PREcision Event Monitoring of PatienTs with Heart Failure using HeartLogic™

PREEMPT-HF

C1926

CLINICAL INVESTIGATION PLAN

Sponsored By

Boston Scientific Corporation
4100 Hamline Avenue North
St. Paul, MN 55112

Contact Information

Role	Contact
Clinical Contacts	Stephen Ruble, PhD Clinical Fellow Boston Scientific, Inc. Rhythm Management 4100 Hamline Ave N. St. Paul, MN 55112, United States Phone +1 651.582.4397 e-mail: Stephen.Ruble@bsci.com Maria Paz López-Chicharro Alvarez Senior Clinical Trial Manager Guidant Europe, a Boston Scientific Company Rhythm Management Green Square, Lambroekstraat 5D 1831 Diegem, Belgium Phone Tel. +34 686076599 e-mail: Maria.Lopez-Chicharro@bsci.com Karen Reidt Senior Clinical Trial Manager Boston Scientific, Inc. Rhythm Management 4100 Hamline Ave N. St. Paul, MN 55112, United States Phone: +1.651.202.8033 e-mail: karen.reidt@bsci.com Guidant Europe NV Lambroekstraat 5D 1831 Diegem Belgium Boston Scientific Pty. Ltd. Level 5 247 Coward Street Mascot NSW Australia 2020

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Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
A	14-Mar-2018	92120219 AA	NA	Ver A	Ver A	NA
B	06-Apr-2018	92120219 AA	Synopsis; 1; 3.1; 4;. Figure 2; 4.2; Figure 3; 5.2; Figure 4; 6.4; 7.3; 8.2; 8.4; 9.5; 9.5.1; 9.6; 9.7; 9.8; 9.11; Table 9; 10.1.2; 10.1.3; 10.3; 10.5.1; 10.5.2; 10.7; 11.2; 14.6; 17.1; Table 17.2; 17.5; 17.7; 17.8; 18; 20.3; 21;	Ver A	Punctuation, grammatical and formatting corrections	NA
B	06-Apr-2018	92120219 AA	3.1	Removed: If feasible, the linked data set will be used to compare claims-based inpatient events with study collected hospitalizations, assess the accuracy of claims-based algorithms to identify	NA	Redudant information

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
				sensor detected events, and estimate the cost savings from avoidable hospitalizatio ns.		
B	06-Apr-2018	92120219 AA	5.2, 3.; 10.3	Removed: non-study	Replaced: third-party	Clarification
B	06-Apr-2018	92120219 AA	8.2	Removed: If the patient opts in for data linkage in the informed consent, then additional device data may be used for data linkage beyondthe point of withdrawal as specified in section 9.5	NA	Consistency with informed consent
B	06-Apr-2018	92120219 AA	9.5.1	Removed: investigate the feasibility of linking study data to non study data. Therefore the informed consent will contain a specific provision for patients to opt in for the use of their study for future research conducted by Boston Scientific	also link study data to third-party data sources	Consistency with informed consent

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
				related to data linkage.		
B	06-Apr-2018	92120219 AA	9.5.1	N/A	Added: Data linkage will focus on disease states and comorbidities common in device patients such as heart failure, hypertension, cardiac arrhythmias, acute coronary syndrome, heart valve disorders, respiratory disease, renal disease, gastrointestinal disease, sleep apnea, infectious disease etc.	Added additional detail regarding purpose of data linkage.
B	06-Apr-2018	92120219 AA	9.5.1	Removed: The non-study data	Replaced: The PREEMPT-HF study data	Clarification
B	06-Apr-2018	92120219 AA	9.5.1	N/A	Added: PREEMPT-HF study data will be used in combination with internal BSC databases (e.g., device tracking database) to obtain, use and disclose certain protected health information to third parties. This may include device serial and model	Clarification regarding data linkage

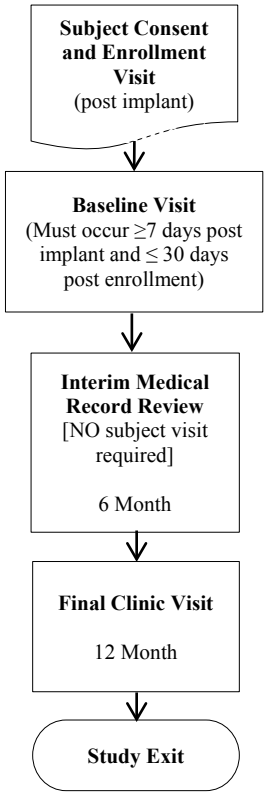
Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
					number, last name, date of birth, address, zip code, the last four digits of the subject's social security number, implant date, and the hospital where the implant procedure was performed.	
B	06-Apr-2018	92120219 AA	9.5.1	N/A	Added: (wording in red): The third-party data sources include but are not limited to payer administrative claims and health analytics (e.g., Medicare, Medicaid. Truven, Optum)	Clarification
B	06-Apr-2018	92120219 AA	9.5.1	Removed: In patients who opt in, study data (such as device and lead serial and model number) will be used with internal BSC databases (e.g., device tracking database) to obtain, use and disclose certain protected health information to third parties to enable database	Added: The subject may withdraw permission for the use and sharing of personal health information at any time if provided in writing to the study doctor. Please notify Boston Scientific of any subjects that submit in writing their request to withdraw their permission for the use of personal health	Added details regarding personal health information; added details on how a patient can withdraw consent for the use of personal information.

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
				linkage. Device sensor data available through LATITUDE and the information from the aforementioned data sources may be linked for up to seven (7) ears after study completion.	information.	
B	06-Apr-2018	92120219 AA	9.8		If this review coincides with an in-clinic visit, the subject must be asked whether he or she had any reviewable clinical events (RCEs) since the baseline visit. As defined in section 5.1, an RCE is defined as either an all-cause hospitalization, or HF outpatient visit. If the subject reports having an RCE at a center not participating in the study, every effort should be made to obtain medical records from the center.	Clarification

1 Protocol Synopsis

PREcision Event Monitoring of PatienTs with Heart Failure using HeartLogic™ (PREEMPT-HF)	
Study Objective(s)	The goal of the PREEMPT-HF study is to collect device and clinical event data to evaluate extended applications of the HeartLogic™ Heart Failure Diagnostic (HeartLogic) in a broad spectrum of heart failure (HF) patients with an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D). There are no primary safety and/or efficacy endpoints for this study. Subjects will be followed for approximately 12 months after the baseline visit to collect the required number of clinical events to support the study objectives. These events are called Reviewable Clinical Events (RCEs), and include all-cause hospitalizations and HF outpatient visits. Clinical event definitions are as follows: • **Hospitalization (all-cause)**: the subject is admitted to inpatient hospital care and discharged on a different calendar date. • **HF Hospitalization**: the subject is admitted with signs/symptoms of congestive heart failure (CHF) and receives unscheduled augmented HF therapy with oral or intravenous medications, ultrafiltration therapy or other parenteral therapy. • **HF Readmission (30-day)**: the subject is admitted for an unplanned hospitalization for any cause within 30 days post discharge from a HF hospitalization. • **HF Outpatient Visit**: the subject has signs/symptoms of CHF, and receives unscheduled intravenous decongestive therapy (e.g., IV diuretics, IV inotropes, IV vasoactive drugs, ultrafiltration) in a setting that does not involve a hospitalization (e.g., emergency room, HF clinic, primary care clinic, etc.). **Primary Objective** The primary objective of the PREEMPT-HF study is to investigate the association between HF sensor data and 30-day HF readmissions. **Additional Objectives** 1. Characterize HF sensor data for: o Association with risk for device VT/VF therapy o Phenomapping of HF events o Association with non-HF hospitalizations including

<table>
<tr><th colspan="2">PREcision Event Monitoring of PatienTs with Heart Failure using HeartLogic™ (PREEMPT-HF)</th></tr>
<tr><td></td><td>cardiac non-HF events and non-cardiac events
2. Collect subject Sleep Incline Sensor data prior to and following reviewable clinical events
3. Link study data to third-party data, such as Center for Medicare and Medicaid Services (CMS) administrative claims (US only). Association of clinical study events and sensor data with other data sources will be investigated. Any study data linkage will abide by all applicable laws, regulations, and data use agreements, and patients will be consented accordingly.</td></tr>
<tr><td>Indication(s) for Use</td><td>The study will use commercially approved Boston Scientific CRT-D and ICD devices that contain the HeartLogic feature. Only subjects that meet the eligibility criteria will be enrolled in the study.</td></tr>
<tr><td>Commercial Device/System</td><td>The LATITUDE™ system, ICD and CRT-D devices with the HeartLogic feature, and programmed as follows:
<table>
<tr><th>Feature/Sensor</th><th>Programmed</th></tr>
<tr><td>Heart Failure Sensors</td><td>ON</td></tr>
<tr><td>Respiratory Sensor</td><td>ON</td></tr>
<tr><td>Sleep Incline Sensor</td><td>ON</td></tr>
<tr><td>HeartLogic</td><td>Disabled on LATITUDE</td></tr>
</table></td></tr>
</table>

Study Design	The PREEMPT-HF study is a global, multi-center, post-market prospective, non-randomized study. 
Planned Number of Subjects	Up to 3750 subjects will be enrolled. An interim analysis is planned to determine final sample size.
Planned Number of Sites / Countries	Up to 200 sites in the United States, Canada, Europe and Asia Pacific.
Primary Safety Endpoint	This is a post-market study with no primary safety endpoint.
Primary Effectiveness Endpoint	This is a post-market study with no primary effectiveness endpoints.
Additional Endpoints	This is a post-market study with no secondary endpoints.

Method of Assigning Patients to Treatment	There is no randomization as all subjects are assigned to a single group and are followed with HeartLogic disabled. The investigator will have access to an electronic database which will be used to generate the patient ID and all eCRFs for subjects enrolled in the clinical study.
Follow-up Schedule	The required protocol study visits and medical record reviews are as follows: • Enrollment visit • Baseline visit • Interim medical record review (6 month, does not require a clinic visit) • Final clinic visit (12 month, or at the point of withdrawal) Subjects will exit the study following their final clinic visit.
Study Duration	The study duration is estimated to be 6 years from first patient enrollment to study closure.
Participant Duration	The study duration for each subject is expected to be approximately 12 months from enrollment to the final clinic visit. A patient can be in the study for up to 460 days (15 months) if the maximum visit windows are taken in to account.
Inclusion Criteria	• Subject is age 18 or above, or of legal age to give informed consent specific to each country and national laws. • Subject has a documented diagnosis of heart failure. • Subject has a Boston Scientific CRT-D or ICD device implant that has HeartLogic, with Heart Failure Sensors turned ON, Respiratory Sensor turned ON, and Sleep Incline Sensor turned ON. • Subject has an active bipolar RV lead implant. • Subject is enrolled in LATITUDE (NXT 5.0 or future version), and is willing to be remotely monitored from the baseline visit for approximately 12 months with HeartLogic disabled.
Exclusion Criteria	• Subject has received or is scheduled to receive a heart transplant or ventricular assist device (VAD). • Subject is enrolled in any concurrent clinical study without prior Boston Scientific written approval (excluding registries). • Subject has a life expectancy of less than 12 months. • Subject has a history of non-compliance to medical care or known inability to comply with requirements of the clinical study protocol.

