Multiple c**A**rdiac se**N**sors for m**A**na**GE**ment of **H**eart **F**ailure (**MANAGE-HF**)

Post-Approval Study of HeartLogic™ Heart Failure Diagnostics

CLINICAL INVESTIGATION PLAN

C2041

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Revision History

Revision Number	**Release Date**	**Template number and version**	**Section**	**Change**	**Reason for Change**
92076904 Version A	February 6, 2017	Rev/Ver AH	NA	NA	Initial Release
92076904 Version B	April 6, 2017	Rev/Ver AH	Throughout	Fixed typos, added clarifications,	Corrections
92076904 Version B	April 6, 2017	Rev/Ver AH	Synopsis	Multiple	Updated content to reflect changes in the protocol
92076904 Version B	April 6, 2017	Rev/Ver AH	Synopsis	Added text: "A detailed description of HeartLogic is available in the HeartLogic Technical Guide which is available through the Boston Scientific website."	Clarification
92076904 Version B	April 6, 2017	Rev/Ver AH	Section 6	Deleted "unscheduled from "Additional unscheduled visits will occur in response to HeartLogic alerts"	Additional visits may include unscheduled and well as scheduled visits
92076904 Version B	April 6, 2017	Rev/Ver AH	Section 6	Modified "After 200th Phase I subject completes 12 month visit" to read as "After Phase I subjects complete 12	Clarify all actively enrolled phase I subjects will be exited.

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				month visit"	
92076904 Version B	April 6, 2017	Rev/Ver AH	Section 8.2	Added "Boston Scientific will communicate to the sites the strategy for exiting subjects at the end of the study."	Strategy for exiting patients at the end of the study clarified
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 6.1, Table 9-1, Section 9.3.2,	Modified "Baseline visit (minimum 45 days of heart failure sensor data collection)" to read as "Baseline visit (minimum 45 days of heart failure sensor data collection; maximum 4 mo from Enrolment)"	Added upper bound of 4 months
92076904 Version B	April 6, 2017	Rev/Ver AH	Section 9.3.3.1	Added text: "An in-clinic visit may substitute for the phone call, but the CRF must still be completed per protocol."	Clarification
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-1,	Modified "Informed consent process (subject must meet inclusion and exclusion	Corrected to clarify that eligibility criteria requires that the Patient

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Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				criteria)" to read as "Informed consent process (subject must meet eligibility criteria)"	meets the inclusion and do not meet the exclusion criteria
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-1,	Modified "LATITUDE and HeartLogic enabled confirmation" to read as "LATITUDE and heart failure sensors enabled confirmation, including weight and blood pressure home unit	Clarified LATITUDE sensors information
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-1,	Modified "Demographics, Cardiac Disease History, Comorbidities" to read as "Demographics, and Medical History"	Medical history will include cardiac disease and comorbidities
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-1,	Deleted "Medical History" and replaced with "Physical Exam"	Medical History is combined with "Demographics " and add requirement of 'Physical exam"

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Revision Number	**Release Date**	**Template number and version**	**Section**	**Change**	**Reason for Change**
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-1,	Separated "Heart failure patient assessment" from "NYHA Class"	Data collection requirements are different for various visits
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-1,	Added "HeartLogic Index Programming"	Mandate collection of data during various visits
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-1,	Added Blood chemistry and EKG as a part of standard of care medical evaluation	Provide option for reporting of blood labs and EKG done as part of standard of care evaluation
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-1,	Added EQ-5D-5L	Added as an additional quality of life measure that is commonly used in Europe.
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-1,	Added Oxygen Saturation	Additional data item
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-1, 9.4.1	Deleted "heart failure" from "Qualified heart failure treatment upon alert"	Clarification that qualified treatment may include other conditions that might trigger HeartLogic alert
92076904 Version B	April 6, 2017	Rev/Ver AH	Figure 9.1	Modified figure	Consistency with protocol
92076904 Version B	April 6, 2017	Rev/Ver AH	9.3	Changes to follow up visits	Updated section to align with

Revision History

Revision Number	**Release Date**	**Template number and version**	**Section**	**Change**	**Reason for Change**
					modification in Table 9.1
92076904 Version B	April 6, 2017	Rev/Ver AH	9.3	Added "The alerts will be turned on by Boston Scientific and that data will begin to transmit through the patient bedside communicator once you have completed the CRF for the baseline visit. If you have questions, please contact your Boston Scientific representative."	Clarified the HeartLogic alert can only be turned on by Boston Scientific.
92076904 Version B	April 6, 2017	Rev/Ver AH	Section 9.4	Modified HeartLogic Alert Action Visit	The process for HeartLogic Alert visit described in detail
92076904 Version B	April 6, 2017	Rev/Ver AH	Figure 9.2	Modified HeartLogic Alert Management Process figure	Consistency with protocol and to avoid deviations due to patient non-compliance with visits and phone calls
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9.4	Data Collection at HeartLogic Alert Action Visit	Updated table to align with Table 9.1

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Revision Number	**Release Date**	**Template number and version**	**Section**	**Change**	**Reason for Change**
92076904 Version B	April 6, 2017	Rev/Ver AH	Section 9.5	The disc or flash drive should be kept in the subject's MANAGE-HF study binder at the investigative site, and copy should be mailed to the sponsor.	Instruction for back up data collection if LATITUDE transmissions are not available
92076904 Version B	April 6, 2017	Rev/Ver AH	Table 9-5	Updated Source Documentation Requirements	Updated to align with study requirements
92076904 Version B	April 6, 2017	Rev/Ver AH	Section 17.2	Added reference Physician's Technical Manuals for the study devices	Clarification regarding Anticipated Adverse Device Effects
92125179 Version C	May 25, 2017	Rev/Ver AH	Section 1	Typo	Requirements was misspelled
92125179 Version C	May 25, 2017	Rev/Ver AH	Section 2, Section 6, Section 6.1	Typos	Section 2: Added parentheses; "Hospitalizations" misspelled Section 6: "initiate" were misspelled Section 6.1: concluded was missing the "ed"
92125179 Version C	May 25, 2017	Rev/Ver AH	Section 9.1	Cross reference error	Removed duplicate reference to Table 9-1

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Revision Number	**Release Date**	**Template number and version**	**Section**	**Change**	**Reason for Change**
92125179 Version C	May 25, 2017	Rev/Ver AH	Sections 9.3.2.1 and 9.3.2.2	Added text: "After the baseline visit the nominal setting may be changed with appropriate documentation and approval from Boston Scientific."	Clarification of the programmability of the HeartLogic feature.
92125179 Version C	May 25, 2017	Rev/Ver AH	Sections 9.3.3.1, 9.3.3.2, 9.3.4.1, 9.3.4.2, Table 9.4	Added text: "if changed from nominal setting of 16"	Clarification of the programmability of the HeartLogic feature.
92125179 Version C	May 25, 2017	Rev/Ver AH	Table 9.1	Broken cross-reference link to section 9.3.4.1; removed text "screening form"; added "in-clinic only" for physical exam upon alerts	Administrative and clarification
92125179 Version C	May 25, 2017	Rev/Ver AH	Sections 9.3.2.1, 9.3.2.2 and 9.3.3.2	Formatting (added a hard return to create a bullet point)	Administrative
92125179 Version C	May 25, 2017	Rev/Ver AH	Section 9.3.2.1	Added the text "optional" for EKG and blood chemistry	Consistent with Table 9.1
92125179 Version C	May 25, 2017	Rev/Ver AH	Section 9.3.4.1	Added "in-clinic only" for physical exam	Consistent with Table 9.1

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Revision Number	**Release Date**	**Template number and version**	**Section**	**Change**	**Reason for Change**
92125179 Version C	May 25, 2017	Rev/Ver AH	Section 9.3.4.2	Typo	Deficiencies was misspelled
92125179 Version C	May 25, 2017	Rev/Ver AH	Section 9.4.1	Added this text: "of the same class" and deleted "e.g. a second b-blocker"	Clarification
92125179 Version C	May 25, 2017	Rev/Ver AH	Section 9.4	Removed the word "the"	Duplicate word
92125179 Version C	May 25, 2017	Rev/Ver AH	Section 9.5	Added the word "be"	Administrative
92125179 Version C	May 25, 2017	Rev/Ver AH	Section 9.6	Added "endpoint"	Clarification as to what study data are blinded
92125179 Version D	Oct 31, 2017	Rev/Ver AH	Contact Information	Updated clinical contact information	Reflect personnel change
92125179 Version D	Oct 31, 2017	Rev/Ver AH	Section 1.0	Changed planned sites for Phase I from"40" to "50"	Correction to reflect increase in number of potential sites
92125179 Version D	Oct 31, 2017	Rev/Ver AH	Sections 9.3.2.1, 9.3.2.2, 9.4.1 and 9.7 Tables 9-1 and 9-3	Clarified text and formatting; removed incorrect line in table referring to a "42 month" visit	Clarifications and Typos
92125179 Version E	Feb 1, 2018	Rev/Ver AH	Section 6.4	Clarified timing of randomization for Phase II	Clarification
92125179 Version E	Feb 1, 2018	Rev/Ver AH	Sections 9.3.2.1, 9.3.2.2, 9.3.3.2, 9.7	Clarified requirement of posture sensor calibration as an attempt to	Clarification of the possibility of an unsuccessful calibration

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Revision Number	**Release Date**	**Template number and version**	**Section**	**Change**	**Reason for Change**
				calibrate	
92125179 Version E	Feb 1, 2018	Rev/Ver AH	9.3.5	Clarified that alert configuration at the end of study is at the discretion of the clinician	Clarification
92125179 Version E	Feb 1, 2018	Rev/Ver AH	9.5	Added language to further clarify the types of device interrogation that may be used	Clarification
92125179 Version E	Feb 1, 2018	Rev/Ver AH	18.7	Added the same language that is in Section 9.5 to clarify device interrogation upon death	Clarification
92125179 Version E	Feb 1, 2018	Rev/Ver AH	9.3.4.2	Clarification that documentation only needs to occur if there are changes in medications, programming or reportable adverse events or device deficiencies	Clarification

1 Protocol Synopsis

Multiple cArdiac seNsors for mAnaGEment of Heart Failure (MANAGE-HF)	
Study Objective(s)	MANAGE–HF has two objectives and will fulfill the requirements of the post-approval study: 1. To evaluate and optimize HeartLogic™ Heart Failure Diagnostics (called HeartLogic from here on) clinical integration and the alert management process (Phase I) 2. To evaluate HeartLogic in regards to patient outcomes of death and heart failure hospitalizations (Phase II)
Planned Indication(s) for Use	The study will use commercially approved CRT-D and ICD devices that have the HeartLogic feature. Only patients that meet the eligibility criteria will be eligible to enroll in the study.
Test Device	Phases I and II: ICD and CRT-D devices with HeartLogic alerts turned ON
Control Device	Phase I: Not applicable; Single arm Phase II: ICD and CRT-D devices with HeartLogic alerts turned OFF
Device Sizes	All devices range in size from 28.5-32.5 cc (volume) depending on the specific model
Study Design	The MANAGE-HF study is a multi-center, global, prospective, open label, multi-phase trial. Phase I will be non-randomized. Phase II will be randomized.
Planned Number of Subjects	Between 1700 and 2700 subjects will be enrolled in the study. • Phase I: Up to 200 subjects • Phase II: 1500 to 2500 subjects
Planned Number of Investigational Sites / Countries	Phase I: Up to 50 sites globally (at least 50% of the subjects coming from the US). Phase II: Up to 120 sites globally (at least 50% of the subjects coming from the US)
Primary Endpoint(s)	The primary endpoint will evaluate all-cause mortality and heart failure hospitalizations, comparing Phase II patients randomized to HeartLogic Alerts ON vs. HeartLogic Alerts OFF. Phase I patients will not count toward the primary endpoint.

