Protocol & Statistical Analysis Plan
Cover Page

SMART Registry

Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy Registry

CLINICAL INVESTIGATION PLAN

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Study Reference Number: C1949

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Vendors/Labs	A list of vendors/laboratories involved in the trial is maintained by the sponsor.

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Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AA	**20-JAN-2017**	90702637 Rev./Ver. AH	N/A	Original Release	
B	**06-FEB-2017**	90702637 Rev./Ver. AH	Cover Page Header	SMART CRT Registry Protocol by SMART Registry Protocol	No CRT mention required
B	**06-FEB-2017**	90702637 Rev./Ver. AH	Page 29 Header	SMART CRT Registry Protocol SMART Registry Protocol	No CRT mention required

2. Protocol Synopsis

Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy Registry SMART Registry	
Study Objective(s)	To learn in a general Cardiac Resynchronization Therapy Defibrillators (CRT-D) population, which optimization techniques are used and how effective they are. It will compare 12-month response rates among different optimization methods and characterize which selected subject subgroups achieve better response than others. A subset of SMART Registry subjects will contribute to the NG4 Post Market Clinical Follow Up (PMCF) Cohort whose objective is collecting data on the NG4 CRT-D features and device usage in a real world setting and monitor long term safety associated with these devices to support CE Mark.
Planned Indication(s) for Use	All implanted devices will be used within the current labeled indications for use. CRT-D devices are intended to provide cardiac resynchronization therapy and provide anti-tachycardia pacing and defibrillation therapy.
Test Device	The quadripolar BSC CRT-D models in the NG3 family (AUTOGEN, INOGEN and DYNAGEN families) used in the study are approved for commercial use. Future generation of quadripolar BSC CRT-D models in the NG4 family (RESONATE MOMENTUM, CHARISMA and VIGILANT) will be used in the study once approval by the local regulatory body will be obtained. Although the NG4 family of models (with the exception of CHARISMA) may become approved in the US during the study, the RESONATE, MOMENTUM, VIGILANT families of devices are not to be used in the SMART Registry in the US until device approval is received by FDA and the devices are available at the participating sites. All CRT-D devices utilized in the study include LV VectorGuide™ and SmartDelay™ features. The Left Ventricular MultiSite Pacing (LV MSP) feature is available in the NG4 family of CRT-D devices (RESONATE HF, RESONATE, CHARISMA VIGILANT, and MOMENTUM devices). These devices have quadripolar headers and accept LV quadripolar leads according to the corresponding Physician Technical Manual

Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy Registry

SMART Registry

NG3 CRT-D devices:

Device Name	EU Model Numbers	US Model Numbers
AUTOGEN™ X4	G177 and G179	G166 and G168
DYNAGEN™ X4	G156 and G158	G156 and G158
INOGEN™ X4	G146 and G148	G146 and G148

NG4 CRT- D devices:

Device Name	EU Model Numbers	US Model Numbers*
RESONATE™ HF	G528, G537, G547 and G548	G528, G537, G547 and G548
RESONATE™ X4	G428, G437, G447 and G448	G428, G437, G447 and G448)
MOMENTUM™ X4	G128 and G138	G128 and G138
VIGILANT™ X4	G228, G237, G247 and G248	G228, G237, G247 and G248
CHARISMA™ X4	G328, G337, G347 and G348	Not available

** The NG4 family of CRT-D devices may not be available in the US during a portion of the study. NG4 devices may not be used in the US until device approval is received from FDA.*

Study Design	Global, multicenter, prospective, observational, single-arm post market study (Registry)
Planned Number of Subjects	Approximately 2000 subjects will be enrolled in the study. To reduce the impact of individual center bias, each site may enroll up to a maximum of 200 subjects. NG4 PMCF Cohort will be constituted by a minimum of the first 103 European subjects identified by the Sponsor enrolled in the SMART Registry, implanted with an NG4 device and that had LV MSP feature enabled at any time during the initial 12 months follow up. The actual belonging to the NG4 PMCF study cohort will be based on sponsor's becoming aware date of the MSP feature being enabled, therefore following a chronological order.

Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy Registry SMART Registry	
Planned Number of Participating Sites / Countries	A maximum of 200 sites in Europe, United States, Canada and Asia-Pacific region.
Primary Endpoint(s)	CRT Response rate at 12 months, defined by a Clinical Composite Score (Full Registry). ➢ All-cause mortality ➢ Heart failure events ➢ NYHA Class ➢ Quality of life (Patient Global Assessment instrument)
NG4 PMCF Endpoint	The Post Market Clinical Follow Up (PMCF) endpoint is NG4 PG Related Complication Free rate at 36 months (NG4 PMCF Cohort only).
Additional Endpoints	Multivariate analyses to determine which covariates and optimization methods are associated with response (Full Registry)
Method of Assigning Patients to Treatment	Subjects implanted with a qudripolar NG3 or NG4 CRT-D device in conjunction with a quadripolar lead from any manufacturer will be selected based on the inclusion/exclusion criteria and if deemed to be eligible for participation, will be asked to sign the informed consent form. Subjects who meet the eligibility criteria and have signed and dated the Informed Consent Form are considered enrolled in the study.
Follow-up Schedule	Each enrolled subject will be followed at the at the following visits: ➢ Enrollment and consent at post implant visit ➢ 12 months Clinic Visit (per site Standard of Care) NG4 PMCF Cohort will be followed additionally at: ➢ 24 months Clinic Visit ➢ 36 months Clinic Visit ➢ Annually until the last PMCF cohort subject has completed 36 months visit. There are no other additional study-related visits required. Additional visits occurred per the site Standard of Care (SOC) in the first 12 months of follow up may be collected.

Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy Registry SMART Registry	
Study Duration	The study duration is estimated to be approximately 6 years from first enrollment to study closure. Each subject will be followed for a minimum of 12 months. • NG4 PMCF Cohort will be followed until the last actively followed PMCF subject achieves 36 months of follow-up. The study will be considered complete after the last actively followed subject from the NG4 PMCF Cohort of subjects achieves 36 months of follow up or the last actively followed subject from the full registry achieves 12 months of follow up, whichever happens later.
Key Inclusion Criteria	• Subject implanted or upgraded with a NG3 or NG4 CRT-D device connected with any manufacturer quadripolar LV lead based on BSC labeling for devices in specific geographies. • Subjects must be enrolled between 1 and 21 calendar days post CRT-D implantation procedure. • Subject is age 18 or above, or of legal age to give informed consent specific to each country and national laws • Subject is willing and capable of complying with follow-up visits and procedures as defined by this protocol
Key Exclusion Criteria	• Subject with documented life expectancy of less than 12 months • Subject currently on the active heart transplant list or has a current Left Ventricular Assist Device or other assist device (mechanical circulatory support device). • Subject who have had a pre-existing CRT device • Subject enrolled in any other concurrent clinical trial without prior written approval from BSC Clinical Trial Manager • Women of childbearing potential who are or might be pregnant at time of study enrolment • Any contra-indication to receive a CRT-D device per local guidelines
Statistical Methods	
Primary Statistical Hypothesis	The proposed observational study (Registry) does not have formal hypothesis testing and is exploratory in nature.
Statistical Test	The Clinical Composite Score allows for three levels of CRT Response: Improved, Unchanged or Worsened. The number and percent of SMART

Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy Registry SMART Registry	
Method	Registry subjects contributing to each level of CRT Response will be calculated. CRT Response rates will be compared between selected subgroups. Due to the ordinal nature of the three CRT response levels defined by the Clinical Composite Score, statistical tests accounting for ordinality of response will be used, when appropriate. In analyses comparing two subgroups, a Cochran-Armitage test for trend will be employed. If more than two subgroups will be compared, a cumulative logit model or some other appropriate test will be used.
Sample Size Parameters	Due to a lack of hypotheses for this objective, the sample size cannot be determined through traditional statistical powering techniques. It is, however, desired to have a high degree of confidence in the CRT Response rates obtained in the study. In order to obtain a two-sided 95% confidence interval width of the overall SMART Registry CRT Response rate that does not exceed 5%, a total of 2000 subject enrollments are required. Additionally, it is expected that with a total of 2000 enrollments, each subgroup analysis will include a sufficient sample of approximately 50 subjects

3. Table of Contents

3.1. *Table of Figures*

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4. Introduction

Heart failure may be exacerbated by the presence of an interventricular conduction delay. This delay in conduction, evidenced by a wide QRS pattern on an ECG, results in an inefficient asynchronous contraction pattern. Cardiac resynchronization therapy (CRT) is the application of electrical stimuli to both ventricles with an implanted device.