Statistical Methods	
Primary Statistical Hypothesis	There is no statistical hypothesis. The primary objective of the PREEMPT-HF study is to investigate association between HF sensor data and 30-day HF readmissions.
Statistical Test Method	The following statistical analyses will be used to evaluate the objectives of the study: Primary Objective The difference in sensor trends pre-admission and post-discharge will be compared between subjects with and without a 30-day HF readmission. The comparison will be evaluated using a two-sample t-test for each HF sensor measurement. Additional Objectives 1. Association with risk for device VT/VF: will be evaluated using an odds ratio. 2. Phenomapping of HF events: will be evaluated using cluster analysis. 3. Association with non-HF hospitalizations including cardiac non-HF events and non-cardiac events: will be evaluated using a paired t-test for each HF Sensor.
Sample Size Parameters	Up to 3750 enrolled subjects are necessary to evaluate the primary objective. An index HF hospitalization refers to the first HF hospitalization during the study follow-up period. A HF hospitalization is deemed usable if sensor data is available during the event and sufficient follow up time is recorded to determine if a readmission occurs. A total of 215 usable index HF hospitalizations are required to have at least 80% power to detect a standardized difference of 0.5 in the mean sensor change (admission – discharge) between the groups with and without a 30-day HF readmission. It is expected that of the 215-usable index (first during the study) HF hospitalizations, 43 will be followed by a 30-day readmission (20%). Based on the following assumptions, a total of 215 usable index HF hospitalizations are required: • 80% Power to detect a standardized mean difference of 0.5 between groups • Two-sided Type I error (alpha) of 0.05 • 3:1 ratio of group sizes (no-readmission:30-day HF readmission), where the no-readmission group will exclude index HF

	hospitalizations with 31 to 60-day readmissions Assuming a 20% loss of usable HF events due to proximity to study start and exit (completion or withdrawal), a total of 270 index HF hospitalizations are required to obtain 215 usable HF hospitalizations. Based on the following assumptions, up to 3750 subject enrollments are required to obtain the 270 required HF hospitalizations: • 9 % index HF hospitalization rate • 20% death/withdrawal over entire length of the study • Average of 12 months of sensor data per patient

2 Table of Contents

2.1 Table of Figures

2.2 Table of Tables

3 Introduction

3.1 Study Rationale and Background

Heart failure (HF) is a complex clinical syndrome with high morbidity, mortality, and economic burden[1, 2]. Chronic HF is persistent, gradually progressive, and punctuated by episodes of acute worsening leading to hospitalizations[3]. Therefore, there remains an unmet clinical need to slow the progression of HF and prevent hospitalizations. HeartLogic™, available in Boston Scientific cardiac resynchronization therapy devices and defibrillators (CRT-Ds and ICDs), combines novel sensor parameters such as heart sounds and respiration with other measurements like thoracic impedance, heart rate, and activity into a HeartLogic Index for the early detection of worsening HF[4, 5]. However, there is limited data on the association of HeartLogic with the risk of HF readmissions and tachyarrhythmias, or for phenotyping the broad spectrum of HF patients.

Thus, the goal of the PREEMPT-HF study is to collect data aimed at extending HeartLogic applications. Specific study objectives are listed below.

(1) *Associate HF sensor data with HF 30-day readmission*: Hospitalizations due to worsening HF are associated with high post-acute re-hospitalization and mortality, which in turn has led payers to impose financial penalties targeted at reducing readmissions while improving care quality[6]. Recent data from fee-for-service Medicare beneficiaries indicate that these incentives have reduced readmission rate; but, the magnitude of readmission reduction has been modest (from 23.5% in 2008 to 21.4% in 2014), the rate of decline has slowed, and the mortality has not improved[7]. Readmission risk stratification algorithms developed to date have utilized clinical and patient data[8, 9]. The ability to further reduce readmissions will require new approaches. For example, implantable device diagnostics have been used to risk stratify HF patients for readmissions[10], and pulmonary artery pressure guided HF management has been associated with a 59% reduction in 30-day HF readmissions[11]. The PREEMPT-HF study will evaluate the novel HF sensor parameters for readmission detection and patient risk stratification. In order to evaluate the incremental benefit of sensor data for readmissions, only patients with HeartLogic disabled will be included in the study.

(2) *Characterize HF sensor data for association with risk of tachyarrhythmias and device therapy*: Acute HF exacerbations are presumed to trigger atrial and ventricular tachyarrhythmias through a number of mechanisms including increased cardiac filling pressure and neurohormonal activation[12-15]; however patient risk assessment for malignant arrhythmias is subjective and device sensor based algorithms for risk stratification using traditional device sensors have had only modest accuracy[16-19]. Similarly, a new onset or worsening of atrial or ventricular tachyarrhythmia may itself be a trigger for worsening of HF. The PREEMPT-HF study will investigate the association between the HeartLogic Index and patient risk for device ventricular tachycardia/fibrillation (VT/VF) therapy.

(3) *Characterize HF sensor data for phenomapping of HF events*: Clinical practitioners have recognized that HF is comprised of multiple heterogeneous entities including HF with reduced, preserved, and mid-range ejection fraction (HFrEF, HFpEF, and HFmEF)[20]. Similarly, acute worsening HF has been classified by hemodynamic profiles incorporating congestion (wet/dry) and perfusion (warm/cold). However, physiological measurements underlying clinical classifications exhibit significant variation. For example, even though the majority (>80%) of patients admitted for worsening HF show clinical signs or symptoms of volume overload, there is a wide distribution of body fluid and its composition[21]. Data driven approaches such as cluster analysis has been applied to phenotype HFrEF[22] and HFpEF[23], but continuous data collected by implanted devices have not been utilized. The PREEMPT-HF study will collect data to investigate machine learning and clustering approaches for event classification using HF sensor data and baseline clinical variables. This type of unbiased dense phenotype mapping is known as phenomapping.

(4) *Characterize association of HF sensor data with non-HF hospitalizations*: Due to aging and the convergence of cardiac disease and other comorbid conditions, approximately 3 out of 4 hospitalizations in HF patients are classified as unrelated to HF by event adjudication committees[24, 25]. Therefore, strategies to reduce hospitalizations should consider both cardiac and non-cardiac conditions. Preliminary data from the MultiSENSE showed that non-cardiac hospitalizations were associated with sensor changes including impedance, heart rate, heart rate variability and the first heart sound; however additional data are needed in more specific event subgroups[26]. The interrelationship of HF with other disease states is underscored by the observation that pulmonary artery pressure driven HF management is associated with a reduction in hospitalizations related to respiratory disease[27]. Data from the PREEMPT-HF study will be used to further investigate the relation between diverse HF Sensor measurements and non-HF related events.

(5) *Collect data on patient sleep incline leading up to and following clinical events*: Because orthopnea and paroxysmal nocturnal dyspnea are hallmarks of worsening HF, devices with HeartLogic are equipped with a Sleep Incline Sensor to measure the subject's night-time elevation angle. A cross-sectional analysis of data from the MultiSENSE study (N=46 patients in 65 visits) showed that orthopnea symptoms were associated with increased sleep incline angle (mean±SEM of 23.2±2.8 degrees vs. 10.7±1.7 degrees)[28]. The PREEMPT-HF study will extend this analysis to a longitudinal assessment of sensor measurements in the vicinity of hospitalization events.

(6) *Investigate feasibility of linking study data to administrative claims*: The capability to cost-effectively develop and test future device diagnostics may be dependent on the ability to link broad data sets, and validate knowledge obtained from multiple sources using data driven approaches, while ensuring the protection of patient privacy and data confidentiality[29, 30]. The utilization of claims data linked to remote monitoring

data offer a glimpse into how device features can be evaluated without expensive clinical trials[31-33]. The PREEMPT-HF study aims to assess the feasibility of linking claims data with comprehensive device and other study data in applicable geographies. For example, in the United States the Centers for Medicare and Medicaid Services (CMS) has instituted an Innovator Research Program to allow access to claims data for research[34].

4 Commercial Device Description

4.1 Device Description

The PREEMPT-HF study will use Implanted Cardioverter Defibrillator (ICD) or Cardiac Resynchronization Therapy Defibrillator (CRT-D) device models that are commercially approved and contain the HeartLogic HF diagnostic feature (Figure 1). For a full description of the HeartLogic feature, please refer to the labeling.

The implanted portion of the study system includes the CRT-D or ICD pulse generator (PG), along with its associated commercially available leads. For the PREEMPT-HF study, BSC CRT-D and ICDs can be associated with leads from any manufacturer. The models being used are shown in Table 4-1, but future device models with the HeartLogic feature may also be included as they become commercially available. In addition, a Programmer Recorder Monitor (PRM) with appropriate software must be used to interrogate the device (Model 2868 Application Software, v4.04 or other compatible version).

Figure 1: Example of Implantable Devices Used in PREEMPT-HF Study

Table 4-1 Device Models

Device Trade Names*	RESONATE™ X4 CRT-D Models – G447 RESONATE™ EL ICD Models – D432, D433 MOMENTUM™ CRT-D Models – G124, G125, G126 MOMENTUM™ X4 CRT-D Models – G138 MOMENTUM™ EL ICD Models – D120, D121 VIGILIANT™ X4 CRT-D Models – G247 VIGILIANT™ EL ICD Models – D232, D233 PERCIVA™ ICD Models – D400, D401, D412, D413 Model 2868 Application Software, v4.04 (or future equivalents)

**Future models that are compatible with the study may also be used.*

4.2 Medical Equipment Description

The external portion of the system includes the commercially available LATITUDE NXT 5.0 patient management system (or future versions) and the PRM. LATITUDE is a remote monitoring system (Figure 2) that gathers data from the PG and external sensors (blood pressure monitor and weight scale) and transmits it to a web server. LATITUDE enables physicians to remotely monitor both device and patient status. The LATITUDE communicator uses wireless telemetry to transfer data from the implanted device and external sensors to the web server, which can be accessed by the study doctor and Boston Scientific.