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Additional Endpoints	The following secondary endpoints will be evaluated, comparing the HeartLogic Alerts ON vs. Alerts OFF: • Freedom from all-cause mortality • Freedom from heart failure hospitalizations (time-to-first event) • Risk of multiple heart failure hospitalizations • Change in NYHA classification • Change in Quality of Life • Change in NT-proBNP • Change in Medication Status Phase I patients will not count toward the secondary endpoints.
Method of Assigning Subjects to Treatment	Phase I: • Single arm • All subjects will be assigned to HeartLogic Alerts ON starting at the baseline visit. Phase II: • 1:1 randomization will occur in the electronic data capture (EDC) system. • Subjects will be randomized at the baseline visit to HeartLogic Alerts ON (treatment group) or HeartLogic Alerts OFF (control group). • Randomization will be stratified by investigational center and device type (ICD or CRT-D)

Follow-up Schedule	The required protocol study visits are as follows:
	• Enrollment Visit
	• Baseline Visit
	• Scheduled follow-up visits
	  ○ Annual Phone Calls (6, 18, 30, 42 months, … from baseline visit)
	  ○ Annual In-Clinic (12, 24, 36, 48 months, … from baseline visit)
	• Additional Follow-up Visits
	  ○ HeartLogic Alert Action Visit
	  ○ Additional Subject Interactions (i.e., Not in Response to HeartLogic Alerts)
	• End of Study

Multiple cArdiac seNsors for mAnaGEment of Heart Failure (MANAGE-HF)	
	Phase I subjects will be followed until the last Phase I subject has completed the 12 month visit, or upon recommendation from Steering Committee. Phase II subjects will be followed until the necessary number of primary endpoint events has been accrued.
Study Duration	The trial duration is estimated to be up to 7 years from 1st enrollment in Phase I to study closure in Phase II.
Inclusion Criteria	1. Subject is age 18 or above, or of legal age to give informed consent 2. Implanted with an CRT-D or ICD device that has HeartLogic 3. Current symptomatic heart failure or NYHA Class II or III at the time of enrollment 4. Remotely monitored by LATITUDE NXT 5.0 (or future versions) 5. Willing and capable of participating in all study visits and complying with medication/treatment requirements associated with this clinical study at an approved clinical study center. 6. Meet at least ***one*** of the three following conditions: • At least one documented hospitalization with a primary diagnosis of worsening for heart failure during the 12 months prior to enrollment; or • Unscheduled outpatient visit with IV diuretic therapy for acute worsening of HF during 90 days prior to enrollment; or • NT-proBNP greater than 600 pg/mL or BNP greater than 150 pg/mL at any time during 90 days prior to enrollment
Key Exclusion Criteria	1. The subject is unable to sign or refuses to sign the patient informed consent 2. Symptomatic heart failure at rest or NYHA Class IV at the time of enrollment 3. The subject is implanted with unipolar RA or RV leads 4. Subject has received or is scheduled to receive a heart transplant or ventricular assist device within the next 6 months

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	5. Subject is pregnant or planning to become pregnant during the study 6. Subject is enrolled in any other concurrent study (without prior written approval from BSC, excluding registries) 7. GFR <25 mL/min who are non-responsive to diuretic therapy or are on chronic renal dialysis 8. Regularly scheduled IV heart failure therapy (e.g. inotropes or diuretics) 9. A life expectancy of less than 12 months per clinician discretion 10. APPLICABLE TO PHASE II ONLY: Subject enrolled in Phase I of MANAGE-HF 11. APPLICABLE TO PHASE II ONLY: Subject has been managed with HeartLogic Alerts ON at anytime within the past 6 months.
Statistical Methods	
Primary Statistical Hypothesis	Phase I: There are no formal hypotheses or endpoints in Phase I Phase II: The following set of hypotheses will be evaluated: H_0: The risk of mortality and heart failure hospitalization for the HeartLogic group will be greater than or equal to the risk for the control group H_A: The risk of mortality and heart failure hospitalization for the HeartLogic group will be less than the risk for the control group
Statistical Test Method	Statistical methodologies used to evaluate the primary endpoint are described in a separate Statistical Analysis Plan that is not a part of this study protocol.
Sample Size Parameters	Phase I: Up to 200 enrolled subjects are required in Phase I to build critical knowledge regarding the clinical integration of HeartLogic and the alert management process. Phase II: An event-driven design will be used. Between 1500 and 2500 subjects will be enrolled in Phase II to accrue the necessary number of primary endpoint events. Parameters used to calculate the sample size

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	range are described in a separate Statistical Analysis Plan. Final sample size will be determined during the study using a sample size re-estimation interim analysis.

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2 Introduction

Heart failure (HF) hospitalizations are associated with high mortality, readmission, and economic burden, with a direct cost of over $20 billion attributed [1]. Monitoring of weight and symptoms is encouraged [2] but hasn't been shown to reduce hospitalizations [3]. Thus, new diagnostic tools are needed to decrease cost and improve patient outcomes.

Improvement of patient outcomes with the help of a HF diagnostic rests on two crucial components: 1) the HF diagnostic must be able to detect HF worsening on top of standard clinical care; 2) the HF diagnostic must be properly integrated into clinical workflow.

Cardiac implantable electronic devices (Implantable Cardioverter Defibrillators (ICD), cardiac resynchronization therapy (CRT)) with sensors have been used to develop HF diagnostics which indicate early changes leading up to hospitalizations [4, 5]. Yet studies using these diagnostics have failed to reach endpoints on sensitivity and false positive rate, and have not shown reductions in HF events [6-8]. Most of these studies used single sensors which make prediction of outcomes challenging in a complex condition such as heart failure [9-11]. A more robust approach has been to combine information from a diverse set of sensors to develop an algorithm and alert for detecting worsening heart failure [12].

However, alert algorithm performance alone is not sufficient. The alerts must be translated to drive clinical action in order to improve patient outcomes. Initial tele-monitoring trials based on single sensors demonstrated that compliance with algorithm-generated alerts was often inadequate [3, 4] failing to give the diagnostic an opportunity to add benefit, or even leading to worsened patient outcomes [6]. Given the significant variation in HF care pathways [13] and remote monitoring utilization[14], subsequent investigations that have more closely integrated diagnostics with clinical practice have shown measurable and sustained impact on patient outcomes [7, 15, 16]. Additionally, data recently presented from a retrospective sub-analysis of the CHAMPION trial showed that the HF hospitalization rate in patients in whom interventions were based only on clinical findings (e.g. signs and symptoms) was not different from control, whereas patients in whom interventions were influenced by pulmonary pressure readings, guided by the study specific clinical intervention guidelines, had a 67% reduction in HF hospitalization rate [17]. Recently presented data from the REM-HF study [18], which included manual review of multiple individual device parameters also failed to show improvement in patient outcomes.

Boston Scientific has developed a high-performing algorithm which detects early onset of HF events. The development was performed via MultiSENSE study [12]. The MultiSENSE (Multisensor Chronic Evaluations in Ambulatory Heart Failure Patients) was a single arm, multi-center, observational, non-randomized study designed to collect chronic ambulatory data from multiple sensors available to implanted cardiac devices in order to develop an algorithm for the early detection of worsening Heart Failure. The study was conducted in 93 centers worldwide and designed to enroll up to a total of 990 patients with implanted COGNIS® CRT-D devices. Upon enrollment, the patient's CRT-D device was converted

into Sensor Research Device (SRD-1) by downloading investigational software to enable the collection of sensor data without affecting the device hardware or the delivered therapy. Patients were followed for up to a year. The sensor data were continuously collected by the device. The sensor data included metrics derived from accelerometer-based first and third heart sounds, thoracic impedance, respiration rate, relative tidal volume, heart rate, and patient activity. In addition to device-based sensor data, clinical data was captured. The clinical data included clinical assessments and measurements required by the MultiSENSE study that were entered by site personnel. Event adjudication was performed by an independent clinical events committee.

A subset of 400 patients was sequestered (Test Set) and the set of the remaining 500 patients was used to develop the HeartLogic algorithm - a multi-sensor algorithm for detection of usable HF events. Usable HF events were defined as HF hospitalization or outpatient intravenous decongestive therapy with sufficient sensor data available. The algorithm was then validated on the Test Set with predefined endpoints for sensitivity and unexplained alert rate. The results showed that the HeartLogic algorithm passed pre-specified endpoints and effectively detected usable HF events with a median early notification of 34 days, a sensitivity of 70%, and an unexplained alert rate of 1.46 per patient per year.

HeartLogic algorithm and its supporting sensors, referred to as HeartLogic Heart Failure Diagnostic Service, will be available in the RESONATE family of pulse generators, including CRT-Ds and ICDs. MANAGE-HF will be the first prospective post-market study to evaluate HeartLogic integration, utilization, and impact on heart failure hospitalization and patient mortality. Phase I will be used to develop an alert management and treatment process. The importance of developing the alert management and treatment process is evident from previous clinical trials. Proper clinical utilization of a HF diagnostic, in addition to its performance, is crucial for improving patient outcomes [3, 6-8, 13-16, 19]. Phase II will then test HeartLogic in reducing mortality and heart failure hospitalizations by comparing patients that have HeartLogic Heart Failure Diagnostic Service ON vs. HeartLogic Heart Failure Diagnostic Service OFF.

Phase II of the MANAGE-HF trial will begin after the primary objective of Phase I – to evaluate and optimize HeartLogic clinical integration and the alert management process – has been fulfilled. Boston Scientific will communicate to sites the authorization to initiate enrollment into Phase II. Subjects enrolled in Phase I will be ineligible to enroll in Phase II.

3 Device and HeartLogic Feature Description

Both Phase I and Phase II of the MANAGE-HF study will use device models that are commercially approved and have HeartLogic. The feature being studied in MANAGE-HF is called HeartLogic Heart Failure Diagnostic Service (or simply HeartLogic). A detailed

description of HeartLogic is available in the HeartLogic Technical Guide which is available through the Boston Scientific website.

The HeartLogic feature is comprised of a composite trend called the HeartLogic Index and a configurable yellow alert. These data and alerts are delivered to the clinical team and to Boston Scientific via the LATITUDE™ remote monitoring system. HeartLogic has been validated as a diagnostic tool to detect gradual worsening of heart failure over days or weeks using multiple physiologic measurements [12].

The HeartLogic Index aggregates measurements from multiple device-based sensors (Heart Sounds, Thoracic Impedance, Respiration, and Night Heart Rate) and reflects changes over time in the subject's sensor trend data from their respective baseline values. HeartLogic provides additive information for clinicians to use in context with standard-of-care patient treatment. However, it should not replace standard-of-care treatment.

There are three HeartLogic states defined in this protocol – Alerts On, Alerts Off and Sensors Disabled. Descriptions of each state are found in the table below.

Table 3-1: HeartLogic State

State	HeartLogic Sensors Enabled and Collecting Data	Access to HeartLogic Index	Access to HeartLogic Alerts
HeartLogic Alerts ON	Yes	Yes	Yes
HeartLogic Alerts OFF	Yes	No	No
HeartLogic Disabled	No	No	No

The CRT-D or ICD device, along with its associated leads, constitutes the implantable portion of the system. The external portion of the system includes the commercially available LATITUDE NXT 5.0 System (or future versions) and the Model 3120 Programmer Recorder Monitor (or future versions). The external portion of the system allows interrogation and programming of the PG, as well as access to the PG's diagnostic features.

Communication between the internal and external portions of the system is conducted through a handheld wand and/or wireless telemetry. Data are then transmitted to the clinician care team. The complete LATITUDE NXT 5.0 system is shown in Figure 3-1. Data will automatically be uploaded and transmitted to the clinician for review on the scheduled interval. When the HeartLogic alert threshold is met or exceeded, a yellow alert is generated which triggers the health care professional to review the data and take appropriate action.

Boston Scientific has performed safety risk management activities, design verification and design validation testing to demonstrate that devices with the HeartLogic feature 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.

Figure 3-1: LATITUDE NXT 5.0 System

4 Study Objectives

There are two objectives of the MANAGE-HF multi-phase study :

- Phase I: To evaluate and optimize HeartLogic clinical integration and alert management process.
- Phase II: To evaluate HeartLogic in regards to patient outcomes of death and heart failure hospitalizations. Additionally, Phase II will fulfill regulatory requirements of post-approval study for HeartLogic.

Phase II of the MANAGE-HF trial will begin following completion of Phase I. Subjects enrolled in Phase I will be ineligible to enroll in Phase II.

