



# Hemodynamic-GUIDEd management of Heart Failure (GUIDE-HF)

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## Background

Hemodynamic-guided heart failure (HF) management using pulmonary artery (PA) pressures reduces HF hospitalizations (HFHs) in previously hospitalized HF patients with New York Heart Association (NYHA) class III symptoms. It remains uncertain whether this approach reduces not only HFHs but all-cause mortality and if benefits extend to patients with NYHA class II and IV HF or to those symptomatic patients with elevated natriuretic peptides without recent HFH.

## Methods

GUIDE-HF is a prospective trial with 2 arms enrolling patients with HF regardless of ejection fraction (EF). The randomized arm is a single-blind, randomized, controlled trial of PA pressure-guided therapy in NYHA class II-IV patients (n = 1,000) with either a previous HFH or

elevated natriuretic peptides (B-type natriuretic peptide/NT-pro-B-type natriuretic peptide). All consenting subjects will receive an implantable PA pressure sensor (CardioMEMS HF System) followed by randomization to either a treatment group, managed with provider remote access to the hemodynamic data, or a control group, managed without provider access to these data. Subjects in the control group will receive scheduled, scripted, sham contacts from the study team to maintain blinding as to their study group assignment. The primary study end point is the composite of cumulative HF events and all-cause mortality at 12 months. Secondary end points include quality-of-life and functional assessments. The single arm of the trial is an observational arm in which NYHA class III patients (n = 2,600) with either a previous HFH or elevated natriuretic peptides (but no recent HFH) will be implanted with a PA pressure sensor and observed for occurrence of the primary composite end point of cumulative HF events and mortality at 12 months. This arm will test the hypothesis that hemodynamic-guided care is similarly effective in HF patients enrolled on the basis of elevated natriuretic peptide levels but no recent HFH and those with a recent HFH.

## Conclusions

GUIDE-HF is the largest clinical trial of hemodynamic-guided HF management across a broad population of HF patients, with a study design and sample size adequate to examine survival, cumulative HF events, quality of life, and functional capacity.

Hemodynamic-guided heart failure (HF) management using remote, longitudinal assessment of pulmonary artery (PA) pressures recorded by a permanently implanted sensor is a novel means to maintain clinical stability in patients with symptomatic HF syndromes.<sup>1-6</sup> In several clinical trials using different implantable devices, changes in PA pressure have been shown to anticipate HF events. The degree of elevation in PA pressures is also directly related to the risk of HF events and mortality.<sup>7,8</sup> Targeted efforts to reduce PA pressures are associated with incrementally lower rates of

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hospitalizations for the management of worsening HF (HFHs) in the presence of guideline-directed medical therapy.<sup>4,7-9</sup> The degree of reduction in PA pressure is correlated with improved survival in patients with HF.<sup>9</sup> These data support the hypothesis that hemodynamic-guided HF management may improve survival compared to traditional methods of outpatient care.

The CardioMEMS HF System (Abbott, Atlanta, GA) consists of a wireless sensor implanted within the PA and powered by an external interrogation device to provide real-time transmission of PA pressure data from ambulatory patients outside the HF clinic to a secure Web site for provider review to guide decision making regarding HF management. On the basis of the CHAMPION Trial, which demonstrated that active HF management guided by remotely obtained PA pressures using the CardioMEMS HF System in patients with New York Heart Association (NYHA) class III HF symptoms and history of a HFH in the previous 12 months reduced subsequent occurrence of HFHs,<sup>1,2</sup> the Food and Drug Administration (FDA) approved use of the PA pressure sensor to guide HF management in May 2014. In that study, incremental reductions in the PA pressures in the monitored arm were associated with both reduction in the frequency of HFH and improvements in health-related quality of life among patients with both preserved (HFpEF) and reduced ejection fraction (HFrEF).<sup>3,4</sup> Additionally, hemodynamic-guided HF management in the subset of HFrEF patients treated with guideline-directed medical therapy (GDMT) was associated with a strong trend toward improved survival compared to traditional clinical management.<sup>4,7</sup> Consistent benefit is demonstrated in several retrospective studies from the CHAMPION Trial,<sup>10-13</sup> as well as extensive analysis of “real-world” experience,<sup>6,14</sup> and in Medicare claims data managed in a commercial setting.<sup>5,15</sup> Whether the benefits of PA pressure guided therapy can be extended to a broader pool of patients with milder (NYHA class II) or more severe (NYHA class IV) HF or to those without recent hospitalization for HF but with elevation in natriuretic peptide levels remains unclear. In addition, the potential favorable impact of PA sensor-guided HF management on mortality in patients with NYHA class II-IV HF remains to be definitively established.