Figure 2: LATITUDE NXT 5.0 System

The primary means of device data collection for the PREEMPT-HF study is through the LATITUDE patient management system. Therefore, LATITUDE enrollment is required for subject participation in the study, and data transmission via LATITUDE (i.e., referred to as "monitored on LATITUDE") must be confirmed at the baseline visit. During the course of the study if the subject is away from the communicator, sensor data storage to PG memory will continue; however, the next data upload will not occur until the subject is within range of the communicator. To ensure timely data transmission, LATITUDE must be programmed for scheduled follow-ups to occur every 3 months or sooner. At the final study visit, the investigational site must interrogate the subject's device using the PRM. This will trigger a remote data upload to LATITUDE when the subject returns within range of the communicator.

For the PREEMPT-HF study, Heart Failure Sensors must be turned ON. This must be done via the PRM. The Heart Failure Sensors consists of heart sounds (S3 and S3/S1), respiration (respiratory rate and rapid shallow breathing index), impedance, heart rate and activity.

Only subjects with Heart Failure Sensors turned On, Respiratory Sensor turned ON, and HeartLogic disabled are eligible to participate in the study. The state where HeartLogic is **not** enabled on LATITUDE is referred to as HeartLogic disabled. In this state, the device will continue to collect sensor data, but the HeartLogic Index and Heart Sounds sensor trends will not be displayed on the LATITUDE system, and clinicians will not receive HeartLogic alerts. Sensor data will be stored in the PG for 365 days after which the earliest data are overwritten. The subject must be withdrawn from the study if Heart Failure Sensors will be turned OFF, or if HeartLogic will be enabled. Subjects may remain in the study if the Respiratory Sensor or Sleep Incline Sensor are turned OFF; however, this will be considered as a protocol deviation. The Sleep Incline Sensor measures the subject's average elevation angle over the programmed sleep schedule. Sleep schedule can be programmed using the PRM.

Following device implant, the Sleep Incline Sensor requires a minimum of seven (7) days for initialization, after which sensor calibration must be performed. Initialization may take longer if subject lacks diversity in his/her body orientations during this period. Calibration can be performed using a single-position method with the subject in upright posture, or a two-position method using both upright and supine postures. A two-position calibration is recommended when possible. During calibration, the subject must be fully vertical or horizontal when the PRM captures the upright and supine postures respectively.

The impedance and sleep incline trends will be visible on LATITUDE even when HeartLogic is disabled. Therefore, information about the subject's participation in a remote monitoring program using these sensors will be collected at the end of the study and will be used for analysis.

Boston Scientific has performed safety risk management activities, design verification and design validation testing to demonstrate that devices with HeartLogic function safely and effectively per the design intent. The products conform to user needs and intended use, all system-level requirements have been tested with no uncorrected failures, and the risk is

acceptable for normal product use in accordance with product labeling. A copy of the Instructions for Use and device labelling can be provided in local language(s) as required per national regulations.

5 Study Objectives and Endpoints

The PREEMPT-HF study is designed to collect device and clinical event data to evaluate extended applications of HeartLogic in a broad sample of HF subjects with an implantable ICD or CRT-D.

5.1 Primary Objective

The primary objective of the PREEMPT-HF study is to investigate the association between HF Sensor data and 30-day HF readmissions.

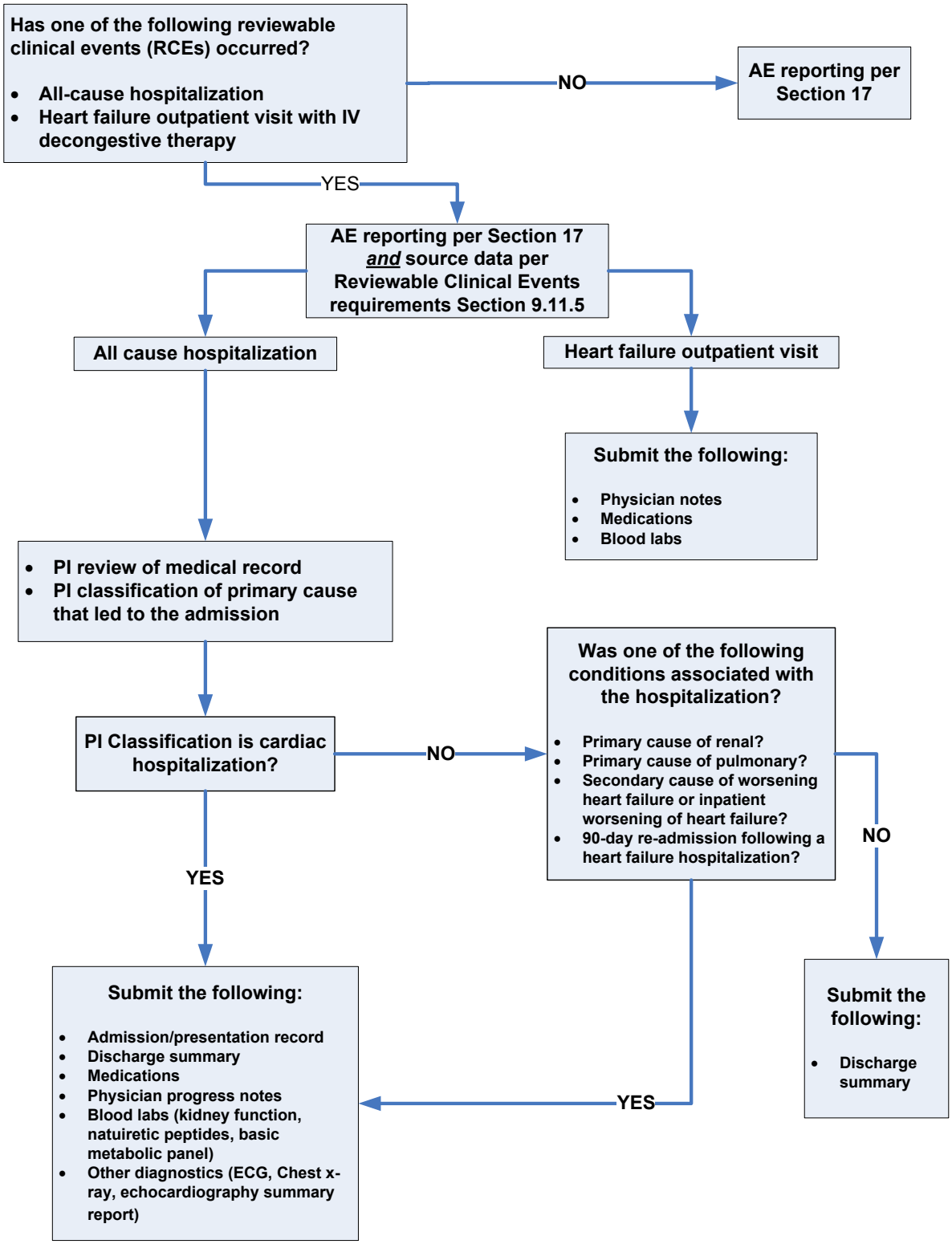
Subjects will be followed for approximately 12 months to collect the required number of clinical events to support the study objectives. These events are called Reviewable Clinical Events (RCEs), and include all-cause hospitalizations and HF outpatient visits (as defined below).

RCEs require the investigational site to review the subject's medical records and complete the appropriate eCRF (Figure 3).

Clinical events for the purposes of data analysis are defined as follows:

- **Hospitalization (all-cause)**: the subject is admitted to inpatient hospital care and discharged on a different calendar date.
- **HF Hospitalization**: the subject is admitted with signs/symptoms of congestive heart failure (CHF) and receives unscheduled augmented HF therapy with oral or intravenous medications, ultrafiltration therapy or other parenteral therapy.
- **HF Readmission (30-day)**: the subject is admitted for an unplanned hospitalization for any cause within 30 days post discharge from a HF hospitalization.
- **HF Outpatient Visit**: the subject has signs/symptoms of congestive HF, and receives unscheduled intravenous decongestive therapy (e.g., IV diuretics, IV inotropes, IV vasoactive drugs, ultrafiltration), in a setting that does not involve a hospitalization (e.g.: emergency room, HF clinic, primary care clinic, etc.).

Figure 3: Reviewable Clinical Events Data Requirements in relation to AE reporting



5.2 Additional Objectives

Additional objectives of the PREEMPT-HF study are intended to:

1. Characterize HF Sensor data for:
    - Association with risk for device VT/VF therapy
    - Phenomapping of HF events
    - Association with non-HF hospitalizations including cardiac non-HF events and non-cardiac events
2. Collect subject Sleep Incline Sensor data prior to and following reviewable clinical events
3. Link study data to third-party data, such as Center for Medicare and Medicaid Services (CMS) administrative claims (US only). Association of reviewable clinical study events with other sources will be investigated. Any study data linkage will abide by all applicable laws, regulations, and data use agreements, and patients will be consented accordingly.

5.3 Study Endpoints

PREEMPT-HF is a non-mandated post-market study. Data will be collected in subjects treated per usual standard of care procedures. However, the device needs to be programmed with Heart Failure Sensors ON and HeartLogic disabled. There are no pre-defined endpoints, and there are no special clinical evaluations or tests that are not a part of standard of care.

6 Study Design

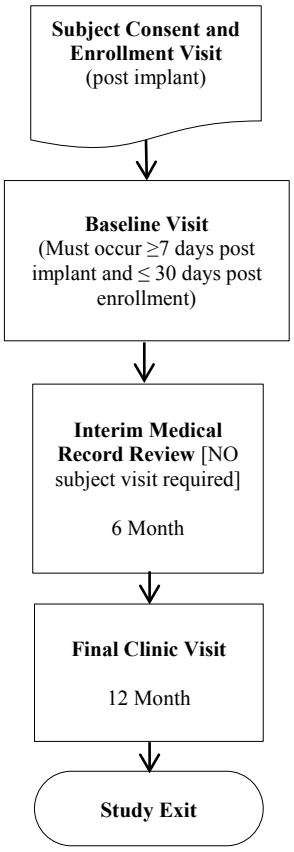
PREEMPT-HF study is a global, multi-center, prospective, non-randomized study. The study objective is to evaluate extended applications of HF sensor measurements in relation to RCEs (i.e., all-cause hospitalizations and HF outpatient visits). Device data will be collected using the LATITUDE remote monitoring system. However, it is critical to report RCEs via the eCRFs as defined in the study protocol.

Prior to enrollment, patients who meet the eligibility criteria (Sections 7.2 and 7.3) and agree to participate in the study will be asked to sign a Subject Informed Consent document approved by an Institutional Review Board/Ethics Committee, or Competent Authority (as applicable per local regulations). The follow-up schedule for subjects is shown in Table 6-1, and the overall study flow is shown in Figure 4.

