective of the GUIDE-HF Randomized Arm is to determine if PA pressure-guided HF management using CardioMEMS™ improves health outcomes in NYHA Class II, III, or IV HF patients with either elevated NT-proBNP (or BNP) and/or a prior HFH. **GUIDE-HF Single Arm:** The objective of the GUIDE-HF Single Arm is to demonstrate the equivalence of the effect of PA pressure-guided HF management on health outcomes between NYHA Class III HF patients with elevated NT-proBNP (or BNP) only and those with a prior HFH only.
Device Under Investigation	The following devices will be used in this clinical investigation:

Device name	Model/Type	Manufacturer	Region/ Country	Investigational or Market Released
CardioMEMS™ PA Sensor and Delivery Catheter	[redacted]	Abbott/SJM	United States	Market Released, but Investigational for this Indication
CardioMEMS™ Hospital Electronic Unit	[redacted]	Abbott/SJM	United States	Market Released, but Investigational for this Indication
CardioMEMS™ Patient Electronic Unit	[redacted]	Abbott/SJM	United States	Market Released, but Investigational for this Indication
Merlin.net™	[redacted]	Abbott/SJM	United States	Market Released

Number of Subjects Required for Inclusion in Clinical Investigation	**Overall sample size:** 3600 **Randomized Arm:** 1000 (successfully implanted and randomized) **Single Arm:** 2600 (successfully implanted)
Clinical Investigation Design	**GUIDE-HF Randomized Arm:** The GUIDE-HF Randomized Arm is a prospective, multi-center, randomized, controlled, single-blind clinical trial of the CardioMEMS™ HF System in NYHA Class II, III, or IV HF patients with either elevated NT-proBNP (or BNP) and/or a prior HFH. The GUIDE-HF Randomized Arm will include approximately

[redacted]

	1000 subjects (following successful implantation and randomization, 500 per group) at approximately 140 sites. [redacted] Each subject will be followed for 12 months, with follow-up visits at 6 and 12 months. Following successful implantation of the CardioMEMS™ HF System, subjects within the Randomized Arm will randomized in a 1:1 ratio into one of two groups: • **Treatment Group:** Management of subjects based on PA pressure information derived from the CardioMEMS™ HF System • **Control Group**: Management of subjects per standard of care (signs, symptoms, weight etc.) without knowledge of PA pressure information derived from the CardioMEMS™ HF System **GUIDE-HF Single Arm:** The GUIDE-HF Single Arm is a prospective, multi-center, single-arm clinical trial of the CardioMEMS™ HF System in North America in NYHA Class III HF patients, with either elevated NT-proBNP (or BNP) and/or a prior HFH. The GUIDE-HF Single Arm will include approximately 2600 subjects (following successful implantation) at approximately 140 sites. Each subject will be followed for 12 months, with follow-up visits at 6 and 12 months. [redacted]
Primary Endpoint(s)	**GUIDE-HF Randomized Arm:** The primary endpoint is a composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy or all-cause mortality at 12 months post-implantation (referred to as the Composite Endpoint), to be compared between the Treatment and Control Groups. The following events will be included in the composite: 1) hospitalization (≥ 24 hours) with the primary reason for admission being acute decompensated HF and intravenous administration of diuretic therapy; 2) an unscheduled or unplanned admission to the emergency department, hospital outpatient observation visit, or hospital inpatient visit and intravenous administration of diuretic therapy; 3) all-cause mortality. All events contributing to the primary endpoint will be adjudicated by an independent Clinical Events Committee (CEC). **GUIDE-HF Single Arm:** The primary endpoint is a composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy or all-cause mortality at 12 months post-implantation (same as for the Randomized Arm), to be compared between subjects with an elevated NT-proBNP (or BNP) only and subjects with a prior HFH only. Subjects who have both elevated NT-proBNP (or BNP) and a prior HFH will not be included in the analysis for the primary endpoint. All events contributing to the primary endpoint will be adjudicated by the CEC.