The GUIDE-HF trial is designed to address these current knowledge gaps and test the hypothesis that medical intervention intended to lower PA pressures and maintain hemodynamic stability will improve mortality and HFH in patients with NYHA class II-IV symptoms at persistently high risk for poor outcome through a history of previous HFH or elevated natriuretic peptide. In this manuscript, we outline the rationale and design of the GUIDE-HF clinical trial program, which was recently approved as an investigational device exemption trial by the US FDA and the Centers for Medicare and Medicaid Services ([clinicaltrials.gov](http://clinicaltrials.gov), NCT03387813).

## Methods

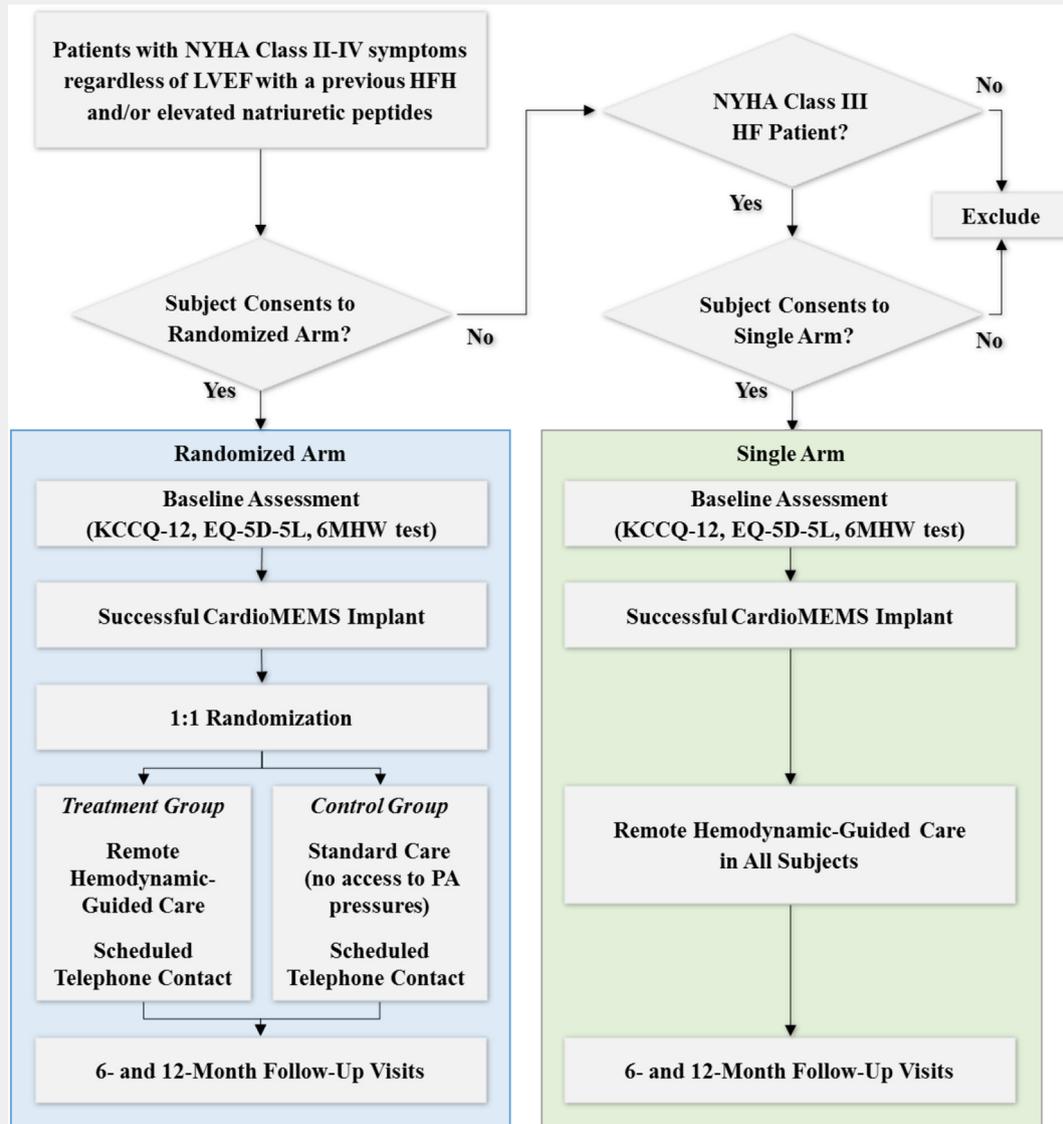
### Trial strategy

The GUIDE-HF Trial consists of 2 component arms (a single-blinded randomized arm and an observational single arm) intended to examine complementary hypotheses (Figure 1). It is funded by Abbott and will be conducted at 140 centers in North America, including the United States and Canada. This 2-arm design was driven by practical considerations related to differential commercial access to the PA pressure sensor by region in the period following FDA approval for use in 2014. Some geographic areas of the United States have received a positive coverage decision from the assigned Medicare Administrative Contractor for active HF management using the CardioMEMS HF System in patients with NYHA class III HF symptoms and history of a HFH in the previous 12 months, whereas others have not. Medicare patients meeting these criteria in Medicare Administrative Contractor coverage regions will be enrolled in the single arm unless the patient and physician chose the randomized arm of the trial. The single arm is designed to provide a pathway for inclusion of NYHA class III patients with a previous HFH meeting the currently labeled indication to determine if the benefits in these patients are matched by those NYHA class III patients who meet natriuretic peptide criteria for enrollment but have not had an HFH.

In the randomized arm, NYHA class II-IV HF patients (N = 1,000) with an HFH in the past 12 months or elevated natriuretic peptide levels in the previous 30 days, regardless of left ventricular EF, will be randomized in single-blind fashion to either treatment (remotely obtained hemodynamic information to guide management) or control group in 1:1 allocation. To mask patient study group assignment among those assigned to the control group, scripted sham calls will be made by the study team to balance the number of subject contacts between the treatment and control groups. The primary end point of the randomized arm is the composite of cumulative HF events and mortality at 12 months. As per the recent FDA guidance,<sup>16</sup> HF events are defined to include both urgent HF visits (including emergency department or hospital outpatient observation unit visits) requiring intravenous diuretic therapy and HFHs. Secondary end points will assess both quality of life (Kansas City Cardiomyopathy Questionnaire [KCCQ-12] and EuroQol 5-Dimension, 5-Level Questionnaire [EQ-5D-5L]) and functional status (6-minute hall walk [6MHW] test).