Cardiac resynchronization therapy, when combined with defibrillation (CRT-D) was first demonstrated to be safe and effective in the CONTAK CD study[1]. This study showed that defibrillator subjects with NYHA Class III-IV heart failure, reduced ejection fraction, and wide QRS who randomized to CRT-D On had significantly improved exercise performance, reduction in symptoms, increased quality of life, and improved cardiac structure and function when compared to subjects randomized to CRT-D Off.

The COMPANION study was a subsequent study of subjects NYHA Class III-IV heart failure, reduced ejection fraction, and wide QRS. Unlike the prior CONTAK CD study, subjects in COMPANION were not indicated for a defibrillator. Subjects in this study were randomized on a 2:2:1 basis to CRT-D, CRT-P (CRT without a defibrillator), or optimal pharmacological therapy. COMPANION not only confirmed the results from the CONTAK CD study, but demonstrated additional benefits of CRT that included significant reduction in all-cause mortality, both alone and in combination with hospitalization due to all-causes, cardiovascular causes, or heart failure[2].

The study of CRT-D was extended in the MADIT CRT trial to defibrillator subjects with NYHA Class I-II, reduced ejection fraction, and wide QRS. Like the COMPANION study before it, MADIT CRT showed that CRT-D was associated with significant reduction in all-cause mortality, alone and in combination with heart failure hospitalization when compared to subjects receiving a defibrillator alone[3]. MADIT CRT also demonstrated significant reduction in left ventricular volumes and improvement in left ventricular ejection fraction.

The benefits of CRT-D are not conferred on every subject implanted with a device, however. Subjects who fail to show improvement are typically referred to as “non-responders”. There is no universally accepted metric for defining response. Commonly used outcome measures in clinical practice include symptomatic relief, quality of life, or exercise tolerance. Improvements in echocardiographic parameters (left ventricular dimensions/volumes and left ventricular ejection fraction) may also be used. Large scale clinical trials tend to use composite endpoints, of which the Clinical Composite Score (CCS) first described by Milton Packer is the most widely used[4]. This endpoint combines four metrics: all-cause mortality, heart failure hospitalization, NYHA Class, and quality of life as measured with the patient global assessment instrument. When clinical metrics are used, the typical non-response rate cited is one-third of patients are non-responders. When echo-based measures are used, the non-response rate is somewhat higher.

Figure 1 below summarizes the Clinical Composite Endpoint (CCE) results for clinical trials that were used to support regulatory approvals of CRT devices or expanded indications. Approximately two-third of Class III-IV patients are responders. Class I-II patients have not been studied as extensively and have response rates about 10 percentage points lower. This disparity is likely due to the less severe nature of heart failure in Class I-II patients. Since

they are less symptomatic than Class III-IV patients, demonstrating improvement is more difficult. For these patients, maintaining the status quo may be a more appropriate therapeutic goal. In these patients, approximately 80% either improve or maintain their heart failure status.