5 Study Endpoints

The primary endpoint will assess the composite of all-cause mortality and heart failure hospitalizations collected in Phase II of the trial, comparing HeartLogic Alerts ON vs. Alerts OFF.

The following secondary endpoints will be evaluated using data collected during Phase II, comparing the HeartLogic Alerts ON vs. Alerts OFF:

- Freedom from all-cause mortality

- Freedom from heart failure hospitalizations (time to first event)
- Change in NYHA classification
- Change in Quality of Life
- Change in NT-proBNP
- Change in Medication Status

All randomized subjects in Phase II will be eligible for inclusion in the analyses of all study endpoints. No data from Phase I will be included in the analysis for the primary or secondary endpoints.

6 Study Design

MANAGE-HF is a multi-center, global, prospective, open label, multi-phase trial. Phase I will be non-randomized and a single arm. Phase II will be randomized in a 1:1 allocation to HeartLogic Alerts ON vs. Alerts OFF. Phase II will begin after the primary objective of Phase I – to evaluate and optimize HeartLogic clinical integration and the alert management process – has been fulfilled. Boston Scientific will communicate to sites the authorization to initiate enrollment into Phase II.

Eligible subjects in Phase I and Phase II will already be implanted with a device that contains HeartLogic, and must meet the inclusion and exclusion criteria as described in Sections 7.2 and 7.3. Subjects in Phase I are ineligible to be enrolled in Phase II.

The follow-up schedules are identical for all subjects in Phases I and II. Only the point of study exit differs between the phases. Follow-up for subjects in each phase are shown in the table below. Additional visits will occur in response to HeartLogic alerts.

Table 6-1: Scheduled Visits

Visit	Window	Phase I	Phase II
Enrollment	After device implant	X	X
Baseline	At least 45 days of heart failure sensor data collection. At most 4 months from enrollment.	X	X
Phone call	180 ± 30 days from baseline 545 ± 30 days from baseline 910 ± 30 days from baseline 1275 ± 30 days from baseline 1640 ± 30 days from baseline	X[1]	X[2]
Annual visit	365 ± 30 days from baseline 730 ± 30 days from baseline 1095 ± 30 days from baseline 1460 ± 30 days from baseline 1825 ± 30 days from baseline	X[1]	X[2]
Subject Study Exit		After Phase I subjects complete 12 month visit[3]	After necessary number of primary endpoint events has been accrued

1. Follow-ups continue for Phase I subjects through the end of Phase I
2. Follow-ups continue for Phase II subjects through the end of Phase II
3. Phase I may complete early upon recommendation from Steering Committee

After a minimum of 45 days of heart failure sensor data collection, all subjects (Phases I and II) will be evaluated at a baseline visit and will be followed annually for in-clinic visits. In addition, a 6 month phone call for all subjects will be placed in between annual visits. Subjects in Phases I and II will continue to be seen until the study phase is completed. Phase I ends when the final subject completes the 12 month follow-up visit, or upon recommendation from the Steering Committee. Phase II ends when the necessary number of primary endpoint events has been accrued. A detailed flow-chart of the study visits can be found in Section 9.

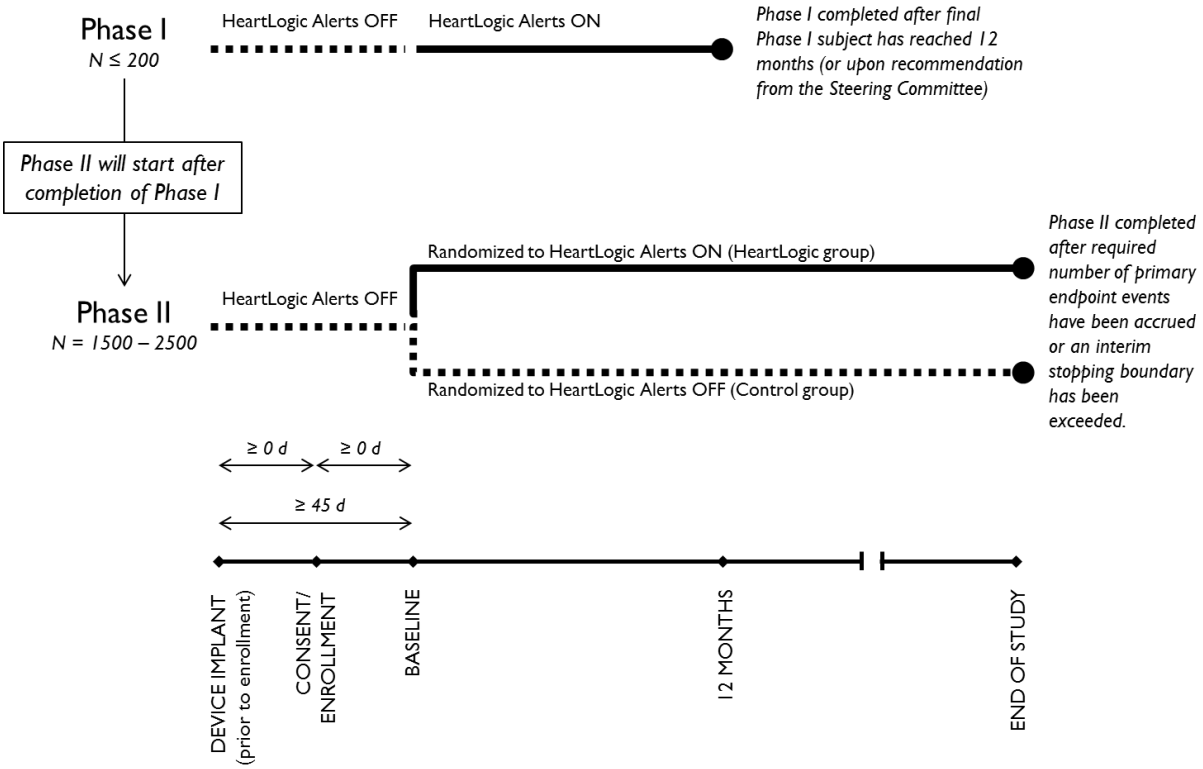
6.1 Scale and Duration

The study will enroll up to a total of 2700 subjects across two study phases. Up to 200 subjects will be enrolled in Phase I in order to build critical knowledge about the clinical integration of HeartLogic and the alert management process. A minimum of 50% of the subjects in Phase I will come from US sites. Phase I will be concluded upon completion of the last Phase I subject's 12 month follow-up, or upon recommendation from the Steering Committee that the study should progress to Phase II. Subjects in Phase I will be ineligible to enroll in Phase II.

Up to 2500 subjects will be enrolled in Phase II to sufficiently power the primary endpoint in Phase II. A minimum of 50% of the subjects in Phase II will come from US sites. Follow-up for Phase II will continue until a pre-specified stopping boundary has been achieved or the necessary number of primary endpoint events has been accrued. Details of the pre-specified Primary Endpoint are defined in Section 10.1 and in a separate Statistical Analysis Plan. Phase I events will not count toward the primary endpoint of the study.

Figure 6-1 illustrates the study flow of both phases of the MANAGE-HF trial. Enrollment durations of Phases I and II are expected to last 15 and 24 months, respectively. A gap in time between completion of Phase I enrollments and initiation of Phase II enrollments is anticipated as Phase I patients may be followed until the final patient finishes the 12 month visit.

Figure 6-1: MANAGE-HF Study Design



6.2 Treatment Assignment

The MANAGE-HF post-approval study is a multi-phase study. Phase I is single arm and open label; all enrolled Phase I subjects will be actively managed with HeartLogic alerts. Subjects in Phase I will be ineligible to be enrolled in Phase II.

Phase II is randomized, controlled, two arm and open label. Phase II subjects will be randomized to HeartLogic Index and Alerts ON or HeartLogic Index and Alerts OFF using a 1:1 allocation. Randomization will be stratified by investigational center and device type (ICD or CRT-D).

The devices are commercially approved for use in patients indicated for an ICD or CRT-D. However, there are specific study criteria that are identical for both phases of MANAGE-HF that must be met to be eligible for enrollment (Section 7).

6.2.1 Treatment and Control

Phase I:

- All subjects in Phase I will be implanted with ICD or CRT-D devices that have the HeartLogic feature.
- HeartLogic Index and Alerts will be ON for all subjects enrolled in Phase I starting at the baseline visit.
- There will be no control subjects in Phase I.
- Subjects enrolled in Phase I will be ineligible for Phase II.
- Phase I data does not count toward Phase II endpoints.

Phase II:

- All subjects in Phase II will be implanted with ICD or CRT-D devices that have the HeartLogic feature.
- Subjects enrolled in Phase II will be randomized to HeartLogic Alerts ON (treatment) or HeartLogic Alerts OFF (control).
- Phase II subjects randomized to the treatment arm will be actively managed with the HeartLogic Alerts ON and the subjects randomized to the control arm will be managed with HeartLogic Alerts OFF.
- Randomized subjects in Phase II are eligible to contribute data to all endpoint analyses.

6.3 Justification for the Study Design

The multi-phase nature of MANAGE-HF is required to evaluate the multiple objectives of the trial. The use of a single arm in Phase I was chosen as the most appropriate and efficient

design to evaluate and optimize HeartLogic clinical integration and alert management process. Learnings from Phase I will be incorporated into Phase II and reflected in a separate statistical analysis plan that will be approved by Boston Scientific and the FDA. The use of a randomized controlled design in Phase II was chosen to minimize bias in the findings, and is to the gold-standard to demonstrate a true treatment effect.

6.4 Transition from Phase I to Phase II

It is anticipated that 200 subjects followed for a minimum of 12 months is required to fulfill the objectives of Phase I. After the final Phase I subject has completed their 12 month visit, or upon recommendation from the Steering Committee, Boston Scientific will notify sites to begin exiting Phase I subjects from the study.

Boston Scientific will notify sites of Phase II initiation, at which time all approved-to-enroll sites may begin enrolling Phase II subjects. Phase I subjects are ineligible to participate in Phase II. The request for randomization of subjects will occur at the baseline visit for Phase II subjects.

7 Subject Selection

7.1 Study Population and Eligibility

Eligibility for study enrollment is determined by specific inclusion and exclusion criteria as described in Sections 7.2 and 7.3.

7.2 Inclusion Criteria

Inclusion criteria are identical for Phases I and II. Subjects who meet all of the following criteria (see Table 7-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 7.3) is met.

Table 7-1: Inclusion Criteria

CI1	Subject is age 18 or above, or of legal age to give informed consent
CI2	Implanted with an CRT-D or ICD device that has HeartLogic
CI3	Current symptomatic heart failure or NYHA Class II or III at the time of enrollment
CI4	Remotely monitored by LATITUDE NXT 5.0 (or future versions)
CI5	Willing and capable of participating in all study visits and complying with medication/treatment requirements associated with this clinical study at an approved clinical study center.
CI6	Meet at least ***one*** of the three following conditions: • At least one documented hospitalization with a primary diagnosis of worsening for heart failure during the 12 months prior to enrollment; **or** • Unscheduled outpatient visit with IV diuretic therapy for acute worsening of HF during 90 days prior to enrollment; **or** • NT-proBNP greater than 600 pg/mL or BNP greater than 150 pg/mL at any time during 90 days prior to enrollment

7.3 Exclusion Criteria

All exclusion criteria apply to subjects in Phases I and II, except for criteria 10 and 11, which are applicable to Phase II subjects only. Subjects who meet any one of the following criteria (see Table 7-2) will be excluded from this clinical study.

Table 7-2: Exclusion Criteria

CE1	The subject is unable to sign or refuses to sign the patient informed consent
CE2	Symptomatic heart failure at rest or NYHA Class IV at the time of enrollment
CE3	The subject is implanted with unipolar RA or RV leads
CE4	Subject has received or is scheduled to receive a heart transplant or ventricular assist device within the next 6 months
CE5	Subject is pregnant or planning to become pregnant during the study
CE6	Subject is enrolled in any other concurrent study (without prior written approval from BSC, excluding registries)
CE7	GFR <25 mL/min who are non-responsive to diuretic therapy or are on chronic renal dialysis
CE8	Regularly scheduled IV heart failure therapy (e.g. inotropes or diuretics)
CE9	A life expectancy of less than 12 months per clinician discretion
CE10	APPLICABLE TO PHASE II ONLY: Subject enrolled in Phase I of MANAGE-HF
CE11	APPLICABLE TO PHASE II ONLY: Subject has been managed with HeartLogic Alerts ON at anytime within the past 6 months.
Abbreviations: RA=right atrial; RV=right ventricle	

8 Subject Accountability

8.1 Point of Enrollment

All details in this section apply to subjects in Phases I and II.