The observational single arm will include HF patients with NYHA class III symptoms who also have either a previous HFH within 12 months prior to enrollment or elevated natriuretic peptide levels without prior HFH in 12 months (same thresholds as the randomized arm) within 30 days prior to enrollment. The single arm will test the hypothesis that hemodynamic-guided care is similarly effective in HF patients enrolled based on elevated natriuretic peptide levels as in those with a

Figure 1



GUIDE-HF trial schematic.

prior HFH within 12 months. Secondary end points will include cumulative HF event rates in the 12 months postimplant compared to event rates in the 12 months prior to implant.

All subjects involved in the randomized arm or the single arm portion of this investigational device exemption trial who provide informed consent and volunteer for the study will be screened for eligibility. The study will be conducted in accordance with ICH standards on Good Clinical Practice, and the study protocol will be reviewed and approved at each participating site by the appropriate Institutional Review Board prior to enrollment of study patients. All events contributing to the primary end point for either study arm, as well as all

reportable adverse events, will be adjudicated by a Clinical Events Committee. The randomized arm will be monitored to ensure adequate enrollment of female subjects as well as enrollment according to NYHA class.

### Randomized arm

The randomized, control arm will be single-blind, as subjects will not be aware of their randomized group status. The trial will enroll 1,000 eligible subjects with NYHA class II-IV symptoms and a previous HFH in the prior 12 months or elevated circulating natriuretic peptide levels (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP], according to thresholds defined Table D) in the prior 30 days. All consenting

**Table I.** Inclusion and exclusion criteria

**Inclusion criteria**

Diagnosis and treatment for HF (regardless of LVEF) for >90 d prior to the date of consent, and on stable, optimally-titrated GDMT for at least 30 d  
Randomized arm only: NYHA class II, III, or IV HF symptoms documented within 30 d prior to consent.  
Single arm only: NYHA class III HF symptoms documented within 30 d prior to consent.  
HFH within 12 m prior to consent and/or elevated NT-proBNP (or BNP) within 30 d prior to consent defined as:

- Subjects with LVEF  $\leq 40\%$ : NT-proBNP  $\geq 1000$  pg/mL (or BNP  $\geq 250$  pg/mL)
- Subjects with LVEF  $> 40\%$ : NT-proBNP  $\geq 700$  pg/mL (or BNP  $\geq 175$  pg/mL)
- Thresholds for NT-proBNP/BNP corrected for BMI using a 4% reduction per BMI unit over 25 kg/m<sup>2</sup>

Subjects  $\geq 18$  y of age able and willing to provide informed consent

Chest circumference of  $< 65$  in if BMI is  $\geq 35$  kg/m<sup>2</sup>

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

**Exclusion criteria**

Intolerance to all neurohormonal antagonists (ie, intolerance to ACE-I, ARB, ARNi, hydralazine/isosorbide dinitrate, and  $\beta$ -blockers)

ACC/AHA stage D refractory HF (including having received or currently receiving pharmacologic circulatory support with inotropes)