Table 6-1: Visit and Review Schedule

Visit	Window
Enrollment Visit	The subject may be enrolled at any time following device implant
Baseline Visit	The baseline visit must be conducted at least 7 days following implant, and within 30 days of subject consent
Interim Medical Record Review (6 month)	150 to 210 days from baseline visit
Final Clinic Visit (12 month)	350 to 430 days from baseline visit (or at the point of withdrawal)

Figure 4: PREEMPT-HF Study Design



All subjects will be evaluated at the baseline visit and will be followed until the final in-clinic visit (approximately 12 months). Study visits should be scheduled, if possible, to coincide with standard of care visits. At the baseline visit the subject should be provided with a study ID card containing contact numbers for site research staff. The subject should be informed to contact site research staff if hospitalized or treated with IV HF therapy, including events that occur at a non-study hospital or physician's office.

An interim medical record review is required at 6 months to capture study clinical events (see section 6). No subject visit is required. Accurate and comprehensive capture of RCEs is critical for the success of the study. When possible, this medical record review should coincide with an in-clinic standard of care visit so that the investigator can ask the subject about any RCEs that may have occurred since the last visit.

During the final clinic visit (12 months or at the point of withdrawal), a device interrogation using the PRM must be performed. This ensures that the device data will be uploaded the next time the subject is in contact with their LATITUDE system at home. Once the site has confirmed device data transfer via LATITUDE, the end of study eCRF must be completed. There will be no further data collection for that subject. Individual subjects are then exited from the study, and the Heart Failure Sensors and feature can be programmed per clinician discretion.

6.1 Scale and Duration

Up to 3750 subjects will be enrolled in United States, Canada, Europe, and Asia Pacific. Sites may continue to enroll subjects until notified of enrollment completion. The maximum enrollment ceiling per site is 375 subjects. Enrollments are expected to occur over a period of approximately 60 months. Subjects enrolled in the study will be followed for approximately 12 months. A patient can be in the study for up to 460 days (15 months) if the maximum visit windows are taken in to account. The study will be conducted at up to 200 sites globally and the study is expected to be completed in approximately 6 years.

6.2 Treatment Assignment

There is no treatment assignment in this study.

6.3 Treatment and Control

This is an observational study with no treatment or control groups. All enrolled subjects will already be implanted with a commercially available Boston Scientific CRT-D or ICD device. For the specific model numbers see Table 4-1. Devices will have Heart Failure Sensors turned ON, Respiratory Sensor turned ON, Sleep Incline Sensor turned ON, and HeartLogic disabled.

6.4 Justification for the Study Design

The results of the MultiSENSE study[4] were based upon 400 subjects followed for 12 months (test cohort). While this provided sufficient sample size to evaluate HeartLogic performance to predict the initial (index) HF event, it was not sufficient for analyzing HF readmissions. Thus, a much larger sample size is needed to obtain sufficient numbers of subjects with HF readmissions. To evaluate HeartLogic for HF readmissions, subjects cannot be treated by using the feature, and clinicians must be blinded to HeartLogic Index and alerts. Therefore, this study will only enroll subjects who have HeartLogic disabled. Data from this study will be used to evaluate the association of HF sensor measurements with 30-day HF readmissions.

7 Subject Selection

7.1 Study Population and Eligibility

Eligibility for study enrollment is determined by specific eligibility criteria as described in Table 7-1 and Table 7-2.

7.2 Inclusion Criteria

Subjects who meet all of the following inclusion criteria (Table 7-1) may be given consideration for enrollment in this clinical study, provided no exclusion criterion (Table 7-2) is met.

Table 7-1: Inclusion Criteria

Inclusion Criteria	• Subject is age 18 or above, or of legal age to give informed consent specific to each country and national laws • Subject has a documented diagnosis of heart failure • Subject has a Boston Scientific CRT-D or ICD device implant that has HeartLogic, with Heart Failure Sensors turned ON, Respiratory Sensor turned ON, and Sleep Incline Sensor turned ON • Subject has an active bipolar RV lead implant. • Subject is enrolled in LATITUDE (NXT 5.0 or future version), and is willing to be remotely monitored from the baseline visit for approximately 12 months with HeartLogic disabled

7.3 Exclusion Criteria

Subjects who meet any of the following criteria (Table 7-2) cannot be included in this study or will be excluded from this clinical study.

Table 7-2: Exclusion Criteria

Exclusion Criteria	• Subject has received or is scheduled to receive a heart transplant or ventricular assist device (VAD) • Subject is enrolled in any concurrent clinical study without prior Boston Scientific written approval (excluding registries) • Subject has a life expectancy of less than 12 months • Subject has a history of non-compliance to medical care or known inability to comply with requirements of the clinical study protocol

8 Subject Accountability

8.1 Point of Enrollment

Subjects are considered enrolled at the point when they sign and date the informed consent form. The consent may be obtained at any point in time following the calendar day of implantation of the device. There is no limitation on the time from post-implantation to consent. However, the baseline visit must occur within 30 days of consent. The eligibility criteria must be confirmed prior to consenting the patient.

8.2 Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical study, an "End of Study" eCRF must be completed, with the subject status as "withdrawn".

Subjects will be classified as "withdrawn" if at least one of the following conditions are met:

- subject lost to follow-up (Section 8.3)
- subject classification of ineligible or attempt (Section 8.4)
- clinician recommendation
- subject choice
- device explant, device revision, or lead revision

All applicable eCRFs up to the point of withdrawal (including the Final Clinic Visit if possible) and the "End of Study" eCRF must be completed.

After a subject has been withdrawn from the study, additional study data will no longer be collected after the point of withdrawal. All open adverse events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used for analysis.

8.3 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for the final clinic visit and is unable to be contacted by the study site staff.

The following actions need to be taken if a subject fails to return to the clinic for the final clinic visit:

- The site will attempt to contact the subject and reschedule the missed visit and ascertain if the subject wishes to continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (3 documented attempts with a minimum of one certified letter sent to the subject). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she must be withdrawn from the study with a primary reason of lost to follow-up.

8.4 Subject Status and Classification

Subjects will be classified as follows:

- Consent ineligible
    - Refers to a subject that signs the Informed Consent but does not meet eligibility criteria

- Attempt
    - Refers to a subject that signs the Informed Consent and meets the eligibility criteria, but does NOT meet AT LEAST ONE of the conditions below:
        - Subject is monitored on LATITUDE as of the baseline visit
        - HeartLogic is disabled in LATITUDE as of the baseline visit
        - The frequency of scheduled remote follow-ups in the LATITUDE system is 3 months or less
- Monitored on LATITUDE
    - Refers to a subject that signs the Informed Consent, meets the eligibility criteria, and meets ALL the conditions below:
        - Subject is monitored on LATITUDE as of the baseline visit
        - HeartLogic is disabled in LATITUDE as of the baseline visit
        - The frequency of scheduled remote follow-ups in the LATITUDE system is 3 months or less

8.5 End-of-Study Definition

The PREEMPT-HF study is considered completed when participants are no longer being actively followed and/or the last participant's final clinic visit has occurred.

9 Study Methods

9.1 Data Collection

The details of the data collection and the study follow up schedule are shown in Table 9-1. All required data elements must be entered into the PREEMPT-HF study eCRFs.

Table 9-1 Data Collection Schedule

Procedure/ Assessment	Enrollment Visit	Baseline Visit (Day 0)	Interim Medical Record Review[1] (150-210 days)	Final Clinic Visit[2] (350-430 days)
Informed Consent Process, including Signature and Date	X	--	--	--
Inclusion/Exclusion Criteria Assessed	X	--	--	--
Confirmation LATITUDE Transmission	--	X	--	X
Device Information	--	X	X (changes only)	X (changes only)
Distribute Subject ID Card with Site Contact Information	--	X	--	--
Sleep Incline Calibration	--	X	--	--
Demographics	--	X	--	--
Physical Assessment	--	X	--	X
Medical History	--	X	--	--
Blood Labs	--	O	--	O
Cardiac Medications Reviewed	--	X	--	--
Assessment of Adverse Events and Reviewable Clinical Events	--	X	X	X
Supplementary Diagnostics Data Collection	--	--	O	O

[1] *The interim medical record review does not require an in-clinic visit.*
[2] **Please complete the final clinic visit form for subjects withdrawn prior to 350 days*
An "X" indicates a mandatory data requirement. Failure to complete will result in a protocol deviation.
An "O" indicates optional but recommended data.

9.2 Device Interrogation / Collection of Programming Data

The device must be interrogated with a PRM at enrollment, baseline and during the final clinic visit. These interrogations are required to confirm the appropriate programming of the device, including Heart Failure Sensors ON, Sleep Incline Sensor ON, and Respiratory Sensor ON. All other device settings can be programmed per clinician discretion. The PRM must also be used to calibrate the Sleep Incline Sensor.

HF Sensor data and Sleep Incline data will be collected via the LATITUDE patient communicator.

9.3 Study Candidate Screening

Subjects will be recruited from the investigator's pool of patients that have an ICD or CRT-D implant with the HeartLogic feature. The investigator has the responsibility of screening potential subjects and selecting only those who meet the eligibility criteria. For the purpose of this clinical study no screening logs are required, and the site is not required to report screen failures.

9.4 Strategies for Recruitment and Retention

Study recruitment will rely upon the general pool of patients that meet the eligibility criteria and have an ICD or CRT-D implant.

9.5 Informed Consent

Eligible subjects can be consented for the study any time after the calendar day of the ICD or CRT-D implant. Participants who meet all the inclusion criteria and none of the exclusion criteria, and sign and date the informed consent form are considered enrolled in the study. No procedures or data will be collected prior to signing the informed consent form. Legal Authorized Representatives (LAR) must not be used for this study.

9.5.1 Data Linkage

The PREEMPT-HF study will also link study data to third-party data sources. The purpose of data linkage is to conduct research to improve clinical applications such as patient management and therapy (both device and non-device), algorithms for patient risk stratification and prognostic evaluation, health economic evaluation, and clinical trial methodologies. Data linkage will focus on disease states and comorbidities common in device patients such as heart failure, hypertension, cardiac arrhythmias, acute coronary syndrome, heart valve disorders, respiratory disease, renal disease, gastrointestinal disease, sleep apnea, infectious disease, etc.

PREEMPT-HF study data will be used in combination with internal BSC databases (e.g., device tracking database) to obtain, use, and disclose certain protected health information to third-parties. This may include device serial and model number, implant date, the hospital where the implant procedure was performed, subject last name, date of birth, address zip code, and the last four digits of the subject's social security number.