Subjects are considered enrolled at the point when they sign and date the informed consent form. Confirmation that inclusion and exclusion criteria are met must take place prior to consent. The consent may be obtained at any point in time following the implantation of the device, but not before.

8.2 Point of Study Exit

8.2.1 Study Completion

All details described in this section apply to subjects in Phases I and II.

Phase I:
After the final Phase I subject has completed their 12 month visit, or upon recommendation from the Steering Committee, Boston Scientific will notify sites to begin exiting Phase I subjects from the study. Boston Scientific will communicate to the sites the strategy for exiting subjects at the end of the study.

Phase II:
After the necessary number of primary endpoint events has been accrued, Boston Scientific will notify sites to begin exiting Phase II subjects from the study.

8.2.2 Withdrawal

All details described in this section apply to subjects in Phases I and II.

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 investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

A subject who becomes inactive in the study as defined by clinician recommendation, subject choice, has their device explanted, or is lost to follow-up will be classified as "Withdrawal". All applicable case report forms up to the point of withdrawal and a "Subject Status" form must be completed. Investigators who have "lost-to-follow-up" subjects should have at least three documented attempts to contact them prior to completion of the "Patient Status" form.

After a subject has been withdrawn from the study or after a subject has withdrawn his/her consent, for whatever reason, additional data may no longer be collected after the point of withdrawal, and HeartLogic alerts may be turned OFF. 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. Boston Scientific will not actively collect any information on subjects who have been withdrawn from the study after the withdrawal date. However, all post-withdrawal adverse events of which Boston Scientific is notified will be recorded in the patient file.

8.3 Enrollment Controls

Up to 2700 patients will be enrolled in MANAGE-HF – up to 200 in Phase I and up to 2500 in Phase II. A single site may not enroll more than 20 subjects in Phase I or 100 subjects in Phase II without written authorization from Boston Scientific. There are no specific limitations on gender or race.

To ensure Phase I does not exceed 200 subjects, when the study is nearing 200 enrolled subjects sites will be notified that future enrollments must be approved by Boston Scientific. Similarly, when Phase II is nearing the desired enrollment number (between 1500 and 2500, as determined during the study via an interim sample size assessment), sites will be notified that future enrollments must be approved by Boston Scientific.

9 Study Methods

9.1 Data Collection

Details in this section apply to all subjects in Phases I and II.

The data collection schedule is shown in Table 9-1.. Details for each study visit are found in section 9.3. However, all required data elements should be entered into the electronic case report forms that are in the MANAGE-HF database in a timely manner. For HeartLogic alerts, it is imperative to adhere to the timelines for patient contact, treatment and data entry as shown in Figure 9-2 to avoid protocol deviations.

Table 9-1: Data Collection and Visit Schedule

Procedure/Assessment	Enrollment	Baseline visit (minimum 45 days of heart failure sensor data collection; maximum 4 mo from Enrolment)	Follow-up Visits				End of Study
			Annual Phone Call (6, 18, 30, 42 mo… from baseline)	Annual In-Clinic Visit (12, 24, 36, 48 mo… from baseline)[1]	HeartLogic Alert Action (phone calls and/or in-clinic visits)	Additional Subject Interactions (phone calls and/or in-clinic visits)	
Protocol Section	9.2, 9.3.1.1, 9.3.1.2	9.3.2	0	9.3.3.2	9.3.4.1, 9.4	9.3.4.2	9.3.5
Inclusion/Exclusion	R						
Informed consent process (subject must meet eligibility criteria)	R						
Device information (model and serial numbers, implant date)	R						
LATITUDE and heart failure sensors enabled confirmation, including weight and blood pressure home unit	R						
Demographics and Medical History		R					
Phase I, Phase II HeartLogic Alerts ON group: • HeartLogic alerts turned on and threshold set at 16 Phase II HeartLogic Alerts OFF group: • HeartLogic alerts turned off •		R					
Physical Exam		R		R	R (in-clinic only)		
Heart failure patient assessment		R	R	R	R	O	
NYHA[3] Class		R		R	R (in-clinic only)	O	
Posture Sensor Calibration		R		R			
HeartLogic Index Programming		R	R	R	R	R	

Procedure/Assessment	Enrollment	Baseline visit (minimum 45 days of heart failure sensor data collection; maximum 4 mo from Enrolment)	Follow-up Visits				End of Study
			Annual Phone Call (6, 18, 30, 42 mo… from baseline)	Annual In-Clinic Visit (12, 24, 36, 48 mo… from baseline)[1]	HeartLogic Alert Action (phone calls and/or in-clinic visits)	Additional Subject Interactions (phone calls and/or in-clinic visits)	
NT-proBNP		R	O	R	O	O	
Blood chemistry and EKG as a part of standard of care medical evaluation		O	O	O	O	O	
Subject reported outcomes (KCCQ[3] and EQ-5D-5L)		R		R	O		
Weight, Blood Pressure and Heart Rate		R		R	O		
Oxygen Saturation		O		O	O		
Medications		R	R	R	R	R	
Adverse Events/Device Deficiencies[4]		R	R	R	R	R	
Device data (disk download)				R[2]	R[2]	R[2]	
Qualified treatment upon alert					R		

R = required; O = optional but recommended.[1]Phase I subjects will only be followed for annual visits until the final Phase I subject has completed their 12 month visit (or upon recommendation by the Steering Committee), at which point the subject will exit the study and have no additional follow-up visits.
[2] Required per Boston Scientific request, if LATITUDE data are unavailable (Section 9.5)
[3]Abbreviations: NYHA=New York Heart Association; KCCQ=Kansas City Cardiomyopathy Questionnaire
[4]Adverse event data also includes hospital admission regardless of cause.

9.2 Enrollment Screening

Details in this section apply to all subjects in Phases I and II. Subjects will be recruited from the investigator's general heart failure population. The investigator has the responsibility of screening potential subjects and selecting only those who meet the eligibility criteria. Screening logs should be maintained for all screened subjects and kept at investigative sites. Screen failures should be entered in the RAVE database and the date of screening, and the reason for screen failure will be captured.

9.3 Study Visits

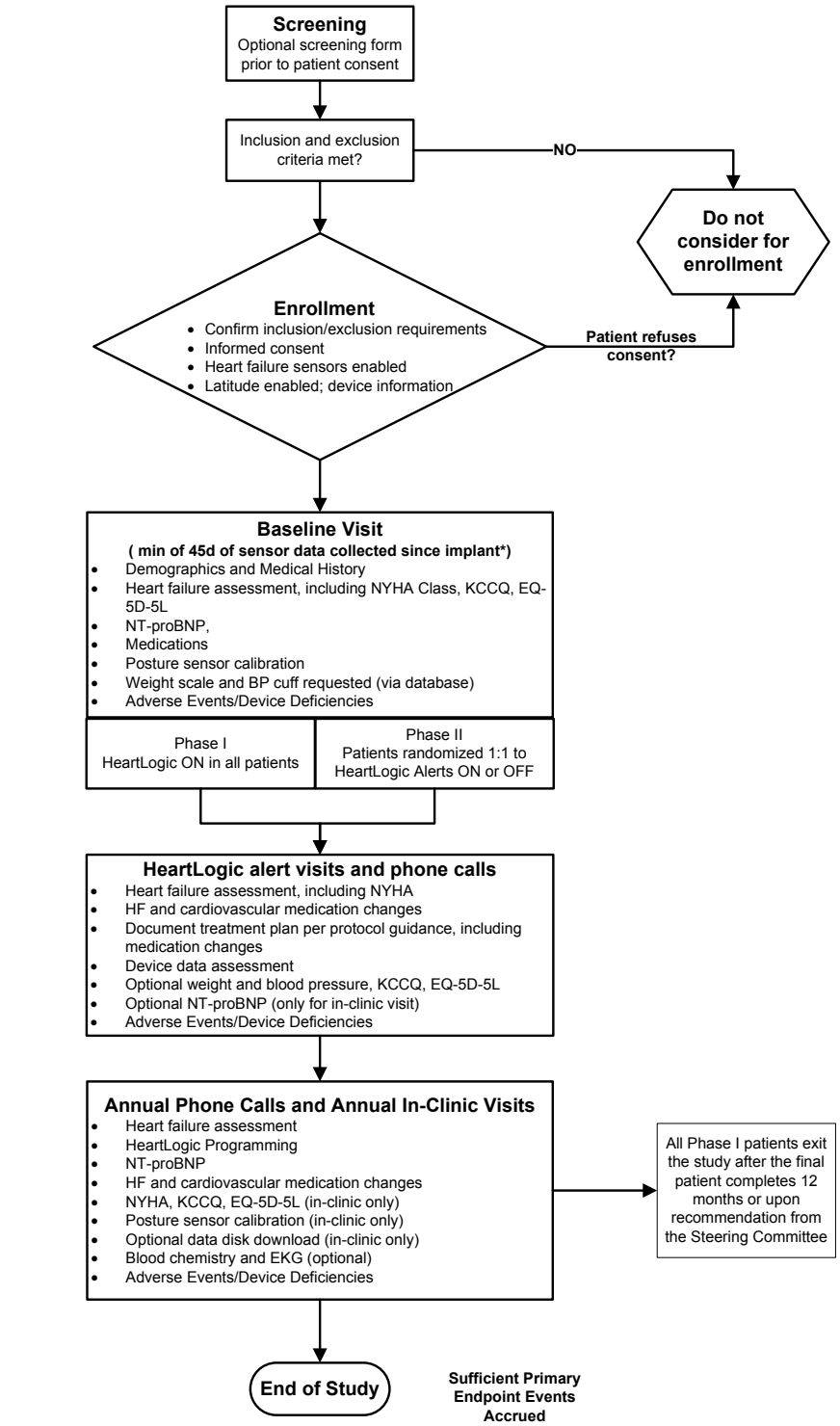
Details in this section apply to all subjects in Phases I and II.

The required protocol study visits are as follows:

- Enrollment Visit
- Baseline Visit
- Scheduled follow-up visits
    - Annual Phone Calls (6, 18, 30, 42 months, … from baseline visit)
    - Annual In-Clinic (12, 24, 36, 48 months, … from baseline visit)
- Additional Follow-up Visits
    - HeartLogic Alert Action Visit
    - Additional Subject Interactions (i.e., Not in Response to HeartLogic Alerts)
- End of Study

Phase I subjects will be followed until the last Phase I subject has completed the 12 month visit, or upon recommendation from Steering Committee. Phase II subjects will be followed until the necessary number of primary endpoint events has been accrued.

Figure 9-1: MANAGE-HF Detailed Study Flow Chart



*If less than 45 days, reschedule baseline visit

9.3.1 Enrollment Visit

Details in this section apply to all subjects in Phases I and II.

9.3.1.1 Informed Consent Process

All subjects must undergo the informed consent process, and sign and date the informed consent before any study procedures are performed. Subjects will be considered enrolled at the time of informed consent. 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.

9.3.1.2 Enrollment Visit Data Collection

The following information must be gathered for the implanted CRT-D or ICD system and entered into the RAVE database in a timely manner:

- Inclusion/Exclusion Screening Form
- Manufacturer, model and serial number of pulse generator and active leads
- Implant date for all active devices
- Anatomical locations of pulse generator and leads
- Confirmation that subject has been or will be remotely monitored with LATITUDE NXT 5.0 (or equivalent)
    - If the subject has at least 45 days of heart failure sensor data collection the subject may also complete the baseline visit (see section 9.3.2).
    - If subject does not have at least 45 days of heart failure sensor data, schedule baseline visit accordingly.