Received or are likely to receive an advanced therapy (eg, mechanical circulatory support or cardiac transplant) in the next 12 m

NYHA class IV HF patients with: continuous or chronic use of scheduled intermittent inotropic therapy for HF and an INTERMACS level of  $\leq 4$ , or persistence of fluid overload with maximum (or dose equivalent) diuretic intervention

eGFR  $< 25$  mL/min/1.73 m<sup>2</sup> and nonresponsive to diuretic therapy, or receiving chronic dialysis

Inability to tolerate or receive dual antiplatelet therapy or anticoagulation therapy for 1 m postimplantation

Significant congenital heart disease that has not been repaired and would prevent implantation of the CardioMEMS PA Sensor

Implanted with mechanical right heart valve(s)

Unrepaired severe valvular disease

Pregnant or planning to become pregnant in the next 12 m

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).

History of current or recurrent ( $\geq 2$  episodes within 5 y prior to consent) pulmonary emboli and/or deep vein thromboses

Major cardiovascular event (eg, unstable angina, myocardial infarction, percutaneous coronary intervention, open heart surgery, or stroke) within 90 d prior to consent

Implanted with CRT-P or CRT-D for less than 90 d prior to consent

Enrollment into another trial with an active treatment arm

Anticipated life expectancy of  $< 12$  m

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 (eg, transpulmonary gradient  $> 15$ ) at implant RHC, a history of noncompliance, or any condition that would preclude CardioMEMS PA Sensor implantation

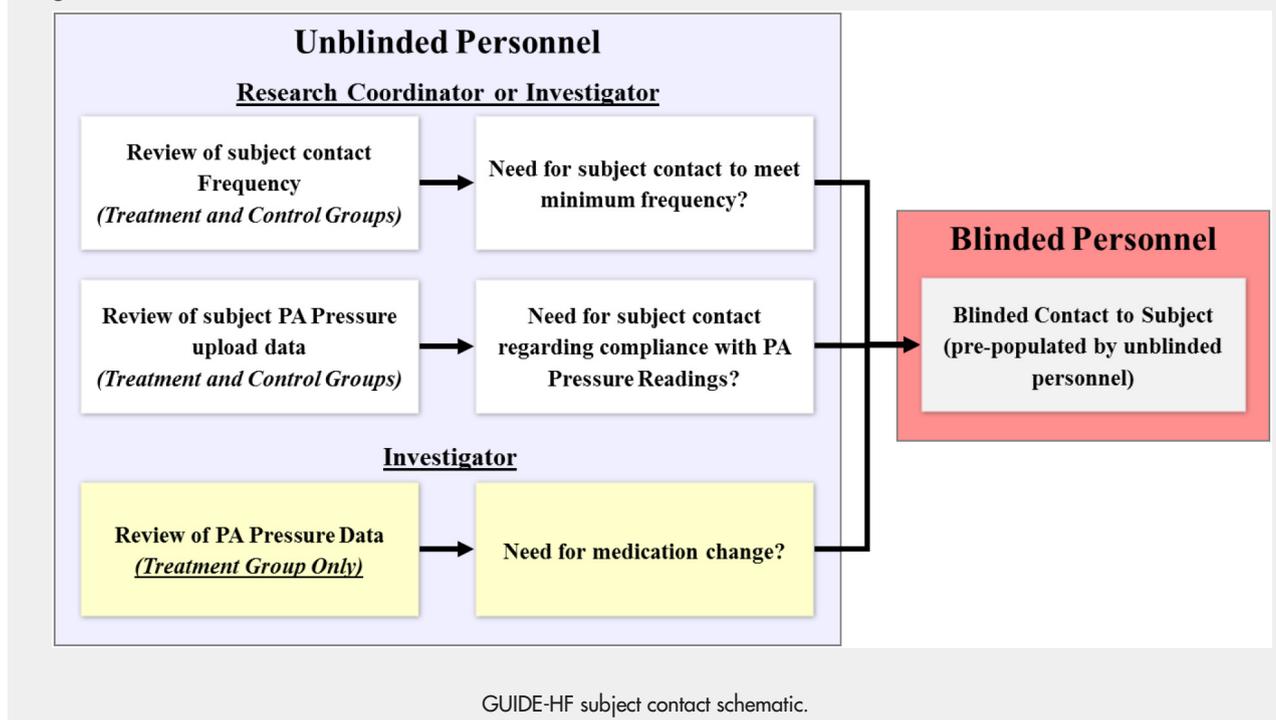
*BMI*, Body mass index; *ACE-I*, angiotensin converting enzyme-inhibitors; *ARB*, angiotensin receptor blockers; *ARNi*, angiotensin-neprilysin inhibitors; *ACC*, American College of Cardiology; *AHA*, American Heart Association; *eGFR*, estimated glomerular filtration rate; *CRT-P*, cardiac resynchronization therapy–pacemaker; *CRT-D*, cardiac resynchronization therapy–defibrillator.