The third-party data sources include but are not limited to payer administrative claims and health analytics (e.g., Centers for Medicare and Medicaid Services, Truven, Optum), provider electronic health records (EHRs), pharmacy benefit management (or other third-party administration of prescription drug programs), clinical registries (used for post market surveillance or quality improvement), biobanks, and government databases (such as census data, or social security death index).

The subject may withdraw permission for the use and sharing of personal health information at any time if provided in writing to the study doctor. Please notify Boston Scientific of any subjects that submit in writing their request to withdraw their permission for the use of personal health information.

Boston Scientific will abide by all applicable laws, regulations, and data use agreements associated with data linkage to third-party data sources. This research could not practicably be conducted without access to and use of the protected health information. Additionally, Boston Scientific will employ reasonable administrative, physical and technical safeguards that are designed to protect against data loss, misuse of data, unauthorized access or disclosure of data, and alteration or destruction of data. This includes implementation of adequate plans to use only minimum identifiable data needed in a finder file to enable linkage, and the removal and destruction of the finder file after each linkage is complete at the earliest opportunity consistent with conduct of research.

9.6 Enrollment Visit

Enrollment cannot occur on the same calendar day of the implant procedure, but may occur before the patient is discharged from the hospital where the implant occurred.

At the enrollment visit the following activities are required:

- Confirmation of subject consent
- Confirmation that the subject meets all the inclusion and none of the exclusion criteria (Sections 7.2 and 7.3)

9.7 Baseline Visit [Day 0]

The baseline visit must be conducted no sooner than seven (7) days post-device implant to allow for automatic initialization of the Sleep Incline Sensor. Enrollment and baseline visits can be completed on the same day provided the device has been implanted for at least seven (7) days with the Sleep Incline Sensor turned ON. However, the baseline visit must be conducted no later than 30 days following enrollment.

The following information must be gathered and entered into the eCRFs in a timely manner.

- Subject device information
    - Manufacturer, model and serial number of pulse generator and active leads
    - Implant date for all active devices
    - Anatomical locations of pulse generator and leads
- LATITUDE monitoring
    - Confirm that the subject is monitored in LATITUDE
    - Review in LATITUDE at the patient level that HeartLogic is disabled
    - Confirm scheduled remote patient monitoring follow-ups are programmed to occur at a frequency no less often than once every three (3) months.

- Sleep Incline Sensor calibration and data collection:
  Important: The device will NOT collect any Sleep Incline data until a body calibration has been performed. Calibration is a required step to ensure the PG is collecting sleep incline data.
  - Sleep Incline Sensor calibrations are performed by the clinician using the PRM. Calibration should be performed using the two-position method for increased accuracy. This requires the patient to sit and to lie down, so the calibration must be conducted in a room with adequate facilities. Care must be taken to ensure that the subject is fully vertical or horizontal when the PRM captures the upright and supine postures. Once the patient is in position, the clinician will run the software on the PRM for the data collection. It takes approximately 10 seconds of data collection for each position. The entire procedure should take about 1-2 minutes. For patients unable to perform the two-position calibration, a single position may be performed.
  - Regardless of whether the Sleep Incline Sensor has been calibrated prior to the PREEMPT-HF Study baseline visit, please re-calibrate. Document the calibration in the patient medical record.
  - If the Sleep Incline Sensor is turned ON, but the Sensor initialization is incomplete seven (7) days after implant, then calibration cannot be performed. Please document in the eCRF if initialization failure resulted in the inability to calibrate the sensor. If initialization failure occurs, calibration may be performed at a subsequent standard of care office visit.
  - Record the details of the sleep incline calibration in the patient medical record as source documentation.
- Provide subject with an ID card containing PREEMPT-HF study site contact information. Subjects should be instructed to inform the study coordinator or any other study site personnel if they are hospitalized for any reason, or receive IV HF treatment)
- Subject demographics (see Appendix for details)
- Physical assessment (Appendix)
- Medical history (Appendix)
- Enter all cardiac medications
- Blood labs: If available in the medical records, enter the most recent blood lab values collected for the following:
  - Natriuretic peptides (BNP or NT-proBNP) and date of collection
  - Creatinine and date of collection
- Indicate if the subject is implanted and monitored using a commercial pulmonary artery pressure sensor, or if the subject is monitored using serial natriuretic peptides.
- Review subject medical records since the enrollment and assess for Reviewable Clinical Events (RCEs) and reportable AEs (See Figure 3).

In addition, subjects located in the United States (US) who own a smart phone may be provided with the option to use a geo-location tracking app to ensure timely reporting of hospitalizations. The app contains the location of all hospitals in the US. If a subject exceeds the pre-specified and programmable amount of time at a hospital, the app will prompt the patient to confirm a hospitalization. In addition, the investigational site will get a notification that the patient may be hospitalized. To protect patient privacy, Boston Scientific will not receive these notifications.

9.8 Interim Medical Record Review [150-210 days]

The interim medical record review must be conducted 150 to 210 days following the baseline visit. It is encouraged to perform the interim medical record review at the time of an in-clinic standard of care visit. If this review coincides with an in-clinic visit, the subject must be asked whether he or she had any reviewable clinical events (RCEs) since the baseline visit. As defined in section 5.1, an RCE is defined as either an all-cause hospitalization, or HF outpatient visit. If the subject reports having an RCE at a center not participating in the study, every effort should be made to obtain medical records from the center. An overview of the activities and data to be collected is provided below.

- Review subject medical records since the date of the baseline visit and assess for RCEs and reportable AEs
- If RCEs are identified during the medical record review (see Figure 3 for details), complete the "Reviewable Clinical Event" eCRF.
    - Each newly identified RCE must have a unique eCRF. For example, if the subject had two HF outpatient visits for an on-going AE it must be captured in two separate "Reviewable Clinical Event" eCRFs.
    - If a single RCE is associated with multiple AEs, only the primary AE (i.e., the chief complaint leading to the clinic/hospital visit) should be associated with an "Reviewable Clinical Event" eCRF. For example, if a subject was admitted due to symptoms of gastrointestinal bleeding but developed worsening HF during the course of hospitalization, the gastrointestinal bleeding would be the primary AE, and therefore it would be associated with the "Reviewable Clinical Event" eCRF. A separate "Reviewable Clinical Event" eCRF is not required for the in-patient worsening of HF even if it is reported as a separate AE.
- For hospitalizations, the Principal Investigator must review the patient's medical records and classify the primary organ cause in the "Reviewable Clinical Event" eCRF (see Appendix for details). Appropriate classification is important for event subgroup analysis. Classification also triggers the request for medical record documentation to be sent to BSC.
- Supplementary diagnostics data collection: This eCRF sub-folder is created only if the investigational site confirms that the subject is routinely monitored using pulmonary artery (PA) pressure data from an implanted commercially-approved device, or using serial natriuretic peptides (BNP or NT-proBNP). If the site

confirms the use of supplementary diagnostic data, the following should be entered in the corresponding eCRF:

- PA pressure readings
- Serial natriuretic peptide values
- Volume status of the subject (hypervolemic, hypovolemic, euvolemic)
- Treatments initiated in response to the diagnostic data

The sponsor retains the right to restrict the total amount of supplemental data that would be collected during the course of the study. In this event, sites would be notified to stop reporting supplemental data, and the data base eCRF may be locked for further data entry.

9.9 Final Clinic Visit [350-430 days]

The final visit must be performed in-clinic 350 to 430 days following the baseline visit. If the patient is withdrawn prior to the window for the final clinic visit, please complete the final clinic visit at the point of withdrawal. An overview of the data to be collected at this visit is provided below.

- Review subject medical records since the date of the baseline visit and assess for RCEs and reportable adverse events.
  - Collect and report using the same process used in the interim medical record review (See section 9.8).
- Physical assessment (See Appendix)
- Blood labs: Enter the most recent blood lab values since the baseline visit for the following.
  - Natriuretic peptides (BNP or NT-proBNP) and date of collection. If serial natriuretic peptide data has already been entered in the supplementary diagnostics form, the same values need not be entered in the final visit eCRF.
  - Creatinine and date of collection
- Supplementary diagnostics data collection:
  - Collect using the same process as in the interim medical record review (See section 9.8).
- Interrogate the device with a PRM. This ensures that the device data will be uploaded when the patient returns to within range of the communicator.
- Confirm that a LATITUDE transmission occurred in the previous 90 days. If transmission has not occurred instruct patient to do a patient initiated interrogation when they are in range of their communicator.
- Remote monitoring usage:
  - Provide information about the frequency and use of remote monitoring to manage the patient's HF condition over the past 12 months (e.g. sleep incline, weight, blood pressure, arrhythmia burden).

9.10 Study Completion

An "End of Study" eCRF must be completed when the subject's participation concludes for one of the following reasons:

- The subject completes the final in-clinic visit after 350 days (minimum final clinic visit window). At this point, the subject will exit the study, and device settings can be configured per clinician discretion. The subject status will be "completed study."
- The subject withdraws from the study. At this point, the subject will exit the study, and device settings can be configured per clinician discretion, and the subject status will be "withdrawn". All applicable eCRFs (including the Final Clinic Visit if possible) and the "End of Study" eCRF must be completed with information up to the point of withdrawal. Complete a review of the medical records for RCEs to the point of withdrawal, and interrogate the PG (See section 9.9 for visit details). PG interrogation ensures that the device data will be uploaded when the patient returns to within range of the communicator.
- The study is terminated by Boston Scientific. At this point, the subject will exit the study, and device settings can be configured per clinician discretion. The subject status will be "withdrawn."

9.11 Source Documents

The following tables detail the data collection and the required source documentation.

9.11.1 Enrollment Visit

Data Collection	Source Documentation
Informed Consent	Study Center
Inclusion/Exclusion Criteria	Study center
Confirmation of LATITUDE Enrollment	LATITUDE printout at the Study Center
Confirmation of Heart Failure Sensors ON, Sleep Incline Sensor ON, and Respiratory Sensor ON	Study Center (documented in the patient medical record)

9.11.2 Baseline Visit

Data Collection	Source Documentation
Confirmation of LATITUDE transmission and HeartLogic is disabled	LATITUDE printout at the Study Center
LATITUDE Remote Scheduled Follow-up Programming	LATITUDE printout at the Study Center

Sleep Incline Sensor calibration	Study Center (documented in the patient medical record)
Demographics, Medical History, Physical Assessment, Blood Labs	Study Center
Assess for RCEs and reportable AEs	Retain original at study center and submit a copy to Boston Scientific (see Section 9.11.5 for additional details regarding RCEs)

9.11.3 Interim Medical Record Review

Data Collection	Source Documentation
Assess for RCEs and reportable AEs	Retain original at study center and submit a copy to Boston Scientific (see Section 9.11.5 for additional details regarding RCEs)
Supplementary Diagnostics Data	Study Center

9.11.4 Final Clinic Visit

Data Collection	Source Documentation
Assess for RCEs and reportable AEs	Retain original at study center and submit a copy to Boston Scientific (see Section 9.11.5 for additional details regarding RCEs)
Physical Assessment	Study Center
Blood Labs	Study Center
Supplemental Diagnostics	Study Center
Remote Monitoring Usage	Study Center

9.11.5 Reviewable Clinical Events

Table 9-2 summarizes specific source data requirements for the RCEs, along with the additional required reporting of all SAEs. It is preferable that original source documents are maintained on site. In lieu of original source documents, copies are required to be maintained.