If the Enrollment Visit does not occur on the same day as the Baseline visit, the clinician (and if needed with assistance from Boston Scientific) will ensure that HeartLogic Alerts are OFF and Heart Failure Sensor Data Collection have not been disabled (i.e., still in nominal setting).

9.3.2 Baseline Visit

The baseline visit will occur for all enrolled subjects (Phases I and II) who have a minimum of 45 days of heart failure sensor data in the pulse generator. If there are fewer than 45 days, the baseline visit must be rescheduled. The baseline visit will occur after the subject has consented, but can occur on the same day as enrollment. The baseline visit must occur at most 4 months from enrollment.

Procedures followed and data collected differ by phase and are presented separately by phase in Sections 9.3.2.1 (Phase I) and 9.3.2.2 (Phase II).

9.3.2.1 Phase I Baseline Visit

The following actions must be taken at the baseline visit for Phase I subjects:

- Required Blood Draw:
    - NT-proBNP per investigative site procedures. Other BNP values are not permitted in the study.
- Required Programming at Baseline visit:

  - Through the LATITUDE system, HeartLogic Alert Threshold must be programmed to 16 (nominal HeartLogic Alert Threshold setting) and "daily interrogations until alert condition is resolved" programmed on . After the baseline visit, the nominal HeartLogic Alert Threshold setting of 16 may be changed with appropriate documentation, in the RAVE database, of the rationale for changing this value.
    - Required for all patients in Phase I and Phase II HeartLogic ON group
  - All other therapies/device settings are at the discretion of the clinician.
- Required attempt to calibrate the posture sensor

The following information must be entered into the electronic database:

- Patient demographics and medical history
- Physical Exam
- Heart failure assessment
- NYHA Classification
- Posture sensor calibration (Section 9.7)
- HeartLogic Alert Threshold activated
- NT-proBNP
- Blood chemistry and EKG as a part of standard of care medical evaluation (optional)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EQ-5D-5L
- Weight, Blood Pressure and Heart Rate
- Oxygen saturation (optional)
- Changes to heart failure and cardiovascular related medications and treatments
- Applicable adverse event/device deficiency reporting (Section 18)

At the end of the visit, the clinician, with assistance from Boston Scientific, will ensure that the HeartLogic feature is activated and that the HeartLogic Alert Threshold is programmed to 16 (nominal setting). After the baseline visit, the alerts will be turned on once you have completed the CRF or called Boston Scientific, and the data will begin to transmit through the patient bedside communicator If you have questions, please contact your Boston Scientific representative. This ensures that if the alert threshold is met or exceeded, an alert will be sent to the clinician and to the Alert Monitoring Center (AMC Section 9.6). Physicians may adjust the threshold, but the change must be documented in the RAVE database. Refer to the HeartLogic Technical guide for information on how adjusting the alert threshold affects the sensitivity and the alert rate.

9.3.2.2 Phase II Baseline Visit

If subjects has had HeartLogic Alerts ON at any point between enrollment and the baseline visit, the subject must be exited from the study. Use of HeartLogic Alerts prior to the randomized portion of the study may bias the endpoint results.

The following actions must be taken at the baseline visit for Phase II subjects:

- Randomization of subjects to HeartLogic Alerts ON and HeartLogic Alerts OFF
- Required Blood Draw:

  - NT-proBNP per investigative site procedures. Other BNP values are not permitted in the study.
- Required Programming at Baseline visit:
  - HeartLogic Alert Threshold must be programmed to 16 (nominal setting). After the baseline visit the nominal setting may be changed with appropriate documentation, in the RAVE database, with the rationale for changing this value.
    - Phase II HeartLogic ON group
  - All other therapies/device settings are at the discretion of the clinician.
- Required attempt to calibrate the posture sensor

The following information must be entered into the electronic database:

- Patient demographics and medical history
- Physical Exam
- Heart failure assessment
- NYHA Classification
- Posture sensor calibration (Section 9.7)
- HeartLogic Alert Threshold activated
- HeartLogic Index Programming
- NT-proBNP
- Blood chemistry and EKG as a part of standard of care medical evaluation (optional)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EQ-5D-5L
- Weight, Blood Pressure and Heart Rate
- Oxygen saturation (optional)
- Changes to heart failure and cardiovascular related medications and treatments
- Applicable adverse event/device deficiency reporting (Section 18)

For subjects randomized to HeartLogic Alerts ON:
At the end of the visit, the clinician, and if needed with assistance from Boston Scientific, will ensure that the HeartLogic feature is activated and that the HeartLogic Alert Threshold is programmed to 16 (nominal setting). The alerts will be turned on by Boston Scientific and that data will begin to transmit through the patient bedside communicator once you have completed the CRF for the baseline visit. If you have questions, please contact your Boston Scientific representative. This ensures that if the alert threshold is met or exceeded, an alert will be sent to the clinician and to the AMC. Following a HeartLogic Alert, physicians may adjust the threshold, but the change must be documented in the RAVE database. Refer to the HeartLogic Technical guide for information on how adjusting the alert threshold affects the sensitivity and specificity.

For subjects randomized to HeartLogic Alerts OFF:
At the end of the visit, the clinician, and if needed with assistance from Boston Scientific, will ensure that HeartLogic Alerts are OFF and that Heart Failure Sensor Data Collection have not been disabled (i.e., still in nominal setting).

9.3.3 Scheduled Follow-up Visits

Details in this section apply to all subjects in Phases I and II.

9.3.3.1 Annual Phone Calls (6, 18, 30, 42 months,…)

Starting at 6 months after the baseline visit, the clinician must call the subject to assess changes in medications and to collect adverse event information. The visit windows are listed below.

Table 9-2: Annual Phone Call Schedule

Visit	Visit Window
6 month	180 ± 30 days from baseline
18 month	545 ± 30 days from baseline
30 month	910 ± 30 days from baseline
42 month	1275 ± 30 days from baseline
54 month	1640 ± 30 days from baseline
66 month	2005 ± 30 days from baseline
78 month	2370 ± 30 days from baseline

The annual phone calls will continue until the completion of the study phase. Completion of Phase I will occur after the final Phase I subject has completed their 12 month visit, or upon recommendation from the Steering Committee. Completion of Phase II will occur after the necessary number of primary endpoint events has been accrued.

Since the previous visit, the clinician will call the subjects to determine if there are any reportable adverse events (Section 18) and failure treatments (Section 9.4.1).

The following information must be entered into the electronic database:

- Heart failure assessment
- HeartLogic Index Programming (if changed from nominal setting of 16)
- NT-proBNP (optional)
- Blood chemistry and EKG as a part of standard of care medical evaluation (optional)
- Changes to heart failure and cardiovascular related medications and treatments
- Applicable adverse event/device deficiency reporting (Section 18)

9.3.3.2 Annual In-Clinic Visits (12, 24, 36, 48 months, …)

Starting at 12 months after the baseline visit, the subjects must be seen in-clinic annually. The visit windows are listed below.

Table 9-3: Annual In-Clinic Visit Schedule

Visit	Visit Window
12 month	365 ± 30 days from baseline
24 month	730 ± 30 days from baseline

36 month	1095 ± 30 days from baseline
48 month	1825 ± 30 days from baseline
60 month	2190 ± 30 days from baseline
72 month	2555 ± 30 days from baseline

The following actions must be taken at the annual in-clinic visit for all subjects:

- Required Blood Draw:
  - NT-proBNP per investigative site procedures. Other BNP values are not permitted in the study.
- Required attempt to calibrate the posture sensor.

The following information must be entered into the electronic database:

- Physical Exam
- Heart failure assessment
- NYHA Classification
- Posture sensor calibration (Section 9.7)
- HeartLogic Alert Threshold activated
- HeartLogic Index Programming (if changed from nominal setting of 16)
- NT-proBNP
- Blood chemistry and EKG as a part of standard of care medical evaluation (optional)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EQ-5D-5L
- Weight, Blood Pressure and Heart Rate
- Oxygen saturation (optional)
- Changes to heart failure and cardiovascular related medications and treatments
- Applicable adverse event/device deficiency reporting (Section 18)
- Device data (disk download) Required per Boston Scientific request, if LATITUDE data are unavailable (Section 9.5)

9.3.4 Additional Follow-up Visits

9.3.4.1 HeartLogic Alert Action Visit

Details apply to subjects in Phases I and II with HeartLogic Alerts ON. The follow-ups that must be documented in response to a HeartLogic alert or re-alert are described in Section 9.4.

The following information must be entered into the electronic database:

- Physical Exam (required for in-office only)
- Heart failure assessment
- NYHA Classification (in-clinic only)
- HeartLogic Index Programming (if changed from nominal setting of 16)
- HeartLogic alert assessment
- NT-proBNP (optional)
- Blood chemistry and EKG as a part of standard of care medical evaluation (optional)

- Kansas City Cardiomyopathy Questionnaire (KCCQ) (optional)
- EQ-5D-5L (optional)
- Weight, Blood Pressure and Heart Rate (optional)
- Oxygen saturation (optional)
- Changes to heart failure and cardiovascular related medications and treatments
- Applicable adverse event/device deficiency reporting (Section 18)
- Device data (disk download) Required per Boston Scientific request, if LATITUDE data are unavailable (Section 9.5)
- Qualified treatment upon alert

9.3.4.2 Additional Subject Interactions (i.e., Not in Response to HeartLogic Alerts)

Details apply to all subjects in Phases I and II. Research personnel must document an additional subject interaction if a subject is contacted by phone or has an in-clinic visit (other than a protocol-mandated follow-up or follow-up response to HeartLogic Alert) and there is a change in medications, device programming, device deficiencies or any reportable adverse event information, including heart failure related events. Blood chemistry analysis and EKG are optional data items which can be reported as a part of the standard of care visit.

If settings for HeartLogic Alert Threshold are changed complete HeartLogic Programming CRF (for subjects with HeartLogic Alerts ON)

The following information must be entered into the electronic database:

- Heart failure assessment (optional)
- NYHA Classification (optional)
- HeartLogic Index Programming (if changed from nominal setting of 16)
- NT-proBNP (optional)
- Blood chemistry and EKG as a part of standard of care medical evaluation (optional)
- Changes to heart failure and cardiovascular related medications and treatments
- Applicable adverse event/device deficiency reporting (Section 18)
- Device data (disk download) Required per Boston Scientific request, if LATITUDE data are unavailable (Section 9.5)

9.3.5 End of Study

Details apply to all subjects in Phases I and II.

End of study for a subject occurs when the subject dies, withdraws, completes study/phase participation or is withdrawn by the investigator. The clinician must document reason for study exit and date of study exit. HeartLogic Alerts may be configured at the discretion of the clinician at the end of the study.

9.4 HeartLogic Alert Action Visit

Details in this section apply to subjects in Phases I and II with HeartLogic Alerts ON.

The LATITUDE communicator will collect and compute HeartLogic data as part of the daily alert checks. Patients should be in daily contact with the LATITUDE communicator to maximize access to HeartLogic data. Extended absence from the communicator (e.g., > 7 days) is discouraged.