Secondary Endpoints	**GUIDE-HF Randomized Arm:** The secondary effectiveness endpoints, to be compared between the Treatment and Control Groups, are:
	• Composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy
	• Health status at baseline, 6, and 12 months post-implantation as assessed by the EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire
	• Health status at baseline, 6, and 12 months post-implantation as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ-12)
	• Six Minute Hall Walk (6MHW) test at baseline, 6, and 12 months post-implantation
	• In addition, the individual components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints:
	  ○ HFHs at 12 months post-implantation
	  ○ Emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation
	  ○ All-cause mortality at 12 months post-implantation
	The secondary safety endpoint is freedom from device/system related complications (DSRCs) at 12 months post-implantation. The secondary safety endpoint will be evaluated for all subjects enrolled in the Randomized Arm (i.e. with an attempted implant, whether successful or unsuccessful) and reported for the entire subject cohort and by subject group.
	
	GUIDE-HF Single Arm: The secondary effectiveness endpoints are:
	• Composite of recurrent HFHs or emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation
	• HFHs at 12 months post-implantation compared to HFHs in the 12 months prior to implantation. All subjects who receive a CardioMEMS™ PA Sensor implant will be included in the analysis of this endpoint.
	• In addition, the individual components of the primary endpoint will each be evaluated as descriptive secondary effectiveness endpoints:
	  ○ HFHs at 12 months post-implantation
	  ○ Emergency department/hospital outpatient observation visits for intravenous diuretic therapy at 12 months post-implantation
	  ○ All-cause mortality at 12 months post-implantation
	The secondary safety endpoint is freedom from DSRCs at 12 months post-implantation. The secondary safety endpoint will be evaluated for all subjects enrolled in the Single Arm (i.e. with an attempted implant, whether successful or unsuccessful) and reported for the entire subject cohort and by subject group.

Inclusion Criteria	1. Diagnosis and treatment for HF (regardless of LVEF) for > 90 days prior to the date of consent: a. Subjects should be on stable, optimally titrated medical therapy for at least 30 days, as recommended according to current AHA/American College of Cardiology (ACC) guidelines as standard-of-care for HF therapy in the United States, with any intolerance documented. 2. **GUIDE-HF Randomized Arm Only**: NYHA Class II, III or IV HF symptoms documented within 30 days prior to consent.

	3. **GUIDE-HF Single Arm Only**: NYHA Class III HF symptoms documented within 30 days prior to consent. 4. HFH within 12 months prior to consent and/or elevated NT-proBNP (or BNP) within 30 days prior to consent defined as: a. Subjects with LVEF ≤ 40%: NT-proBNP ≥ 1000 pg/mL (or BNP ≥ 250 pg/mL). b. Subjects with LVEF > 40%: NT-proBNP ≥ 700 pg/mL (or BNP ≥ 175 pg/mL). c. Thresholds for NT-proBNP and BNP (for both LVEF ≤ 40% and LVEF > 40%) will be corrected for BMI using a 4% reduction per BMI unit over 25 kg/m^2 5. ≥ 18 years of age 6. Chest circumference of < 65 inches, if BMI is > 35 kg/m^2 7. Written informed consent obtained from subject 8. Willing and able to upload PA pressure information and comply with the follow-up requirements
Exclusion Criteria	1. Intolerance to all neuro-hormonal antagonists (i.e., intolerance to angiotensin converting enzyme-inhibitors (ACE-I), angiotensin receptor blockers (ARB), angiotensin-neprilysin inhibitors (ARNi), hydralazine/isosorbide dinitrate, ***and*** beta-blockers) 2. ACC/AHA Stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes) 3. Received or are likely to receive an advanced therapy (e.g., mechanical circulatory support or cardiac transplant) in the next 12 months 4. NYHA Class IV HF patients with: a. Continuous or chronic use of scheduled intermittent inotropic therapy for HF and an INTERMACS level of ≤ 4, OR b. Persistence of fluid overload with maximum (or dose equivalent) diuretic intervention 5. Glomerular Filtration Rate (eGFR) < 25 mL/min/1.73m^2 and non-responsive to diuretic therapy, or receiving chronic dialysis 6. Inability to tolerate or receive dual antiplatelet therapy or anticoagulation therapy for one month post-implantation 7. Significant congenital heart disease that has not been repaired and would prevent implantation of the CardioMEMS™ PA Sensor 8. Implanted with mechanical right heart valve(s) 9. Unrepaired severe valvular disease 10. Pregnant or planning to become pregnant in the next 12 months 11. 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). 12. History of current or recurrent (≥ 2 episodes within 5 years prior to consent) pulmonary emboli and/or deep vein thromboses 13. Major cardiovascular event (e.g., unstable angina, myocardial infarction, percutaneous coronary intervention, open heart surgery, or stroke, etc.) within 90 days prior to consent 14. Implanted with Cardiac Resynchronization Therapy (CRT)-Pacemaker (CRT-P) or CRT-Defibrillator (CRT-D) for less than 90 days prior to consent 15. Enrollment into another trial with an active treatment arm 16. Anticipated life expectancy of < 12 months 17. 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 CardioMEMS™ PA Sensor implantation