Table 9-2 Source Documentation Requirements for Reviewable Clinical Events

Clinical Events			Source Document(s) *Medical records*	Disposition Options
REVIEWABLE CLINICAL EVENTS	All-Cause Hospitalizations	Cardiac hospitalizations	• Admission/presentation record • Discharge summary • Medications • Physician progress notes • Blood labs (kidney function, natriuretic peptides, basic metabolic panel), • Other diagnostics (ECG, Chest x-ray, echocardiography summary report) • Further documentation may be requested by BSC	Upload into RAVE or Email to PREEMPT.Safety@bsci.com or Fax: 651-582-5847
		Non-cardiac hospitalizations within 90 days of discharge from a previous HF Hospitalization (i.e., 90-day readmission)		
		Non-cardiac hospitalizations where HF was secondary contributing cause, or where inpatient worsening of HF occurred		
		Non-cardiac pulmonary or renal events		
		All other Non-cardiac hospitalizations	• Discharge summary • Further documentation may be requested by BSC	
	HF Outpatient Visits (with decongestive IV therapy)		• Physician notes • Medications • Blood lab reports • Further documentation may be requested by BSC	
	All Other AEs as required by the protocol (section 17)		• Further documentation may be requested by BSC	

10 Statistical Considerations

10.1 Primary Endpoint

There are no primary endpoints or formal hypotheses, as the purpose of this study is exploratory. The primary objective is to investigate the association between HF Sensor data and 30-day HF readmissions.

10.1.1 Hypotheses

There are no formal hypotheses. The purpose of this study is exploratory.

10.1.2 Sample Size

Approximately 3750 enrollments will be required for this study. The sample size was determined based on the estimated number of HF index hospitalizations and 30-day HF readmissions needed to evaluate the primary objective. Final sample size will be determined by an interim analysis as described in Section 10.9. An index HF hospitalization refers to the first HF hospitalization during the study follow-up period. A HF hospitalization is deemed usable if sensor data is available during the event and sufficient follow up time is recorded to determine if a readmission occurs.

A total of 215 usable index HF hospitalizations are required to have at least 80% power to detect a standardized difference of 0.5 in the mean sensor change (admission – discharge) between the groups with and without a 30-day HF readmission. It is expected that of the 215 index HF hospitalizations, 43 will be followed by a 30-day readmission (20%).

A total of 215 usable index HF hospitalizations was determined based on the following assumptions:

- 80% Power to detect a standardized mean difference of 0.5 between groups
- Two-sided type I error (alpha) of 0.05
- 3:1 ratio of group sizes (no-readmission : 30-day HF readmission), where the no-readmission group will exclude index HF hospitalizations with 31 to 60-day readmissions

Assuming a 20% loss of usable HF events due to proximity to study start and exit (completion or withdrawal), a total of 270 index HF hospitalizations are required to obtain 215 usable HF hospitalizations.

Approximately 3750 enrollments are required to obtain the 270 required index HF hospitalizations. This was determined based on the following assumptions:

- 9 % index HF hospitalization rate per patient year
- 20% death/withdrawal rate throughout duration of study
- Average of 12 months of sensor data per subject

10.1.3 Statistical Methods

The primary objective will be evaluated using an independent two sample t-test. A comparison of mean sensor value change (admission – discharge) will be made between the no-readmission group and the 30-day readmission group. All subjects with a usable index HF hospitalization and all subjects with a 30-day HF readmission will be included in the primary analysis. Subjects with a 31-60-day HF hospitalization will be excluded from the analysis. A two-sided alpha of 0.05 will be used.

10.2 Secondary Endpoints

There are no secondary endpoints.

10.3 Other Objectives/Measurements

The additional objectives are described below along with planned statistical methods and analysis data to be used.

- Characterize HF sensors for the association with risk for VT/VF therapy
  - This will be assessed using an odds ratio
  - All subjects with usable sensor and episode data will be included in the analysis
- Characterize HF sensors for phenomapping of HF events
  - This will be assessed using cluster analysis
  - All subjects with a HF event and usable sensor data will be included in the analysis
- Characterize HF sensors for association with non-HF hospitalizations (including cardiac non-HF events and non-cardiac events)
  - This will be assessed using a paired t-test
  - All subjects with a non-HF hospitalizations and usable sensor data will be included in the analysis

- Collect Sleep Incline Sensor data leading up to clinical events: Subjects who were enrolled in a remote monitoring program using sleep incline data will be excluded and sensor data in the remaining patients will be analyzed using a paired t-test.

- Link study data to third-party data sources. Data linkage will be included in the analysis to assess feasibility to link to claims data (see Section 9.5) and other data sources. The linked data set will be used to compare claims-based events with study RCEs, assess the accuracy of claims-based algorithms to identify sensor detected events, and estimate the cost savings from avoidable hospitalizations. Comparisons will be made using paired and un-paired t-tests and receiver operator curve (ROC) analyses.

10.4 General Statistical Methods

All sample size calculations were performed and all statistical analyses will be done with SAS version 9.3 or higher.

10.5 Analysis Sets

10.5.1 Primary analysis

All subjects with a usable index HF hospitalization and all subjects with a 30-day HF readmission will be included in the primary analysis. Subjects with a 30-60-day HF hospitalization will be excluded from the analysis.

10.5.2 Additional analyses

- All subjects with usable sensor and episode data will be included in the analysis of characterizing HF sensors for the association with risk for device VT/VF therapy
- All subjects with a HF event and usable sensor data will be included in the analysis of characterizing HF sensors for phenomapping of HF events
- All subjects with a non-HF hospitalization and usable sensor data will be included in the analysis of characterizing HF sensors for association with non-HF hospitalizations

10.6 Control of Systematic Error/Bias

The purpose of this study is exploratory and to characterize the association of HF sensor data with various clinical events. No formal tests of hypothesis are planned, no claims of safety or efficacy are intended, and no adjustment for multiple testing will be performed.

10.7 Number of Subjects per Investigational Site

A single site cannot enroll more than 375 patients.

10.8 Other Endpoints/Measurements

There are no endpoints or other measurements captured in this study.

10.9 Interim Analyses

An interim analysis is planned after 1000 subjects have been enrolled and have completed all required follow-up visits. The purpose of the interim analysis is to verify enrolling rates and HF hospitalization rate and withdrawal rate.

10.10 Subgroup Analyses

Analyses may be performed to evaluate the study objectives in various subgroups. The list of baseline characteristics and their corresponding subgroups to be analyzed include, but are not limited to, the following:

- Device – CRT-D and ICD
- Sex – Male and Female
- Age – < 65 and ≥ 65 years
- NYHA Class – Class I, II, III, IV
- LVEF – < 25% and ≥ 25%
- Etiology – Ischemic and Non-Ischemic
- Renal dysfunction – Yes and No

Details of subgroup analyses will be documented in a separate Statistical Analysis Plan not included in this protocol.

10.11 Justification of Pooling

Pool-ability of data across investigational sites and geographic regions will be tested. Details of pooling analysis are documented in a Statistical Analysis Plan.

10.12 Multivariable Analyses

Multivariable exploratory analyses may be performed to determine if clinical or patient characteristics are associated with sensor measurements or clinical outcomes. Details of multivariable analyses are documented in a Statistical Analysis Plan.

10.13 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in a Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

11 Data Management

11.1 Data Collection, Processing, and Review

Subject data will be recorded in a limited access and secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by the EDC System manufacturer. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated

system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic eCRFs in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

11.2 Data Retention

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigational site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the study has been completed. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other country/regional/local regulations

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

12 Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/REB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using the electronic database CRF. Sites may also be required to report deviations to the IRB/REB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB/REB/EC) notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

13 Device/Equipment Accountability

The devices used in this study are commercially approved in all study geographies. Any device tracking and accountability will occur per the required local regulations for commercial devices.

14 Compliance

14.1 Statement of Compliance

This study will be conducted in accordance with post market clinical follow up guidelines and will follow the applicable sections of ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/REB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/REB/EC or regulatory authority shall be followed, if appropriate.

14.2 Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, the guidance of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC/REB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.

- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.

- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/EC/REB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.

- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

14.3 Delegation of Responsibility

When specific tasks are delegated, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a site, the sub-investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

14.4 Institutional Review Board/ Research Ethics Board / Ethics Committee

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC/REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/EC/REB and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the clinical investigation. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/REC/EC before the changes are implemented to the study. All changes to the ICF will be IRB/REC/EC approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

14.5 Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other

business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep the subject's identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use the subject's health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, third-party data linkage and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

14.6 Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during procedures required by the protocol, and required follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

As allowed per local regulations, at the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during follow-up, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities.

Typical tasks may include the following:

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating study equipment
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from programmers, and other equipment
- Entering technical data on technical source form provided the responsible investigator verifies and signs the completed worksheet
- Print out/download programming reports/parameters directly from the clinician programmer and provide original printouts or electronic data reports to clinical site as source documentation
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance

- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in eCRFs or on paper CRFs

14.7 Insurance

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

15 Monitoring

Monitoring will be performed by Boston Scientific or its designees during the study. A combination of on-site, remote, or central monitoring will be used to assess continued compliance with the protocol and applicable regulations. This includes ensuring proper informed consent process, review of safety data, and adherence to protocol defined visit schedule. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and IRB approved facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

16 Potential Risks and Benefits

16.1 Directions for Use

Please refer to the Directions for Use for an overview of anticipated adverse (device) effects, and risks associated to the commercial device(s).

16.2 Risks Associated with Participation in the Clinical Study

There are no required treatments or therapeutic interventions in this trial. The study involves the collection of sensor data and clinical event data. There are no additional risks of participating above those associated with standard of care.

16.3 Possible Interactions with Concomitant Medical Treatments, if Applicable

There are no concomitant medical treatments.