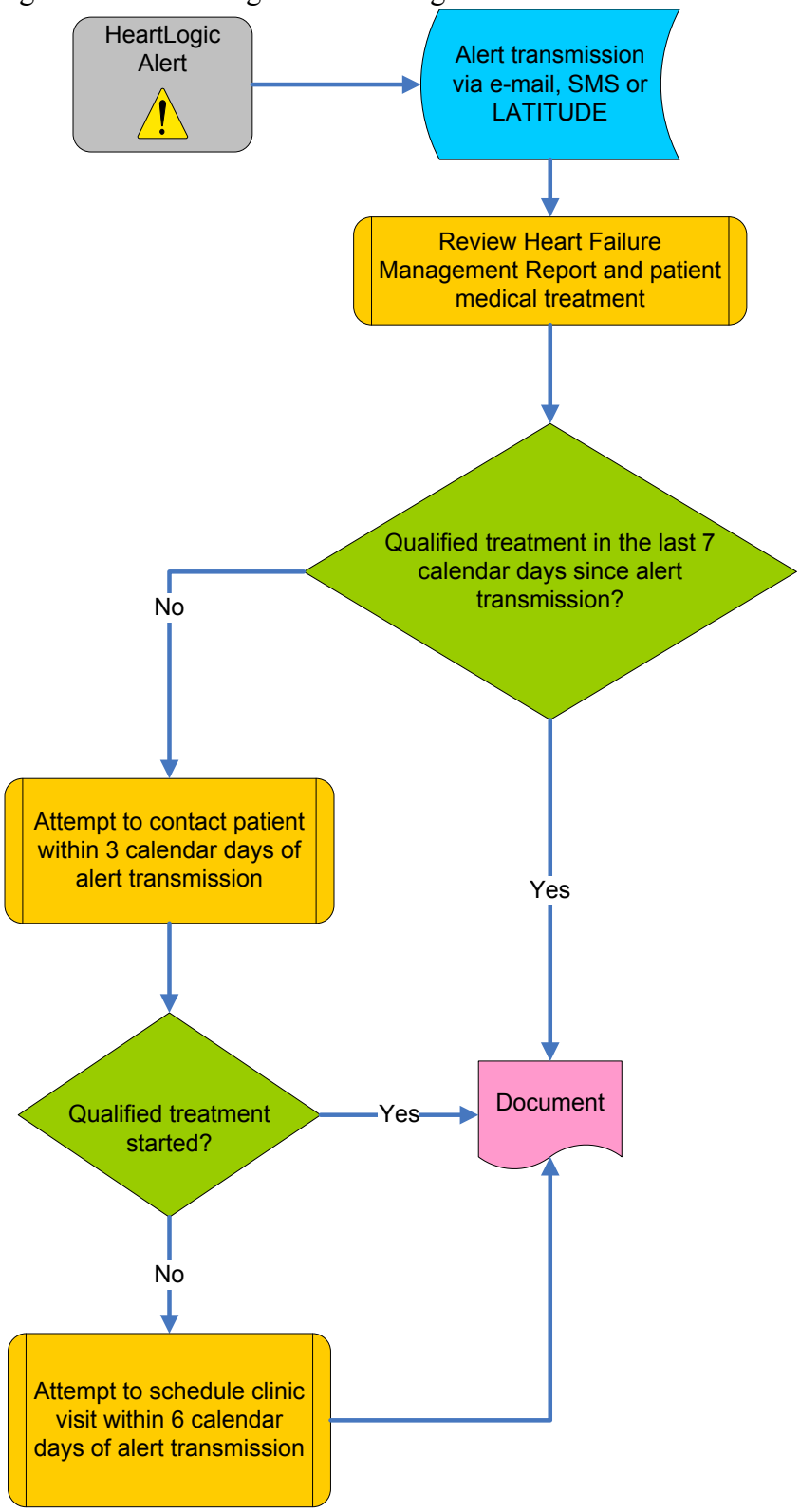
Figure 9-2 details the response to all HeartLogic Alerts (new and re-alerts), and applies to patients in Phase I and Phase II with HeartLogic Alerts ON. Clinicians must treat all patients with alerts unless there is a patient safety concern associated with treatment. Sites may be provided additional guidance regarding treatment in response to HeartLogic alert, based on recommendations from the Steering Committee (see Section 9.4.2 for details regarding the HeartLogic Alert Management Guide). A HeartLogic alert is not itself an adverse event, however it is the responsibility of the investigator to assess the patient and report adverse events to BSC as described in section 18.

When a patient is in alert, the clinician will receive a notification in LATITUDE, and may also opt to receive a text messages and/or email. If patient is in contact with the LATITUDE communicator and the patient is in alert, the site will be notified of the alert via LATITUDE.

For each HeartLogic alert (initial alert or re-alert) the process below must be followed (see figure 9.2). Within 3 calendar days from the alert being transmitted from the communicator to LATITUDE, the clinician should review the Heart Failure Management Report in the LATITUDE system and the patient's medical treatments. If a qualified treatment was initiated within the 7 days prior to the HeartLogic alert transmission or the HeartLogic Index has decreased below the recovery threshold, the site may opt to not contact the patient for evaluation of the alert. Otherwise, the center must attempt to contact the patient (by phone or via in-clinic visit) for evaluation no later than 3 calendar days from alert transmission date. When the patient is contacted, the patient must be assessed using the HeartLogic Alert CRF. The clinician should then initiate a qualified treatment (section 9.4.1) for the patient and document the change. If no treatment is initiated as a result of a phone contact, then the center must attempt to schedule the patient for a clinic visit for further evaluation within 6 days from the date of alert transmission. At the clinic evaluation, a qualified treatment should be initiated and documented (section 9.4.1). If no treatment is initiated the rationale must be documented in the CRF.

If settings for HeartLogic Alert Threshold are changed complete HeartLogic Programming CRF (for subjects with HeartLogic Alerts ON)

Figure 9-2: HeartLogic Alert Management Process



The following table outlines the actions and data collection associated with a HeartLogic Alert Action Visit.

Table 9-4: Data Collection at HeartLogic Alert Action Visit

	Phone call with no treatment, then in-clinic visit	**Phone call with treatment**
Alert Date	X	X
Heart Logic alert assessment	X	X
Phone call documented	X	X
Action taken documented	X	X
Heart Failure Assessment	X	X
Adverse Event Assessment	X	X
NYHA Assessment	X	X
NT-ProBNP	X (Optional)	-
Blood lab values chemistry and EKG as a part of standard of care medical evaluation	X (Optional)	-
Weight/Blood Pressure/Heart rate	X (Optional)	X (Optional)
Oxygen Saturation		
KCCQ and EQ-5D-5L	X (Optional)	-
Data disk if latitude not available	X (Optional)	-
HF medications/cardiac meds changes	X	X
HeartLogic Programming (if changed from nominal setting of 16)	X	X

All alerts will follow the process shown in Figure 9-2, including re-alerts. The process is designed to facilitate remote management of the patient, and to encourage a treatment response when there is an active HeartLogic Alert.

HeartLogic has been validated as a diagnostic tool to detect gradual worsening of heart failure over days or weeks using multiple physiologic measurements. It is possible for an alert to resolve without a commensurate improvement in patient condition. HeartLogic alert resolution should not be used as an indicator of patient health status. Therefore, patients should continue to be evaluated and treated with standard of care after alert resolution per clinician discretion.

9.4.1 Qualified Treatments

Details in this section apply to all subjects in Phases I and II.

Qualified treatments in response to a HeartLogic Alert or in response to worsening of heart failure are:

- If patient is not adhering to medications; enforce adherence.
- Change in current medications related to worsening symptoms of heart failure:
    - Increase dose of at least one currently prescribed medication (e.g. doubling of diuretic dose; may be temporary)
    - Addition of a new class of medication (e.g. adding an MRA when none was being taken)
    - Adding an additional medication of the same class
    - Change of medication within the same class (e.g. switching ß-blockers)

- Other treatments for conditions believed to have triggered a HeartLogic alert, with appropriate rationale and documentation.

Note: while reminders of diet, hydration and exercise are encouraged as a part of chronic heart failure care, when taken alone, do not qualify as a treatment response to a HeartLogic Alert or worsening heart failure.

9.4.2 Heart Logic Alert Management Guide

The HeartLogic Alert Management Guide is a separate document that will be generated for the sharing of best practices identified by the Steering Committee and informed by the study investigators. This document may provide referrals to heart failure management guidelines, frequently asked questions, rates of adverse events associated with HeartLogic false positives and logistical solutions to common implementation problems. The document will not prescribe specific treatments and will not be informed by the Phase II results.

9.5 Device Interrogation

Details apply to all subjects in Phases I and II.

There are no required routine device interrogations for this study because data will be available through home communicator uploads to LATITUDE. However, if device interrogation using a home communicator is not possible (e.g during extended hospitalization) , sites will be notified when the data must be manually obtained through one of two methods of device interrogation: using a Consult or using a programmer. If a programmer interrogation is used, the "device data dump" (not "save all to disk") option should be chosen. If data are stored on a disc or flash drive, the disc or flash drive should be kept in the subject's MANAGE-HF study binder at the investigative site, and copy should be mailed to the sponsor.

9.6 Alert Monitoring Center

Details apply to all subjects in Phases I and II.

The AMC is operated by Boston Scientific staff that is trained to provide technical support of all commercial pacemaker and defibrillator devices. They also provide support for the LATITUDE patient management system. The AMC does not provide any site monitoring; site monitoring is detailed in Section 16.

During Phases I and II of the MANAGE-HF study, the AMC will provide support to clinical sites.
The AMC will not practice medicine or provide any independent medical recommendations for patients. While the AMC will be blinded to study endpoint data, they will have access to metrics related to integration of HeartLogic into the clinic, and may provide advice in the form of best practices.

Study investigators will also be provided with a HeartLogic Alert Management guide (Section 9.4.2).

9.7 Posture Sensor Calibration

Details apply to all subjects in Phases I and II.

Posture sensor calibrations are attempted by the clinician and patient using the programmer application at baseline and again at every annual follow-up visit. 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. Once the patient is in position, the clinician will run the software on the programmer for the data collection. It takes approximately 10 seconds of data collection for each position. The entire procedure should take about 1-2 minutes.

There may be instances where the posture sensor is unable to be calibrated. This occurs because the sensor is still initializing, or collecting data, and has not yet reached a state in which it can be calibrated. If the calibration is attempted and unsuccessful, the participant does not need to be brought back for an additional visit with the only purpose of attempting the calibration again. However, the calibration may be attempted at the next scheduled visit.

Important: The device will NOT collect any Sleep Incline data until a body calibration has been performed. Thus, an attempt to calibrate the posture sensor is a required step at the baseline and every annual in-clinic follow-up visit. If the calibration is unsuccessful, the attempt and reason for lack of success should be documented.

9.8 Randomization Crossovers (Phase II only)

In Phase II, crossing over from one randomized group to the other group (from HeartLogic Alerts OFF to ON or vice versa) is not allowed.

9.9 Study Completion

Phase I will be complete after the final Phase I subject has been followed for 12 months, or upon recommendation from the Steering Committee. Phase II will be complete after the required number of primary endpoint events has been accrued, or until a futility point has been reached. The study will be complete after Phase II has concluded.

Upon completion of each phase, sites will be notified that the phase has ended and instructed to exit subjects from actively followed in the applicable phase. No additional follow-up visits will occur in the phase, and no additional adverse event reporting will occur once the phase has finished. Subjects will continue to be followed as determined by their health care professional, but not as a part of the clinical trial.

If the study fails to meet the pre-specified primary endpoint, HeartLogic may be turned off if there are patient safety concerns. Importantly, turning off HeartLogic does not affect any other performance aspect of the device.

9.10 Source Documents

Details apply to both phases (Phases I and II) of the MANAGE-HF study.

Source documents are “printed, optical or electronic document containing source data”, the source data being “all information in original records… necessary for the reconstruction and evaluation of the clinical investigation”.

Source documentation is required during this study. The participating investigator must maintain original source documents that are accurate, complete, and current related to the subject's participation in this study. Source documentation must include but is not limited to:

- Medical record verification that subject meets Inclusion and Exclusion Criteria
- Completed patient informed consent
- Patient medical file with all required study data elements
- Prescribed cardiovascular and heart failure medications
- Documentation of adverse events, including hospitalizations
- Printed copies of HeartLogic sensors/alerts and LATITUDE data

Table 9-5: Source Documentation Requirements

Requirement	Disposition
Screening form	Retain at center
Informed consent form	Retain at center
Demographic data	Retain at center
HeartLogic Sensors and Alert Programming	Retain at center
Medications	Retain at center
Heart failure assessment	Retain at center
NT-proBNP	Retain at center
NYHA classification	Retain at center
KCCQ and EQ-5D-5L	Retain at center
Treatment documentation	Retain at center
Device data assessment	Retain at center
Adverse events	Retain at center
Weight and blood pressure	Retain at center
Protocol deviations	Retain at center
Hospitalizaion	Retain at center and send a copy to BSC
Death Information	Retain at center and send a copy to BSC
Subject Randomization	Electronic Data Capture system

Abbreviations: NYHA: New York Heart Association; KCCQ: Kansas City Cardiomyopathy Questionnaire; AMC: Alert monitoring center

10 Study Endpoints and Statistical Considerations

All analyses described in this section apply to subjects randomized in Phase II. No data from subjects enrolled in Phase I will contribute data to any endpoint analyses.