Clinical Trial Procedures and Subject Follow-up

Visit Trial Activity	Baseline (up to -60 days)	Implant (time zero)	Prior to Discharge	Phone Contact[1] (Randomized Arm Only)	6 Months (+/-14 days)	12 Months (+/-30 days)
Informed Consent Process	X					
Assessment of Inclusion/Exclusion Criteria	X[2]					
Demographic Information	X					
Cardiovascular History	X					
BMI (and Chest Circumference if BMI > 35kg/m^2)	X					
Limited Echo for EF (if no EF documented)	(X)					
EQ-5D-5L and KCCQ-12 Administration[3]	X				X	X
Creatinine and Calculation of eGFR	X				X	X
NT-proBNP (or BNP)	X				X	X
Medication Review and Documentation	X		X		X	X
HF Exam (Including NYHA Assessment)	X				X	X
6MHW Test[3]	X				X	X
CardioMEMS™ HF System Information		X				
Catheterization Laboratory PA Pressure Measurements		X				
Randomization (Randomized Arm Only[4])			X			
Subject Teaching / Compliance Assessment			X	X	X	X
Subject Contact Worksheet				X		
Medication Update Documentation		(X)	(X)	(X)	(X)	(X)
Reportable AEs	(X)	(X)	(X)	(X)	(X)	(X)
Protocol Deviation	(X)	(X)	(X)	(X)	(X)	(X)
Non-AE Device Issues		(X)	(X)	(X)	(X)	(X)
Death	(X)	(X)	(X)	(X)	(X)	(X)

(X) If applicable/as it occurs

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[redacted]