16.4 Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

16.5 Anticipated Benefits

There may be no benefits to a subject's participation in the study. However, participation may help future patients benefit from enhanced performance of the HeartLogic algorithm.

17 Safety Reporting

17.1 Reportable Events by Investigational Site to Boston Scientific

It is the responsibility of the Investigator to assess and report to BSC any event which occurs in any of following categories:

- All Serious Adverse Events
- All Device Related Adverse Events
    - Events listed in the arrhythmia logbook, should be reported only if determined to be clinical significant by the investigator and/or delegated site staff (e.g.: ATR, PMT, etc.)
    - All arrhythmias which received inappropriate shock therapy as identified by a study investigator must be reported
- All Serious Adverse Device Events
    - Serious adverse device events that are a result of implant, device revision, lead revision, or device/lead explant are not reportable events per this protocol. Patients that undergo device or lead revision/explant must be withdrawn prior to the procedure.
- All Device Deficiencies related to the pulse generator

- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- HF Related Adverse Events: An adverse event is deemed as a HF Adverse Event if the primary cause is HF and either of following conditions is met:
    - Subject is admitted and discharged with a calendar date change.
    - Subject is not hospitalized but received one or more IV medications including diuretics, inotropes, vasodilators, other parenteral therapy, or aquapheresis.

For event reporting the medical diagnosis must be reported. In case the diagnosis is not available, individual symptoms can be reported to fulfill reporting timelines. If a diagnosis becomes available at a later stage, it must be added to the reported event.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of one (1) specific SAE (see Table 17-1 for AE definitions).

Refer to Directions for Use for the known risks associated with the commercial device(s).

17.2 Definitions and Classification

Adverse event definitions are provided in Table 17-1. Administrative edits were made on the safety definitions from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 17-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the study medical device. **NOTE 1**: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to

Table 17-1: Safety Definitions

Term	Definition
	events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or intentional abnormal use of the study medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: • a life-threatening illness or injury, or • a permanent impairment of a body structure or a body function, or • in-patient hospitalization or prolongation of existing hospitalization, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

Table 17-1: Safety Definitions

Term	Definition
Ref: ISO 14155 *Ref: MEDDEV 2.7/3*	**NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of the study medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

17.3 Relationship to Device(s)

The Principal Investigator must assess the relationship of the reportable AE to the device. See criteria in Table 17-2.

Table 17-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the study device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious

	event.
Unlikely Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the study device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

17.4 Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in

Adverse events must always be reported through the EDC system for PREEMPT-HF. However, in the case of any issues where alternative method of reporting is necessary (i.e. the EDC system is not available); please report the adverse event to Boston Scientific by sending the Event Notification Form via email to the following email address:

PREEMPT.Safety@bsci.com

Table 17-3: Communication Requirements for Adverse Events

Event Classification	Communication Method	Communication Timeline post-market studies* (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study.
	Provide all relevant source documentation (unidentified) for reported event.	• Upon request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 business days after becoming aware of the event or as per local/regional regulations. • For Austria: within 2 business days of first becoming aware of the event • Reporting required through end of study.
	Provide all relevant source documentation (unidentified) for reported event.	• When documentation is available
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event.	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable	Complete DD eCRF with all available new and updated information.	• Within 2 business days of first becoming aware of the event. Reporting required through the end of the study

Event Classification	Communication Method	Communication Timeline post-market studies* (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
event.		
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g., recommend within 30 business days) after becoming aware of the information • Reporting required through end of study
	Provide all relevant source documentation (unidentified) for reported event.	

17.5 Safety definitions

Boston Scientific uses the safety definition below to help with appropriate internal coding and classification of protocol defined reportable adverse events.

Table 17-4 Safety Definitions

Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Clinical Observation *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	A clinical observation is a clinical event that did not result in invasive intervention, injury, or death, and is not an unanticipated adverse event. Corrective actions were simple adjustments such as reprogramming of the pulse generator or antibiotic treatment of a pocket infection
Clinical Complication *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	A clinical complication is a clinical event that required an invasive intervention, injury, or death (e.g., surgical evacuation of a hematoma, lead dislodgment requiring lead repositioning, generator replacement, loss or abandonment of therapy).
Type I *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Related to the investigational device or therapies.
Type II *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Related to protocol or procedures. Specifically related to protocol testing that is not patient standard of care.
Type III *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Not related to the investigational device(s), system component(s), or labeling, but would not have occurred in the absence of the investigational device(s) and/or system component(s). This includes clinical events related to commercially released devices that are used in conjunction with investigational device(s) or protocol procedures.
Type IV *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Related to a change in patient's condition.
Type V	Comments Only. On occasion, comments were inadvertently entered

Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions	in the adverse event text field of the case report form (CRF). Comments identified by the CRF reviewer were assigned a Type V code and not included in this report.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

17.6 Boston Scientific Device Deficiencies

For purposes of the PREEMPT-HF Study, the Boston Scientific Pulse Generator (PG) will be referred to as the device under study. Only device deficiencies related to the PG should be reported; no other PG manufacturers should be reported. When relevant and if possible, the device(s) should be returned to BSC for analysis. Instructions for returning the device(s) will be provided as needed. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not necessarily adverse events. However, a serious adverse event that results from a device deficiency would be recorded as on the appropriate eCRF.

17.7 Reporting to Regulatory Authorities / IRBs / ECs / REBs/ Investigators

BSC is responsible for reporting adverse event information to all participating Principal Investigators, IRBs/ECs/REBs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC/REB, and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

BSC shall notify all participating Chinese study centers if SAEs/SADEs occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study to further minimize the unanticipated risks.

17.8 Subject Death Reporting

A subject death during the study must be reported to Boston Scientific as soon as possible and, in any event, within three (3) calendar days of center aware date. The center's IRB/EC must be notified of any deaths in accordance with that center's IRB/EC policies and procedures. Whenever possible, the device should be interrogated and BSC system components (e.g., the device) should be removed intact and returned promptly to BSC RM for analysis.

A detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death is required. A death narrative in the local language is acceptable, if accompanied by a translation in English. The details listed below should be

addressed in the death narrative, for BSC to understand the circumstance surrounding the death:

- Date and time of death;
- Place death occurred;
- Immediate cause of death;
- Rhythm at the time of death, if known (include any available documentation);
- Whether or not the death was witnessed;
- Whether the subject had worsening HF;
- Any other circumstances surrounding the death;
- Approximate time interval from the initiating event to death (temporal course) – items to consider include, but are not limited to: information regarding last time subject was seen by investigator, last office visit, etc.
- Investigator or co-Investigator signature and date.

Whenever possible, the CRT-D or ICD device is recommended be interrogated. Other Source documents maybe requested at BSC. BSC Medical Safety representatives must review information regarding subject deaths.

18 Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC/REB, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigational site's IRB/EC/REB. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB/EC/REB approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC/REB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

19 Committees

19.1 Safety Monitoring Process

The BSC Medical Safety group reviews unmonitored data as soon as the event is reported, and on a continuous basis. During scheduled monitoring activities, clinical research monitors will support this continuous review through their review of source document and other data information. The BSC Medical Safety group includes physicians with expertise in electrophysiology, and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

19.2 BSC Internal Medical Record Review

Source documentation will be collected for reviewable clinical events per the source data requirements outlined in Table 9-2. Copies of the subject source documents provided by sites will be assembled into clinical event dossier for internal review by Boston Scientific (BSC). The purpose of the BSC internal review is to extract contextual data about the RCE for the association with HF sensors.

20 Suspension or Termination

20.1 Premature Termination of the Study

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

20.2 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

20.3 Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC/REB Approval

Any investigator, or IRB/ EC/ REB in the PREEMPT-HF Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

20.4 Requirements for Documentation and Subject Follow-up

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB, REB or EC terminates participation in the study, participating investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and devices, if supplied by Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

20.5 Criteria for Suspending/Terminating a Study Site

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if subject enrollment at a site is slower than projected rate, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

The IRB/EC/REB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

21 Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). To ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contribution requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

In Japan, Investigators shall register a summary of this research-study in one public database operated by the National University Hospital Council of Japan, the Japan Pharmaceutical Information Center, or the Japan Medical Association. Below are the lists of public databases available:

- UMIN-CTR: http://www.umin.ac.jp/ctr/index-j.htm

- Iyaku Search: http://database.japic.or.jp/is/top/index.jsp
- JMA CCT: https://dbcentre3.jmacct.med.or.jp/jmactr/

Investigators shall update the registered contents appropriately according to revisions of the research-study protocol, the progress of the research-study, and shall register the results of the research-study when the research is completed.

22 Reimbursement and Compensation for Subjects

22.1 Subject Reimbursement

Expenses incurred by subjects as a result of participation may be reimbursed for study required visits if they fall within the follow-up period, and are outside of the standard of care visits. Reimbursement will be done in accordance with pertinent country laws and regulations and per the study site's regulations.

22.2 Compensation for Subject's Health Injury

Boston Scientific Corporation will purchase an insurance policy to cover the cost of potential health injury for study subjects, if required by applicable law.

23 Bibliography

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P. Heart disease and stroke statistics-2017 update: A report from the american heart association. *Circulation*. 2017;135:e146-e603
2. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: Lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014;63:1123-1133
3. Gheorghiade M, Pang PS. Acute heart failure syndromes. *J Am Coll Cardiol*. 2009;53:557-573
4. Boehmer JP, Hariharan R, Devecchi FG, Smith AL, Molon G, Capucci A, An Q, Averina V, Stolen CM, Thakur PH, Thompson JA, Wariar R, Zhang Y, Singh JP. A multisensor algorithm predicts heart failure events in patients with implanted devices: Results from the multisense study. *JACC. Heart failure*. 2017;5:216-225
5. Whellan DJ, Lindenfeld J. Easy to predict, difficult to prevent. *JACC. Heart failure*. 2017;5:226-228