subjects will have undergone implantation of PA pressure sensor. Subject education will be defined by the protocol for all subjects and caregivers, including how to use the system to upload PA pressures from home daily, basic troubleshooting tips, and what to expect with respect to participation in a randomized trial along with planned communications from the investigative site. Hemodynamic data from the implant right heart catheterization (RHC) will be used to develop an initial strategy for subsequent medication changes for all subjects enrolled. After successful implantation of the sensor, subjects will be randomly assigned 1:1 to either a treatment group, which will be managed based on investigator knowledge of daily uploaded PA pressures, or a control group, which will be managed with traditional standard-of-care clinical tools because investigators will not have access to uploaded PA pressures. All subjects will upload hemodynamic information daily from home but will not be made aware of their PA pressures or study group assignment.

For subjects within the treatment group, a regular review of hemodynamic information from the Web site will be completed by study personnel unblinded to the treatment group assignment for each subject, with input from study investigators. Study flow is outlined in Figure 2 for both the randomized and single arms. This review will evaluate whether PA pressure measurements are within the goal range for each subject and, if not, detailing the corresponding action (eg, medication change) to achieve hemodynamic goals. Decisions to change medication based on PA pressure information will be documented and recorded on the applicable case report form (CRF). If a subject's PA pressure measurements fall outside of the goal range and no action is planned, reasons for nonaction will be documented. Any non-PA pressure-based HF medication change for subjects in either randomized group will also be documented, along with the clinical motivation for the change.

Although investigative sites will only have access to PA pressure information for subjects within the treatment

Figure 2



group of the randomized Arm, compliance information reflecting the subject adherence to the daily upload process will be available for both control and treatment subjects. Failure to upload data will generate a contact from the investigative site to discover the reason and to encourage adherence in both groups. Subjects will have protocol mandated in-office clinical encounters at 6 and 12 months following randomization. The nature of all other clinical contacts relating to HF management will also be recorded, along with all medication changes. After the 12-month visit is completed, PA pressure readings for control group subjects will be available for clinical management through the [Merlin.net](http://Merlin.net) website (Abbott, Atlanta, GA).

To ensure ongoing protection of subject blinding with respect to treatment group assignment, several specific measures will be taken including scripted, blinded, and balanced interactions with subjects in both treatment groups; restricted clinician access to hemodynamic information and subject treatment group assignments; and limiting of postimplant hemodynamic information uploads to patient equipment without pressure values.

For balanced site and subject interaction and subject blinding between control and treatment groups, sites will be required to contact all subjects in both groups of the randomized arm at least once in a 2-week interval for the first 3 months and then monthly until study completion. Such site-initiated contacts with subjects will include discussion of any applicable medication changes, as well

as subject compliance with uploading hemodynamic information from home. Although PA pressure information will only be available to providers for treatment group subjects, subject compliance with uploading will be available for both treatment and control group subjects to allow for meaningful discussions regarding device use with the control group.

To further ensure that subjects remain unaware of their study group assignment, each site will designate blinded personnel responsible for any site-initiated subject communication related to HF management. These blinded personnel will not be aware of the subject group assignments and will follow a protocol-directed scripted contact worksheet to communicate any issues regarding upload compliance or changes in therapy without revealing the rationale behind such changes (eg, elevated PA pressures). Any symptoms reported voluntarily by the subject to blinded personnel will be documented, and a scripted response will be provided, if applicable. A separate, unblinded member of the study team will be assigned to remotely monitor hemodynamic information and compliance in collaboration with the investigator, complete the scripted contact worksheet designated for direct subject contact, and transfer to the responsible blinded individual. The subject contact worksheet will include time and date of contact and will be maintained in source documentation, along with the appropriate information documented by unblinded personnel.