Appendix P: Bibliography

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146-603.
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States. Circ Heart Fail. 2013;6(3):606-19.
3. Voigt J, Sasha John M, Taylor A, Krucoff M, Reynolds MR, Michael Gibson C. A reevaluation of the costs of heart failure and its implications for allocation of health resources in the United States. Clin Cardiol. 2014;37(5):312-21.
4. Bourge RC, Abraham WT, Adamson PB, Aaron MF, Aranda JM, Magalski A, et al. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure. J Am Coll Cardiol. 2008;51(11):1073-9.
5. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011;377(9766):658-66.
6. Adamson PB, Abraham WT, Aaron M, Aranda JM, Bourge RC, Smith A, et al. CHAMPION trial rationale and design: the long-term safety and clinical efficacy of a wireless pulmonary artery pressure monitoring system. J Card Fail. 2011;17(1):3-10.
7. Maurer MS, Adamson PB, Costanzo MR, Eigler N, Gilbert J, Gold MR, et al. Rationale and design of the left atrial pressure monitoring to optimize heart failure therapy study (LAPTOP-HF). J Card Fail. 2015;21(6):479-88.
8. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. Lancet. 2016;387(10017):453-61.
9. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail. 2014;7(6):935-44.
10. Givertz MM, Stevenson LW, Costanzo MR, Bourge RC, Bauman J, Ginn G, et al. Benefit of pulmonary artery pressure guided management combined with guideline-directed medical therapies in heart failure with reduced ejection fraction. J Am Coll Cardiol. 2017;In press.
11. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. J Am Coll Cardiol. 2017;70(6):776-803.
12. Desai AS, Bhimaraj A, Bharmi R, Jermyn R, Bhatt K, Shavelle D, et al. Ambulatory hemodynamic monitoring reduces heart failure hospitalizations in "real-world" clinical practice. J Am Coll Cardiol. 2017;69(19):2357-65.
13. Heywood JT, Jermyn R, Shavelle D, Abraham WT, Bhimaraj A, Bhatt K, et al. Impact of practice-based management of pulmonary artery pressures in 2000 patients implanted with the CardioMEMS sensor. Circulation. 2017;135(16):1509-17.

[redacted]

16. Chow SL, Maisel AS, Anand I, Bozkurt B, de Boer RA, Felker GM, et al. Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. Circulation. 2017;135(22):e1054-91.
17. Di Angelantonio E, Chowdhury R, Sarwar N, Ray KK, Gobin R, Saleheen D, et al. B-type natriuretic peptides and cardiovascular risk. Circulation. 2009;120(22):2177-87.
18. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med. 2002;347(3):161-7.

[redacted]

19. Olsson LG, Swedberg K, Cleland JGF, Spark PA, Komajda M, Metra M, et al. Prognostic importance of plasma NT-pro BNP in chronic heart failure in patients treated with a β-blocker: results from the Carvedilol or Metoprolol European trial (COMET) trial. Eur J Heart Fail. 2007;9(8):795-801.
20. Balion C, Santaguida PL, Hill S, Worster A, McQueen M, Oremus M, et al. Testing for BNP and NT-proBNP in the diagnosis and prognosis of heart failure. Evid Rep Technol Assess. 2006;142(1):1-147.
21. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure. Circulation. 2013;128(16):e240-327.
22. McMurray JJV, Packer M, Desai AS, Gong JJ, Lefkowitz MP, Rizkala AR, et al. Angiotensin-Neprilysin Inhibition versus Enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.
23. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin receptor neprilysin inhibition compared with Enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation. 2015;131(1):54-61.
24. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, et al. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF trial. JACC Heart Fail. 2017;5(7):471-82.
[redacted]
26. Cook DJ, Guyatt GH, Laupacis A, Sackett DL, Goldberg RJ. Clinical recommendations using levels of evidence for antithrombotic agents. Chest. 1995;108(4):227S-30S.
27. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg. 2011;128(1):305.
28. Zannad F, Garcia AA, Anker SD, Armstrong PW, Calvo G, Cleland JG, et al. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. Eur J Heart Fail. 2013;15(10):1082-94.
29. Dyer MT, Goldsmith KA, Sharples LS, Buxton MJ. A review of health utilities using the EQ-5D in studies of cardiovascular disease. Health Qual Life Outcomes. 2010;8:13.
30. Agborsangaya CB, Lahtinen M, Cooke T, Johnson JA. Comparing the EQ-5D 3L and 5L: measurement properties and association with chronic conditions and multimorbidity in the general population. Health Qual Life Outcomes. 2014;12:74.
31. Joseph SM, Novak E, Arnold SV, Jones PG, Khattak H, Platts AE, et al. Comparable performance of the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with preserved and reduced ejection fraction. Circ Heart Fail. 2013;6(6):1139-46.
32. Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. Br Med J (Clin Res Ed). 1986;292(6521):653-5.

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[redacted]

53. Spertus JA, Jones PG. Development and validation of a short version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qual Outcomes. 2015;8(5):469-76.

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