10.1 Primary Endpoint

The primary endpoint of the MANAGE-HF trial will assess the freedom from all-cause mortality and heart failure hospitalizations, as adjudicated the Clinical Events Committee (CEC, described in Section 20.3). The primary endpoint will compare randomized HeartLogic and Control groups and be assessed using data collected following randomization in Phase II of MANAGE-HF.

10.1.1 Hypothesis for Primary Endpoint

The following set of hypotheses will be evaluated for the primary endpoint:

H_0: The risk of mortality and heart failure hospitalization for the HeartLogic group will be greater than or equal to the risk for the control group

H_A: The risk of mortality and heart failure hospitalization for the HeartLogic group will be less than the risk for the control group

10.1.2 Sample Size for Primary Endpoint

The sample size required for Phase II of MANAGE-HF is event-driven. Between 1500 and 2500 subjects will be enrolled in the trial to accrue the necessary number of endpoint events to sufficiently power the primary endpoint. Final sample size will be determined during the study using a sample size re-estimation interim analysis. The assumptions used to calculate the sample size are described in a separate MANAGE-HF Statistical Analysis Plan.

10.1.3 Statistical Methods for Primary Endpoint

The methods used to evaluate the Primary Endpoint are described in a separate MANAGE-HF Statistical Analysis Plan.

10.2 Secondary Endpoints

Descriptions of the Secondary Endpoints and associated data evaluated are described in the following sections. The statistical methods used to evaluate the Secondary Endpoints are described in a separate MANAGE-HF Statistical Analysis Plan.

10.2.1 Secondary Endpoint 1: Freedom from all-cause mortality

Survival (freedom from all-cause mortality) between the randomized groups will be assessed, including all deaths occurring during Phase II of the trial.

10.2.2 Secondary Endpoint 2: Freedom from heart failure hospitalizations (time-to-first event)

Freedom from a heart failure hospitalization will be evaluated and compared between the randomized groups. Each subject's first heart failure hospitalization will contribute to the endpoint. Data observed during Phase II of the trial will be included in the analysis.

10.2.3 Secondary Endpoint 3: Risk of multiple heart failure hospitalizations

Multiple heart failure hospitalizations will be evaluated and compared between the randomized groups. All heart failure hospitalizations for each subject will contribute to the endpoint. Data observed during Phase II of the trial will be included in the analysis.

10.2.4 Secondary Endpoint 4: Change in NYHA Classification

Change in NYHA from baseline through 12 months will be evaluated and compared between the randomized groups. Data observed during Phase II of the trial will be included in the analysis.

10.2.5 Secondary Endpoint 5: Change in Quality of Life

Change in Quality of Life from baseline through 12 months will be evaluated and compared between the randomized groups. Data observed during Phase II of the trial will be included in the analysis.

10.2.6 Secondary Endpoint 6: Change in NT-proBNP

Change in NT-proBNP from baseline through 12 months will be evaluated and compared between the randomized groups. Data observed during Phase II of the trial will be included in the analysis.

10.2.7 Secondary Endpoint 7: Change in Medication Status

Change in medication status from baseline through 12 months will be evaluated and compared between the randomized groups. Data observed during Phase II of the trial will be included in the analysis.

10.3 General Statistical Methods

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

10.3.1 Study Success Criteria

The study will be considered successful if the null hypothesis for the primary endpoint is rejected.

10.3.2 Analysis Sets

All primary and secondary endpoint analyses will be performed following intention-to-treat (ITT) methodology, in which each subject is analyzed per their intended (i.e., randomized) treatment assignment. An as-treated analysis will be performed as well, in which subjects would be analyzed per the treatment received and may be time-varying to accommodate cross-overs. A per-protocol analysis will also be performed.

10.3.3 Control of Systematic Error Bias

Selection of subjects for enrollment in both phases will be made from the Investigator's usual subject load. All subjects meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study.

To reduce the possible introduction of selection bias, subjects in Phase II will be randomized to their treatment assignment. To reduce the possible introduction of observer bias, deaths and heart failure hospitalizations will be adjudicated by an independent Clinical Events Committee (CEC).

10.3.4 Control of Type-I Error

Overall Type I error for the primary endpoint will not exceed one-sided 2.5%. Type I error will be split and managed for the interim superiority analyses by employing an O'Brien-Fleming-type error spending function.

Secondary endpoints and other sensitivity analyses will be performed at the nominal one-sided 2.5% and will not be adjusted for the interim primary endpoint analyses.

10.3.5 Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to enroll more than 20 subjects in Phase I and 100 subjects in Phase II for this study, without approval from Boston Scientific.

10.3.6 Interim Analyses

Analyses of adverse events and device deficiencies will occur at frequent intervals during the course of the study. Results of these analyses will be reviewed by an independent Data Monitoring Committee (DMC) and the Boston Scientific Medical Safety Group to evaluate the safety of the subjects under study. Information about the group sequential stopping rules and interim sample size re-estimation are found in the following sections.

10.3.6.1 Sequential Stopping Rules

Interim analyses will be performed during Phase II to assess the superiority of HeartLogic. Five analyses (four interim analyses and one final) are planned. Futility analyses will also be performed at each interim analysis. The Type I error/alpha spending will be managed using an O'Brien-Fleming-type error spending function. The alpha will maintained at an overall one-sided level of 2.5%.

10.3.6.2 Sample Size Re-estimation

At the start of Phase II, a sample size range of 1500 to 2500 patients will be considered. The final sample size will be determined through use of interim sample size re-estimation analyses. The sample size re-estimation analyses will evaluate two items: (1) the primary endpoint event rate in the control group only, and (2) the enrollment rate in the trial. Based on the results of these analyses, a final sample size will be determined that will allow for sufficient primary endpoint powering while minimizing trial burden.

The analysis will be performed in a blinded fashion; neither the primary endpoint event rate in the HeartLogic group nor the hazard ratio comparing groups will be calculated. Due to the blinded nature of the analysis, no

inflation of type I error is introduced. Therefore, the sample size re-estimation can be performed without adjustment to the type I error for the primary endpoint. The analysis will be performed prior to the first sequential interim analysis, as specified in Section 10.3.6.1.

10.3.7 Subgroup Analyses

Analyses will be performed to assess whether significant interactions exist between randomization group and various baseline characteristics. The specific baseline characteristics and their corresponding subgroups that will be analyzed are described in a separate Statistical Analysis Plan.

Regardless of the results of the interaction test for each characteristic, analyses of each subgroup will be performed. Analyses will be conducted for the primary endpoint and all secondary endpoints.

10.3.8 Multivariate analyses

The purpose of the multivariate analyses is to determine covariates associated with the primary and secondary endpoints. Covariates considered for inclusion in the final multivariate models include, but are not limited to, the characteristics studied as part of the subgroup analyses. Details can be found in a separate Statistical Analysis Plan.

10.3.9 Justification of Pooling

Pooling of devices, geographies and sexes for the Primary Endpoint will be evaluated. Details of the pooling analyses are described in a separate MANAGE-HF Statistical Analysis Plan.

10.3.10Health Economic Analyses

Analyses used to understand the health economics associated with HeartLogic usage may be performed during either phase of the study.

10.3.11 Changes to Planned Analyses

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

11 Data Management

Details in this section apply to both phases (Phases I and II) of the MANAGE-HF study.

11.1 Data Collection, Processing, and Review

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

The clinical database will reside on a production server hosted by EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. 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 case report forms (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 Investigator or his/her designee or Investigational site will maintain, at the investigative 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 last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. 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 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 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.

12 Amendments

If a protocol revision is necessary, during Phases I or II, which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

13 Deviations

Details in this section apply to both phases (Phases I and II) of the MANAGE-HF study.

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/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 visit and the reason for the deviation, must be documented and reported to the sponsor using the electronic data base. Sites may also be required to report deviations to the IRB/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 FDA notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

14 Device/Equipment Accountability

Devices used in both phases (Phase I and II) of the MANAGE-HF study are commercially available.

15 Compliance

Details in this section apply to both phases (Phases I and II) of the MANAGE-HF study.

15.1 Statement of Compliance

This study will be conducted in accordance 21 CFR part 56 and part 50, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, and pertinent local laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or the regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or the regulatory authority shall be followed, if appropriate.

15.2 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/, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, 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.
- Prior to beginning the study, sign the Investigator Brochure Signature Page (if applicable) and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- 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 and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- 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 when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC 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.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- 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 clinician 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.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

15.2.1 Delegation of Responsibility

When specific tasks are delegated by an investigator, 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. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

15.3 Institutional Review Board/ Ethics Committee

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC 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 study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

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

15.4 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 these confidential records. 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 subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' 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, 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.

15.4.1 Role of Boston Scientific Representatives

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

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during implant or 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 investigational equipment
- Performing lead diagnostic testing using a Pacing System Analyzer or programmer to obtain pacing and sensing thresholds and impedance measurements
- 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 Pacing System Analyzers, programmers, and other equipment
- Print out programming reports directly from the clinician programmer and provide original 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 electronic data capture systems or on paper case report forms

15.5 Insurance

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

16 Monitoring

Details in this section apply to both phases (Phases I and II) of the MANAGE-HF study.

Monitoring will be performed by Boston Scientific or its designees during the study, on site or remotely, 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.

Monitoring described in this section is different from the responsibilities of the AMC, described in 9.6.

17 Potential Risks and Benefits

Details in this section apply to both phases (Phases I and II) of the MANAGE-HF study.

17.1 Anticipated Adverse Events

The following anticipated adverse events (AE) have been identified for this study:

- Anticipated adverse events with this study are expected to be side effects from the changes in patient care as a result of HeartLogic Alerts. These adverse events would include an increase in side effects as a result of changes to medications, addition of new medications, or other treatments added to avoid further worsening of heart failure.

17.2 Anticipated Adverse Device Effects

There are no anticipated Adverse Device Effects beyond those that would be expected from a commercially approved device. Please refer to the Resonate family of CRT-D and ICD Physician's Technical Manuals for potential adverse events. The HeartLogic Index and Alert do not provide therapy, and do not interfere with the normal function of the CRT-D or ICD.

17.3 Risks Associated with the Study Device(s)

There are no risks associated with the study devices beyond those that would be expected from commercially approved devices. The HeartLogic Index and Alert are not calculated within the device. Calculations are performed in the patient communicator and transmitted to LATITUDE. Therefore, there are no anticipated

Adverse Device Effects with the implanted CRT-D or ICD. The approved labelling for the devices does not list any specific risks associated with the use of HeartLogic.

17.4 Risks associated with Participation in the Clinical Study

The risk of participating in this study is not significantly different from routine clinical care of a subject that is implanted with a BSC commercially approved and market available CRT-D and/or ICD device with the HeartLogic feature. Identifiable risks for subjects enroll in the trial include:

- Bruising or bleeding blood draw
- HeartLogic alerts that result in changes to medications or treatments that lead to adverse events
- Subject anxiety about worsening of their heart failure

17.5 Possible Interactions with Concomitant Medical Treatments

There are no anticipated interactions with concomitant medical treatments.

17.6 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.

17.7 Anticipated Benefits

There may be no benefit to the subject. However, the subject may benefit from more intensive heart failure management and follow up due to the clinical protocol schedule. Subjects may also be followed more carefully and their medical status, as well as their device and lead status, is checked by various study personnel and systems: investigators, data coordinators, monitors and automatic warning systems in the clinical study database set to monitor the data as it is submitted to Boston Scientific.
In addition, the HeartLogic alert is intended to notify the health care professional when the subject is at an increased risk for a heart failure related adverse event. This may lead to earlier medical intervention and could result in avoiding a heart failure event.

17.8 Risk to Benefit Rationale

The CRT-D and ICD device systems and accessories the subjects received prior to enrollment in the study will be commercially available and are considered to be standard of care for subjects indicated for their respective therapy. The risks involved with subject participation in this study are essentially the same as those for subjects not participating in the study. This study is designed to demonstrate clinical integration of HeartLogic is safe, and to establish an appropriate treatment response when an alert is issued. The benefit of reduced heart failure events outweighs any foreseen risks.