**Table II.** Clinical considerations to direct hemodynamic-guided HF management

PA pressure goals		
PA diastolic: 8-20 mm Hg	PA mean: 10-25 mm Hg	PA systolic: 15-35 mm Hg
Optimization phase		
<ul style="list-style-type: none"> <li>• Uptitrate loop diuretic or add oral thiazide diuretic if hemodynamic evidence for excessive intravascular volume is present.</li> <li>• Uptitrate or add hydralazine-nitrates in African-American subjects if vascular resistance is elevated.</li> <li>• Consider hydralazine-nitrates in non-African-American subjects if vascular resistance is elevated.</li> <li>• Uptitrate or add ACE-I or ARB if systemic blood pressure is adequate.</li> <li>• Consider changing angiotensin intervention to ARB/ARNi.</li> <li>• Uptitrate or add <math>\beta</math>-blocker if pressures remain optimal over time.</li> <li>• Uptitrate or add spironolactone if tolerated by renal function and potassium.</li> <li>• Intensify or repeat HF education regarding diet, sodium restriction, etc.</li> <li>• Optimize CRT, if implanted.</li> <li>• Evaluate for sleep apnea or other secondary causes of pulmonary hypertension.</li> <li>• If in atrial fibrillation, maximize rate control or consider more aggressive attempts at normal sinus rhythm.</li> <li>• Consider exercise training or cardiac rehabilitation.</li> </ul>		
Maintenance phase		
<ul style="list-style-type: none"> <li>• Gently increase loop diuretic dosage or add oral thiazide diuretic for rises above baseline.</li> <li>• Consider changing angiotensin intervention to ARB/ARNi.</li> <li>• Uptitrate or add spironolactone if tolerated by renal function and potassium.</li> <li>• Decreasing diuretic intervention should be considered if pressures persistently decline over time and pass the lower-bound threshold set for the individual subject.</li> </ul>		

Additionally, access to PA pressure data and the Web site will be restricted to members of the study team. Similar to subjects, treating clinicians and other site personnel not participating in the trial will not have access to PA pressure readings or device-related information and will remain masked as to study group assignment for each subject. This restriction limits the potential of subject unblinding through personnel outside of the study team.

If a subject is admitted to the hospital, subjects will be encouraged to bring their home system (Patient Electronic Unit, Abbott, Atlanta, GA) with them and continue uploading PA pressure measurements while hospitalized. Outside of subject-uploaded pressure information, which providers on the study team may only access through a secured Web site without subject awareness, no other PA pressure measurements will be performed using hospital equipment to further protect the subject blinding.

### Single arm

The investigational single arm in GUIDE-HF is a prospective, unblinded arm enrolling 2,600 subjects with NYHA class III HF symptoms with either an HFH in the previous 12 months or elevated natriuretic peptides (BNP or NT-proBNP, according to thresholds defined in Table I) in the previous 30 days. The primary end point is a composite of cumulative HF events, as defined previously, and all-cause mortality at 12 months following PA pressure monitor implantation.

Subjects in the single arm will upload hemodynamic information daily and receive hemodynamic-guided HF management according to the protocol (see “Hemody-

namically-Guided Care Protocol” section below). These subjects will be contacted according to clinical need and in response to PA pressure trends, without a protocol-required frequency of phone contact. Subjects will have protocol-required clinical visits at 6 and 12 months following implant. Other clinical visits or contacts will be at the judgment of the investigator personnel. The reason for any HF medication change relating to HF will also be recorded on the CRF.

### Natriuretic peptide inclusion criteria

The natriuretic peptide thresholds for inclusion were chosen based on previous clinical trials with the intent to include patients with a significant event rate and were adjusted for both left ventricular EF (LVEF) and obesity (4% reduction for each BMI unit above 25 kg/m<sup>2</sup>). Although multiple factors can influence natriuretic peptide levels, the thresholds were adjusted only for factors that have been shown to affect natriuretic peptide levels without changing the overall risk of the patient population. Both increased LVEF and increased BMI have been shown to lower natriuretic peptide levels but without a reduction in overall risk for future events, therefore meriting threshold adjustment. Atrial fibrillation has been shown to increase natriuretic peptide levels but with the increased levels reflecting overall increased risk for subsequent events, therefore not meriting adjustment.

### Hemodynamic-guided care protocol

Prior to and following enrollment, investigators will be encouraged to follow current GDMT for all subjects

enrolled in GUIDE-HF particularly optimizing the choice of appropriate agents and ensuring appropriate target dosing according to American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines.

Investigators will be encouraged to carefully use RHC data obtained at the time of sensor implant procedure as well as PA pressure data from the sensor (for treatment group subjects) to develop a strategy for subsequent medication changes. Right atrial pressure, pulmonary capillary wedge pressure, and transpulmonary gradient measurements may help guide initial diuretic choices and use of vasodilator therapies. Medication changes and the associated rationale (eg, in response to PA pressure information or in response to signs and symptoms) will be documented in the CRF throughout the study for all subjects. Specific interventions will be at the discretion of the treating provider. Investigators will be asked to titrate medical therapies to achieve PA pressure goal ranges as in the CHAMPION trial—PA systolic: 15-35 mm Hg; PA mean: 10-25 mm Hg; PA diastolic: 8-20 mm Hg (Table II).