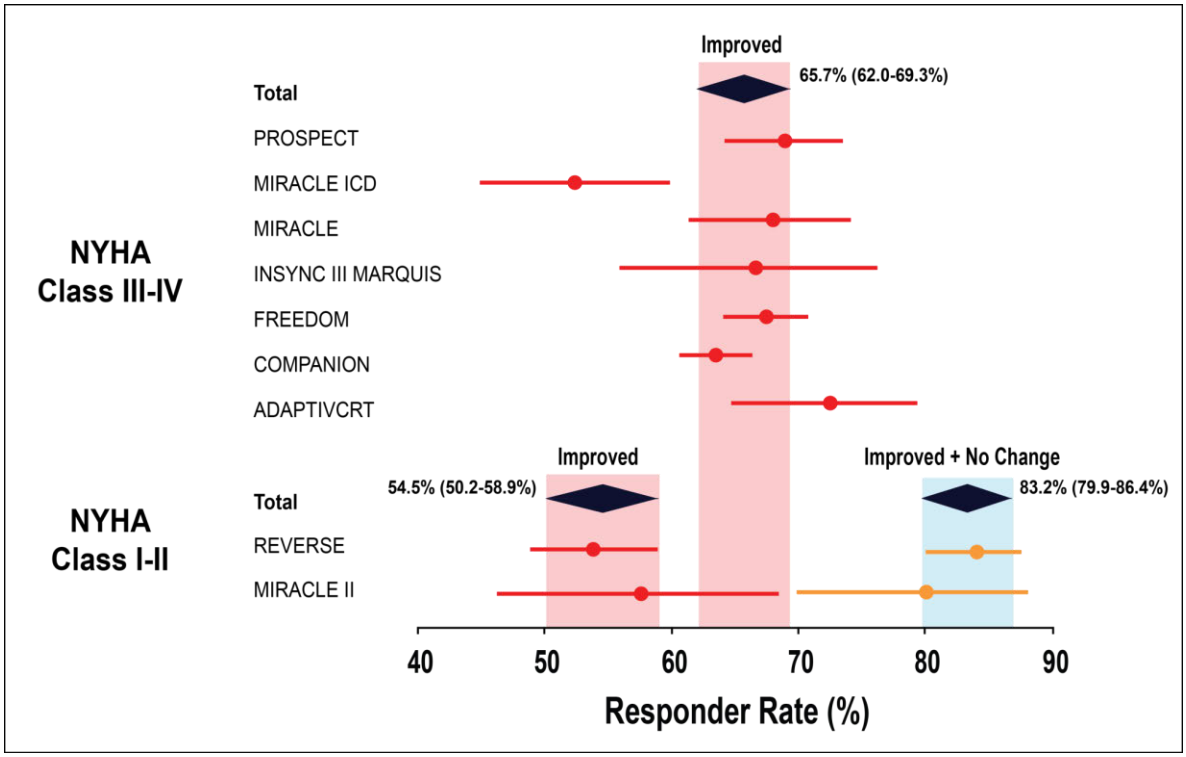

Figure 1: Clinical Composite Events results for clinical trials used to support regulatory approvals of CRT devices or expanded indications

The potential reasons for non-response are varied and include[5]:

- Poor or wrong lead location
- Improper programming
- Myocardial scar
- Lack of baseline dyssynchrony
- Irreversibily advanced heart failure
- Atrial fibrillation

Several strategies have been tested in attempt to identify and reduce the number of non-responders. Such strategies include post hoc analyses of left ventricular (LV) lead placement, pacing at sites of maximal electrical or mechanical delay/dyssynchrony and the use of device-based optimization features. The results of these studies have identified several factors that may impact response. For instance, left ventricular pacing in apical regions is deleterious, whereas pacing at sites of late electrical or mechanical delay is associated with better outcomes.[6-14]

Device-based features have been introduced that modify how CRT is delivered. These include:

- Interventricular timing (V-V timing)
- AV Delay
- Multi-site pacing
- LV-only CRT

To date, the randomized clinical studies conducted have shown equivalence with conventional CRT delivery without demonstrating superiority although subsequent subgroup analyses suggest that some patients may be helped.

V-V Timing: The InSync III Marquis Study[15] using the CCE, DECREASE HF Study[16] using a composite of peak VO2 and LVESD, and RHYTHM ICD V-V Optimization Study[17] using peak VO2 all demonstrated the safety of this feature and non-inferiority to conventional sequential biventricular pacing, but none showed superiority.

LV Only CRT: The DECREASE HF Study[16] using a composite of peak VO2 and LVESD and the B-LEFT HF Study[18] using the CCE demonstrated safety of LV pacing but neither showed that LV Only CRT was superior to conventional biventricular CRT. The AdaptivCRT study, using the CCE, evaluated an algorithm that provided either LV or biventricular pacing depending on AV conduction while also periodically adjusting AV delay and V-V timing. This algorithm was found to be non-inferior to echocardiographic-guided optimization[19].

AV Delay: Randomized studies to determine the effectiveness of optimizing AV delay have been based on algorithms that use measurements of intrinsic conduction to establish an AV delay. These studies include FREEDOM[20] (which also included a V-V timing optimization algorithm) and used the CCE and SMART-AV[21] which used LVESV, which showed these methods were non-inferior to empiric programming. The RESPOND-CRT study, which evaluated a CRT system that employed a hemodynamic sensor to optimize both AV and VV timing, used a modified version of the CCE. This study as well found that the sensor was non-inferior to echocardiographic optimization[22].