18 Safety Reporting

Details in this section apply to both phases (Phases I and II) of the MANAGE-HF study.

18.1 Reportable Events by Investigational site to Boston Scientific

It is the responsibility of the investigator to assess and report to BSC the following adverse events:

- All Serious Adverse Events
- All cardiac related Adverse Events, including new onset of cardiac events, or worsening in severity or frequency of pre-existing cardiac condition(s)
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- Protocol required procedures that result in an adverse event
- Adverse Device Effects including Serious Adverse Device Effects

HeartLogic Alerts are not considered adverse events, but may indicate the presence of an adverse event. If the criteria of a reportable adverse event have been fulfilled, an adverse event must be reported.

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms. Multiple symptoms related to a single medical diagnosis should be reported within one (1) adverse event (i.e. shortness of breath and edema are related to a diagnosis of 'worsening heart failure').

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 experienced by the study subject after informed consent (as defined in study subject classification section) must be recorded in the eCRF. All AEs must be reported until the study phase is completed for each subject.

Underlying diseases are not reported as AEs unless there is an increase in severity of 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 18-1 for AE definitions).

Refer to Section 17.3 for the known risks associated with the study device(s).

18.2 Definitions and Classification

Adverse event definitions are provided in Table 18-1. Events which are required to be reported are listed above. Administrative edits were made on the definition of serious adverse event from ISO 14155and MEDDEV 2.7/3 for clarification purposes.

Table 18-1: Safety Definitions

Term	Definition

Table 18-1: 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 investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational 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 investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational 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 <u>as defined by</u> either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function 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) *Ref: ISO 14155*	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.

Table 18-1: Safety Definitions

Term	Definition
Ref: MEDDEV 2.7/3	
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*	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.

Table 18-1: Safety Definitions

Term	Definition
Pacemaker Lead Adaptor 510(k) Submissions	
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 *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Comments Only. On occasion, comments were inadvertently entered 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

18.3 Relationship to Study Device(s) or Procedures

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in Table 18-2:

Table 18-2: Assessing Relationship of Study Device or Procedure to Adverse Event	
Classification	**Description**
Not Related	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 investigational 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 investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order 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	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	The relationship with the use of the investigational 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	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational 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 investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational 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 investigational device used for diagnosis, when applicable;

Table 18-2: Assessing Relationship of Study Device or Procedure to Adverse Event	
Classification	**Description**
	- In order 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.

18.4 Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 18-3.

Table 18-3: Investigator Reporting Requirements		
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.	d) Within 1 business day of first becoming aware of the event. e) Terminating at the end of the study
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	f) Within 10 business days after becoming aware of the event or as per local/regional regulations. g) For Austria: within,2 business days of first becoming aware of the event. h) Reporting required through the end of the study NOTE: Deaths are reported within 3 calendar days per Section 18.7
	Provide all relevant source documentation (unidentified) for reported event	i) As soon as possible
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	j) Within 2 business days of first becoming aware of the event or as per local/regional regulations. k) Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	l) When documentation is available
Device Deficiencies (including but not	Complete the device deficiency eCRF with	m) Within 2 business days of first becoming aware of the event. Reporting

Table 18-3: Investigator Reporting Requirements		
Event Classification	**Communication Method**	**Communication Timeline post-market studies**** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
limited to failures, malfunctions, and product nonconformities) Note: Any Investigational 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 event.	all available new and updated information.	required through the end of the study
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.	n) In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information o) Reporting required through the end of the study
Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect * Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications. **Please note that post-market studies are clinical studies where the medical devices used in the study bear the regulatory approval and are used for the same approved indications.		

18.5 Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided in the investigator site manual. If it is not possible to return the device, the

investigator should document in the eCRF why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, an adverse event that results from a device failure or malfunction would be recorded as an adverse event on the appropriate eCRF.

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 event.

18.6 Reporting to Regulatory Authorities / IRBs / ECs / Investigators

BSC is responsible for reporting adverse event information to all participating Principal Investigators and regulatory authorities, as applicable.
The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

18.7 Subject Death Reporting

A subject death during the study should be reported to Boston Scientific as soon as possible preferably within three (3) calendar days of notification to the investigational center. The site's IRB/EC must be notified of any deaths in accordance with policies and procedures. A detailed statement (death letter) that provides detailed information describing the circumstances surround the death must be provided. A death letter in the local language is acceptable. The details listed below should be addressed in the death narrative in order for BSC to understand the circumstances surrounding the death:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Rhythm at the time of death
- Relationship to pulse generator, lead, clinical investigation procedure or patient condition
- Whether or not the death was witnessed
- The device status and/or activity at the time of death, if applicable
- Whether or not the patient had worsening heart failure
- Any other circumstances surrounding the death
- The approximate time interval from the initiating event to death (temporal course)
- Investigator or sub-investigator signature and date

Also submit the following documentation if the patient died in the hospital:

- A copy of the medical records for that admission (e.g. test results, operative report, progress notes)
- Death certificate (if available)
- Autopsy report (if available)
- Whenever possible, the IPG should be interrogated.

If the patient died outside the hospital:

- A copy of the most recent clinic visit (if not already submitted)
- Death certificate (if available)
- Whenever possible, the IPG should be interrogated.

Upon death, the device may be interrogated using a Consult or using a programmer. If a programmer interrogation is used, the "device data dump" (not "save all to disk") option should be chosen. If data are stored on a disc or flash drive, the disc or flash drive should be kept in the subject's MANAGE-HF study binder at the investigative site, and copy should be mailed to the sponsor

19 Informed Consent

Details in this section apply to both phases (Phases I and II) of the MANAGE-HF study.

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject. There is a separate consent form for Phase I and Phase II. Subjects can only consent and participate in one phase. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational 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, 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 investigative site's IRB/EC. 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 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 or his/her legal representative,
- 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 under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. 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), 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. The new version of the ICF must be approved by the IRB/EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

An EDC Screening/enrollment may be maintained to document select information about candidates who fail to meet the general or "other specific" entry criteria.

20 Committees

Details in this section apply to both phases (Phases I and II) of the MANAGE-HF study.

20.1 Safety Monitoring Process

To promote early detection of safety issues, the Boston Scientific Medical Safety group and MANAGE-HF Steering Committee will evaluate the ongoing safety of the trial. Success of this approach requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source documents and other data information. The BSC Medical Safety and Steering Committee groups include physicians and nurses with expertise in electrophysiology, heart failure, and general cardiology and with the necessary therapeutic and subject matter expertise to evaluate safety.

20.2 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be formed to monitor patient safety and the trial conduct. A detailed DMC Charter will be written to govern the activities of this committee. The DMC will be independent from the sponsor, the investigators, and the Steering Committee. The board will be composed of three to five members, including at least one with expertise in the following areas: biostatistics, heart failure, and cardiac electrophysiology/device management. At least one member will also have extensive clinical trial experience. The DMC will have access to unblinded patient-level and aggregated study results throughout the

course of the study. The DMC may recommend early termination of the trial if there are safety concerns or if a pre-defined stopping criterion has been fulfilled.

The DMC will convene within 6 months after the first patient is enrolled. The DMC will meet periodically, or as needed, to review the results of the trial and to evaluate any safety issues that may arise during the course of the study.

20.3 Clinical Events Committee

The Clinical Event Committee (CEC) is constituted of a group of independent clinical experts external to the study and to the Sponsor. The CEC will provide an independent review of all Serious Adverse Events (SAE) which resulted in a hospitalization or an outcome of death. The CEC will adjudicate events that count towards the primary endpoint, as indicated in Section 10.1.

Other events, at the discretion of BSC may also be submitted to the CEC for review.

21 Suspension or Termination

21.1 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 administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

21.1.1 Criteria for Premature Termination of the Study

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

- A pre-defined primary endpoint stopping rule has been fulfilled (defined in a separate MANAGE-HF Statistical Analysis Plan).
- The DMC has recommended early termination of the study (Section 20.2).
- 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.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

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

Any investigator, or IRB/ EC in the MANAGE-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, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

21.3 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 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 or EC terminates participation in the study, participating investigators, associated IRBs/ECs, 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 investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

21.4 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 no subjects have been enrolled for a period beyond 6 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions. The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed by their clinician for routine medical care.

22 Publication Policy

Details in this section apply to both phases (Phases I and II) of the MANAGE-HF study.

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 contributorship criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order 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 contributorship 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.

23 Reimbursement and Compensation for Subjects

Details in this section apply to both phases (Phases I and II) of the MANAGE-HF study.

23.1 Subject Reimbursement

Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

23.2 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, and if required by applicable law.

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25 Abbreviations and Definitions

25.1 Abbreviations are shown in Table 25-1.

Table 25-1: Abbreviations

AE	Adverse Event
ACE	angiotensin converting enzyme
ADE	Adverse Device Effect
AHI	Apnea–Hypopnea Index
AMC	Alert Monitoring Center
ARB	Angiotensin Receptor Blocker
ASADE	Anticipated serious adverse device effect
ATP	anti-tachycardia pacing
BNP	Brain Natriuretic Peptide

Table 25-1: Abbreviations

BP	Blood pressure
BSC	Boston Scientific
CA	competent authority
CAPTIVATE	Evaluation of Automatic Threshold Algorithms
CC	cubic centimeter
CEC	clinical events committee
CFR	complication-free rate
CHAMPION	CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure
CNT	Control
COMPASS-HF	Chronicle Offers Management to Patients With Advanced Signs and Symptoms of Heart Failure
COPD	Chronic Obstructive Pulmonary Disease (COPD)
CPAP	continuous positive airway pressure,
CRO	Contract Research Organization
CRT-D	Cardiac Resynchronization Therapy Defibrillator
DOT-HF	Diagnostic Outcome Trial in Heart Failure
DMC	Data Monitoring Committee
DVT	deep vein thrombosis
EC	Ethics Committee
Echo	Echocardiography
ECG	electrocardiogram
eCRF	electronic case report forms
EDC	electronic data capture
EF	Ejection Fraction
ER	Emergency Room
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FU	Follow up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HA	alternative hypothesis
H0	null hypothesis
HF	Heart Failure
HL	HeartLogic
ICD	implantable cardioverter defibrillators
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IPG	Implanted pulse generator

Table 25-1: Abbreviations

IN-TIME	Influence of Home Monitoring on the Clinical Status of Heart Failure Patients With an Impaired Left Ventricular Function
IMPEDANCE-HF	The Non-invasive Lung IMPEDANCE-guided Preemptive Treatment in Patients with Chronic Heart Failure (IMPEDANCE-HF) Trial
ISO	International Organization for Standardization
IRB	Institutional Review Board
IV	intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LBBB	Left bundle branch block
LSS of 4-SITE	Longitudinal Surveillance Study of the 4-SITE Lead/Header System
LV	Left Ventricle
M/Mo	Month
MANAGE-HF	Multiple cArdiac seNsors for mAnaGEment of Heart Failure
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy
Mcg	microgram
Mg	milligram
MI	Myocardial Infarction
MN	Minnesota
ms	milliseconds
MUGA	Multiple gated acquisition scan
MultiSENSE	Evaluation of Multisensor Data in Heart Failure Patients With Implanted Devices
NAVIGATE X4	Evaluation of ACUITY™ X4 Quadripolar Coronary Venous Leads and RELIANCE™ 4-FRONT Defibrillation Leads
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart association
NSAID	nonsteroidal anti-inflammatory drugs
O	optional but recommended
OOS	Out of service
OPT	optimal pharmacologic therapy
PG	Pulse generator
Pt	Patient
R	Required
RA	Right atrium
REM-HF	Remote Management of Heart Failure Using Implantable Electronic Devices
RV	Right Ventricle

Table 25-1: Abbreviations

SADE	Serious Adverse Device Effects
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
Tx	Therapy
TZD	thiazolidinediones
UADE	Unanticipated Adverse Device Effects
US	United States
USADE	Unanticipated Serious Adverse Device Effects
Vs	versus
Yr	Year

25.2 Definitions

Definitions are shown in Table 25-2.

Table 25-2: Definitions

Term	Definition
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