The PA pressure goals and medication interventions are applicable to both the treatment and control groups of the randomized arm, as well as the single arm. However, for subjects within the control group of the randomized arm, only PA pressure information from the initial RHC done at the time of the PA sensor implant or any additional medically necessary RHCs during the trial will be available to the investigators. Remotely uploaded PA pressure information from the control group will be blocked from investigator review. Therefore, other than medication changes resulting from information from RHC procedures, control group subjects will not have pressure-based medication changes over time and should be managed instead according to routine practice as informed by published clinical guidelines.

For treatment group subjects within the randomized arm and those in the single arm, PA pressures will be used by unblinded treating providers to adjust medications to first optimize PA pressures to the goal pressure range and then maintain their stability over time. The protocol suggested interventions to lower PA pressures to goal ranges early after implant are shown in Table II. Once pressures are optimized and stable, a new optimal pressure range for each subject may be established, and investigators are encouraged to enter the “maintenance phase” of hemodynamic-guided care. During this time, investigators are instructed to identify the new PA pressure goal and set ranges around the goal to define when investigators should be notified of a pressure excursion. Subjects whose pressures are out of the goal range will be placed on an automated “patient of interest” report through the Web-based information system to prioritize review of subjects in whom medication changes are likely needed. During the maintenance phase, investigators are encouraged to continue using

automated threshold notifications or reports automatically identifying subjects meriting review, due to pressures outside of thresholds or lack of compliance, to streamline pressure data review and make the workflow of reviewing larger numbers of patients more efficient.

During the maintenance phase of hemodynamic-guided care or if baseline pressures at implantation are within the protocol recommended target range, subacute deviations of pressures above or below the target baseline are usually a reflection of changes in intravascular volume. Typically, a 3- to 5-mm Hg persistent pressure change (increase or decrease) over 2-3 days or a 5-mm Hg change in a single day will be considered “actionable” trends leading to intervention.

## Statistical analysis plan

### Randomized arm

The analysis population of the GUIDE-HF randomized arm will include subjects enrolled, successfully implanted with a PA pressure sensor, and randomized. Primary and secondary end points will be evaluated and compared between groups following 12 months of randomized evaluation.

The primary end point of the randomized arm is a composite of cumulative HF events and all-cause mortality at 12 months postimplantation comparing the treatment versus control groups. All primary end point events will be accounted for using the Andersen-Gill model with robust sandwich estimate of variance to test the hypothesis. The model will contain a single covariate representing randomized group (treatment or control). Simulations for sample size were conducted under a joint-frailty model, with 1-sided hypothesis testing performed using an Andersen-Gill model with robust variance estimate. The sample size estimated to provide approximately 80% power at the 2.5% significance level with 20,000 simulations is 1,000 successfully implanted and randomized subjects (500 per treatment group).

Secondary effectiveness end points of the GUIDE-HF Randomized Arm include cumulative HF events at 12 months postimplantation. Health status, as assessed by the EQ-5D-5L and the KCCQ-12 questionnaires, along with functional status assessed by the 6MHW test will be evaluated at baseline and at 6 and 12 months postimplantation. In addition, the individual components of the primary end point will each be evaluated as descriptive secondary effectiveness end points.

### Single arm

The primary end point of the single arm study is a composite of cumulative HF events and all-cause mortality at 12 months postimplantation. Two subject groups will be compared: (a) subjects having elevated NT-proBNP (or BNP) but without having a HFH in the year prior, who would not have been eligible for enrollment in

CHAMPION, and (b) subjects having an HFH in the year prior but without elevated NT-proBNP (or BNP) who would have been eligible for enrollment in CHAMPION. The analysis population for the primary end point will include subjects enrolled into the single arm with successful sensor implantation and either elevated NT-proBNP (or BNP) only or a recent HFH only. Subjects with both elevated NT-proBNP (or BNP) and a recent HFH will not be included in the analysis for the primary end point. Hypotheses will be tested at the 5% significance level for the single arm primary end point at 12 months using a two, one-sided test (TOST) procedure. To determine equivalence of the 2 groups, the TOST procedure will be performed using a 2-sided 90% CI of the hazard ratio obtained from the Andersen-Gill model using robust sandwich variance estimates with a single covariate representing the 2 subject groups. Primary end point sensitivity analyses will be run with the following covariates in the Andersen-Gill model: subject group, propensity quintile and interaction between subject group, and propensity quintile to adjust for any possible imbalances in covariates. Simulations for sample size estimation were conducted under a joint-frailty model, with TOST hypothesis testing conducted using an Andersen-Gill model with robust variance estimate. The sample size estimated to provide approximately 90% power at the 5% significance level with 20,000 simulations is 2,600 successfully implanted subjects (approximately 780 [30%] with a recent HFH only, 780 [30%] with elevated NT-proBNP [or BNP] only, and 1,040 [40%] with both a recent HFH and elevated NT-proBNP [or BNP]).