6. Desai AS. The three-phase terrain of heart failure readmissions. *Circulation. Heart failure*. 2012;5:398-400
7. Dharmarajan K, Wang Y, Lin Z, Normand ST, Ross JS, Horwitz LI, Desai NR, Suter LG, Drye EE, Bernheim SM, Krumholz HM. Association of changing hospital readmission rates with mortality rates after hospital discharge. *Jama*. 2017;318:270-278
8. Eapen ZJ, Liang L, Fonarow GC, Heidenreich PA, Curtis LH, Peterson ED, Hernandez AF. Validated, electronic health record deployable prediction models for assessing patient risk of 30-day rehospitalization and mortality in older heart failure patients. *JACC. Heart failure*. 2013;1:245-251
9. Ross JS, Mulvey GK, Stauffer B, Patlolla V, Bernheim SM, Keenan PS, Krumholz HM. Statistical models and patient predictors of readmission for heart failure: A systematic review. *Archives of internal medicine*. 2008;168:1371-1386
10. Whellan DJ, Sarkar S, Koehler J, Small RS, Boyle A, Warman EN, Abraham WT. Development of a method to risk stratify patients with heart failure for 30-day readmission using implantable device diagnostics. *The American journal of cardiology*. 2013;111:79-84
11. Adamson PB, Abraham WT, Stevenson LW, Desai AS, Lindenfeld J, Bourge RC, Bauman J. Pulmonary artery pressure-guided heart failure management reduces 30-day readmissions. *Circulation. Heart failure*. 2016;9
12. Ip JE, Cheung JW, Park D, Hellawell JL, Stein KM, Iwai S, Liu CF, Lerman BB, Markowitz SM. Temporal associations between thoracic volume overload and malignant ventricular arrhythmias: A study of intrathoracic impedance. *Journal of cardiovascular electrophysiology*. 2011;22:293-299
13. Sullivan RM, Olshansky B. Optivol fluid index: Does an association with ventricular arrhythmias hold water? *Journal of cardiovascular electrophysiology*. 2011;22:300-301
14. Popjes E, Boehmer JP. Therapeutic implications of implantable device-based monitoring of patients with heart failure. *Current treatment options in cardiovascular medicine*. 2008;10:371-379
15. Abi-Saleh B, Malozzi C, Charaf E, Omar B, Massey C, Khoury M, Verma S. Worsening thoracic impedance as a ventricular tachyarrhythmia risk. *Reviews in cardiovascular medicine*. 2014;15:226-231
16. Hariharan R, Cao M, Sweeney RJ, Zhang Y, Averina V, An Q, Thakur PH, Boehmer JP. Heart failure diagnostic sensor measurements change during atrial arrhythmias. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2017;14:S404
17. Pubbi D, Hudson M, Molon G, Capucci A, Slotwiner D, Cao M, Thakur PH, Averina V, Zhang Y, Wariar R, Thompson J. Af in hf: The chicken or the egg? Role of crt device based sensor data in identifying a causal relationship between af and worsening hf. *Journal of cardiac failure*. 2016;22:S65
18. Jedrzejczyk-Patej E, Kowalski O, Sredniawa B, Pruszkowska P, Sokal A, Szulik M, Mazurek M, Kowalczyk J, Kalarus Z, Lenarczyk R. Trying to predict the

unpredictable: Variations in device-based daily monitored diagnostic parameters can predict malignant arrhythmic events in patients undergoing cardiac resynchronization therapy. *Cardiology journal*. 2014;21:405-412

19. Capucci A, Merkely B, Sweeney RJ, Zhang Y, Thakur PH, Averina V, Boehmer JP. Arrhythmia burden increases prior to worsening heart failure events. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2017;14:S216
20. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 esc guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the european society of cardiology (esc)developed with the special contribution of the heart failure association (hfa) of the esc. *European heart journal*. 2016;37:2129-2200
21. Miller WL, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: Role for blood volume quantitation. *JACC. Heart failure*. 2014;2:298-305
22. Ahmad T, Pencina MJ, Schulte PJ, O'Brien E, Whellan DJ, Pina IL, Kitzman DW, Lee KL, O'Connor CM, Felker GM. Clinical implications of chronic heart failure phenotypes defined by cluster analysis. *J Am Coll Cardiol*. 2014;64:1765-1774
23. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, Bonow RO, Huang CC, Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation*. 2015;131:269-279
24. Desai AS, Claggett B, Pfeffer MA, Bello N, Finn PV, Granger CB, McMurray JJ, Pocock S, Swedberg K, Yusuf S, Solomon SD. Influence of hospitalization for cardiovascular versus noncardiovascular reasons on subsequent mortality in patients with chronic heart failure across the spectrum of ejection fraction. *Circulation. Heart failure*. 2014
25. Anand IS, Carson P, Galle E, Song R, Boehmer J, Ghali JK, Jaski B, Lindenfeld J, O'Connor C, Steinberg JS, Leigh J, Yong P, Kosorok MR, Feldman AM, DeMets D, Bristow MR. Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: Results from the comparison of medical therapy, pacing and defibrillation in heart failure (companion) trial. *Circulation*. 2009;119:969-977
26. Boehmer JP, Wariar R. Implanted sensors identify changes prior to and following non-cardiac hospitalizations in patients with chronic heart failure: Insights from the multisense study. *ESC Congress (Rome)*. 2016
27. Krahnke JS, Abraham WT, Adamson PB, Bourge RC, Bauman J, Ginn G, Martinez FJ, Criner GJ. Heart failure and respiratory hospitalizations are reduced in patients with heart failure and chronic obstructive pulmonary disease with the use of an implantable pulmonary artery pressure monitoring device. *Journal of cardiac failure*. 2015;21:240-249

28. Rials SJ, Hatlestad JD, Smith A, Pubbi D, Slotwiner D, Boehmer JP. Night-time elevation angle in heart failure patients indicates orthopnea and paroxysmal nocturnal dyspnea. *HFSA*. 2017:S81
29. Mayer-Schonberger V. Big data for cardiology: Novel discovery? *European heart journal*. 2016;37:996-1001
30. Solomon SD, Pfeffer MA. The future of clinical trials in cardiovascular medicine. *Circulation*. 2016;133:2662-2670
31. Al-Chekakie MO, Bao H, Jones PW, Stein KM, Marzec L, Varosy PD, Masoudi FA, Curtis JP, Akar JG. Addition of blood pressure and weight transmissions to standard remote monitoring of implantable defibrillators and its association with mortality and rehospitalization. *Circulation. Cardiovascular quality and outcomes*. 2017;10
32. Saxon LA, Hayes DL, Gilliam FR, Heidenreich PA, Day J, Seth M, Meyer TE, Jones PW, Boehmer JP. Long-term outcome after icd and crt implantation and influence of remote device follow-up: The altitude survival study. *Circulation*. 2010;122:2359-2367
33. Akar JG, Bao H, Jones P, Wang Y, Chaudhry SI, Varosy P, Masoudi FA, Stein K, Saxon LA, Curtis JP. Use of remote monitoring of newly implanted cardioverter-defibrillators: Insights from the patient related determinants of icd remote monitoring (predict rm) study. *Circulation*. 2013;128:2372-2383
34. Innovator research (https://www.Resdac.Org/cms-data/request/innovator-research).2017

24 Abbreviations and Definitions

24.1 Abbreviations

Abbreviations are shown in Table 24-1.

Table 24-1: Abbreviations

Abbreviation/Acronym	Term
AE	Adverse Event
ASADE	Anticipated serious adverse device effect
ATR	Atrial Tracking Recovery
BNP	B-Type Natriuretic Peptide
BSC	Boston Scientific Corporation
CA	Competent Authority
CHF	Congestive Heart Failure
CMS	Center for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Clinical Research Organization
CRT-D	Cardiac Resynchronization Therapy-Defibrillator
DD	Device Deficiency
EC	Ethics Committee

Table 24-1: Abbreviations

Abbreviation/Acronym	Term
ECG	ECG electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ER	Emergency Room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF	Heart Failure
HFrEF	HF with reduced ejection fraction
HFpEF	HF with preserved ejection fraction
HFmEF	HF with mid-range ejection fraction
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
LAR	Legal Authorized Representative
LVEF	Left Ventricular Ejection Fraction
MEDDEV	European Medical Device Vigilance System
MultiSENSE	Evaluation of Multisensor Data in Heart Failure Patients With Implanted Devices
NT-ProBNP	NT-proB-type Natriuretic Peptide
NYHA	New York Heart Association
PA	Pulmonary Artery
PG	Pulse Generator
PMT	Pacemaker Mediated Tachycardia
PREEMPT-HF	Precision Event Monitoring of Patients with Heart Failure using HeartLogic
PRM	Programmer
RCE	Reviewable Clinical Event
REB	Research Ethics Board
ROC	Receiver Operator Curve
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAS	Statistical Analysis Software
UADE	Unanticipated Adverse Device Effects
USADE	Unanticipated Serious Adverse Device Effects
US	United States
VAD	Ventricular Assist Device
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

24.2 Definitions

Terms are defined in Table 24-2

Table 24-2: Definitions

Term	Definition
HeartLogic	HeartLogic is a diagnostic tool that includes a composite index monitored over time designed to deliver proactive alerts of worsening heart failure to clinicians.
LATITUDE	Consists of a patient communicator for transmitting device data, weight scale and blood pressure monitor, and a website for clinicians to review data
MEDDEV	European directive on medical devices
RAVE	The electronic data base used for the clinical trial
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records or certified copies).
Source documents	Original documents, data, and records

25 Appendix

25.1 Data Collection Requirements for Demographics, Cardiac Disease History, Physical Assessment and Blood Labs

Demographics	Age
	Gender
	Race and Ethnicity
	Height
	Smoking history
	Socioeconomic status
Cardiac Disease History	Worsening HF hospitalization history
	LVEF
	NYHA or ACC/AHA HF stage
	Ischemic
	Dilated cardiomyopathy
	Idiopathic cardiomyopathy
	Valvular disease
	Valvular surgery
	Thoracic surgery
	Myocardial infarction
	CABG
	Atrial fibrillation
Comorbidities	Hypertension
	Hyperlipidemia
	Diabetes
	Anemia
	Chronic obstructive pulmonary disease
	Hepatic disease
	Cerebrovascular disease
	Peripheral vascular disease
	Pulmonary hypertension and type
	Renal dysfunction
	Depression
	Sleep apnea and AHI classification

Physical assessment	Weight
	BP (systolic and diastolic)
	Dyspnea on exertion
	Dyspnea at rest
	Orthopnea
	Paroxysmal nocturnal dyspnea
	Pulmonary rales
	Jugular venous pressure
	Hepatojugular reflux
	3rd heart sound
	4th heart sound
	Mitral regurgitation
	Tricuspid regurgitation
	Peripheral edema
Blood labs	Natriuretic peptides (NT-proBNP or BNP)
	Creatinine

25.2 PI Classification of Primary Organ Cause

Cardiac	Heart Failure
	MI
	Acute Coronary Syndrome
	Arrhythmia
	Complication of cardiac medication
	Cardiac Procedure
	Other (specify)
Non-Cardiac	Pulmonary
	Renal
	Diabetes
	Infection
	Non-cardiac chest pain
	Gastrointestinal
	Genitourinary
	Vascular
	Neurologic
	Orthopedic
	Oncologic
	Complication of non-cardiac medication
	Other (specify)