The secondary effectiveness end points of the single arm study include cumulative HF events at 12 months postimplantation and the annualized rate of recurrent HFHs at 12 months post-implantation compared to the annualized rate of recurrent HFHs in the 12 months prior to implantation. In addition, the individual components of the primary end point at 12 months postimplantation will each be evaluated as descriptive secondary effectiveness end points: HFHs, urgent HF visits for intravenous diuretic therapy, and all-cause mortality. If the primary end point for the single arm is met, the secondary effectiveness end points will be evaluated hierarchically, with cumulative HF events tested first followed by HFH as 12 months post- versus preimplantation. The analysis population for the secondary effectiveness end points will include subjects enrolled into the single arm and successfully implanted, regardless of NT-proBNP (or BNP) and HFH history unless otherwise noted.

### Safety assessments

Both the randomized arm and single arm of the GUIDE-HF trial will assess device or system-related complication rates as secondary safety end points with comparison to previous trials using the CardioMEMS HF System.<sup>1,2</sup> All reportable adverse events (eg, Serious Adverse Events,

Adverse Device Effects, Serious Adverse Device Effects, Unanticipated Adverse Device Effects, and non-Adverse Event study device issues) identified during scheduled or unscheduled visits will be reported, documented, and adjudicated by the Clinical Events Committee. The analysis population for the secondary safety end point of both arms will include all subjects with an attempted implant (intent to treat) but will be analyzed separately for each arm.

## Discussion

The GUIDE-HF study program is designed to definitively assess the benefit of hemodynamic-guided HF management in ambulatory patients across a broad symptomatic range of symptom severity (NYHA class II-IV) and is powered to determine whether preventing clinical decompensation reduces cumulative HF events and overall mortality. A key secondary hypothesis is that hemodynamic monitoring will benefit the expanded population of NYHA II-IV HF patients without a recent HFH but with elevated natriuretic peptides equivalently to those with NYHA III symptoms and a recent HFH who are within the current FDA-labeled indication for implantable hemodynamic monitoring.

Implantable hemodynamic monitoring has emerged as an effective strategy for reducing HF events in patients with NYHA class III HF symptoms and a prior HFH within 12 months. Despite FDA approval, widespread adoption of this strategy has been limited by remaining gaps in knowledge resulting from the CHAMPION trial indication and design, as well as the lack of power in that study to examine clinical end points beyond HFHs, including cumulative HF events and mortality. Recent analysis has suggested that both PA pressures and relative change of PA pressures resulting from hemodynamic HF management are independent predictors of mortality in HF patients.<sup>4,8</sup> However, the association of PA pressures with mortality and potential to reduce mortality combined with HF events in the HF population has yet to be established in a clinical trial. It is also well known that recurrent HFHs impair quality of life, contribute to HF progression, and increase mortality risk.<sup>17</sup> However, recent data from the PARADIGM-HF trial have demonstrated that any event requiring rescue diuretic therapy, including both HFHs and urgent HF visits, is associated with approximately 5 times higher risk of death.<sup>18</sup> Lastly, substantial evidence suggests that natriuretic peptide levels in ambulatory patients may be a better way to evaluate the presence of persistent congestion compared to NYHA class or a previous hospitalization and may improve efforts to reduce ongoing and recurrent inpatient hospitalizations within health care.<sup>19</sup> The GUIDE-HF trial has several aims designed to address remaining questions about the value of hemodynamic monitoring in HF management. Key design features are

the inclusion of a broader pool of patients across a wide spectrum of HF symptom severity (NYHA class II-IV), the option to include patients without prior HFH but with elevated natriuretic peptide levels, and the analysis of composite HF events, not merely HFHs. The primary end point of cumulative HF events coupled with all-cause mortality will examine whether maintenance of hemodynamic stability fundamentally alters or reverses the underlying disease progression characteristic of either HFpEF or HFrEF. Furthermore, long-term patient-reported outcomes using the KCCQ-12 and EQ-5D-5L and functional status with the 6MHW test will examine patients' life experiences when HF is a component of their medical problem list and the associated impact of hemodynamic stability on quality of life.

## Summary

GUIDE-HF is designed specifically to definitively address the impact of hemodynamic-guided HF management within a broader HF patient population, particularly with respect to patient outcomes as assessed by cumulative HF events and all-cause mortality. Additionally, the GUIDE-HF trial will evaluate whether the effects of hemodynamic-guided on HF events are mirrored by changes in longer-term quality of life and functional capacity. The broad HF patient population, diversity of outcome measures, and significant sample size of the GUIDE-HF trial will uniquely enable the opportunity for exploration into the potential disease-altering effects of hemodynamic-guided HF management.

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