Left Ventricular Multi-Site Pacing: Left ventricular Multi-Site Pacing (LV MSP) has emerged as an option for addressing the non-responder issue with conventional CRT by using a quadripolar lead to pace two sites within the same coronary vein. Studies have shown that LV MSP improved acute hemodynamics and ventricular synchrony, and resulted in faster activation of myocardium and improved clinical responses as measured by the ventricular reverse remodeling and LVEF value comparing to single site LV pacing[23-31]. Furthermore, acute studies on LV MSP have shown no ventricular arrhythmias or other adverse events during acute testing, implant and pre-discharge[27].

Among different LV MSP configurations discussed in the literature, pacing from two sites that are farthest apart (distal to proximal) was the most common optimal configuration as it may recruit a larger area of the myocardium with late activation to achieve better ventricular synchrony[15, 19]. Opting for the two pacing sites that are farthest apart may provide a simple means for pacing vector selection in MSP, in combination with the evaluation of pacing threshold and impedance, and the avoidance of the phrenic nerve stimulation (PNS).

The Multi-Point Pacing (MPP) Trial[32], using a modified version of the CCS, evaluated a CRT-D system that paced the left ventricle from two distinct sites using a quadripolar lead. The study had a 3 month run-in phase that identified non-responders who were then randomized to MPP or conventional CRT. The MPP Trial provided safety data of the MPP

feature. The MPP therapy was found to be non-inferior to conventional CRT in converting non-responders to responders.

Boston Scientific's LV MSP is intended to improve the cardiac resynchronization therapy response by delivering two LV pulses per pacing cycle using quadripolar LV leads. It provides physicians a new set of tools that allow for individualized patient therapy with the goal of improving clinical response in non-responders to conventional CRT therapy.

5. Device Description

5.1. *CRT-D Device*

The quadripolar BSC CRT-D models in the NG3 family (AUTOGEN, DYNAGEN and INOGEN families) used in the study are approved for commercial use. Future generation of quadripolar BSC CRT-D models in the NG4 family (RESONATE, MOMENTUM CHARISMA and VIGILANT) will be used in the study once approval by the local regulatory body has been obtained.

Although the NG4 family of models (with the exception of CHARISMA) may become approved in the US during the study, the RESONATE, MOMENTUM, VIGILANT families of devices are not to be used in the SMART Registry in the US until device approval is received by FDA and the devices are available at the participating sites.

All CRT-D devices utilized in the study will include LV VectorGuide™ (Section 5.1.1) and SmartDelay™ (Section 5.1.2) features.

The Left Ventricular MultiSite Pacing (LV MSP) feature (Section 5.1.3) is available in the NG4 family of CRT-D devices (RESONATE HF, RESONATE, VIGILANT, CHARISMA and MOMENTUM devices).

These devices have quadripolar headers and accept LV quadripolar leads from any manufacturer.

See **Table 5.1-1** for a complete list of eligible CRT-D device models for this trial.

Table 5.1-1: Eligible CRT-D Device Model

NG3 CRT-D devices:

Device Name	EU Model Numbers	US Model Numbers
AUTOGEN™ X4	G177 and G179	G166 and G168
DYNAGEN™ X4	G156 and G158	G156 and G158
INOGEN™ X4	G146 and G148	G146 and G148

NG4 CRT- D devices:

Device Name	EU Model Numbers	US Model Numbers*
RESONATE™ HF	G528, G537, G547 and G548	G528, G537, G547 and G548
RESONATE™ X4	G428, G437, G447 and G448	G428, G437, G447 and G448)
MOMENTUM™ X4	G128 and G138	G128 and G138
VIGILANT™ X4	G228, G237, G247 and G248	G228, G237, G247 and G248
CHARISMA™ X4	G328, G337, G347 and G348	Not available

** The NG4 family of CRT-D devices may not be available in the US during a portion of the study. NG4 devices may not be used in the US until device approval is received from FDA.*

5.1.1. LV VectorGuide™

LV VectorGuide feature allows the clinician to quickly evaluate multiple quadripolar LV pacing vectors in order to identify the best configuration. The following tests can be assessed in each pacing configuration from the LV VectorGuide screen:

- RV sense (RVs) to LV sense (LVs) timing (RVLV timing), the delay between detection of an intrinsic R-waves between the RV and LV EGMs LV lead impedance
- LV lead impedance
- LV pace threshold
- Phrenic Nerve Stimulation (PNS)

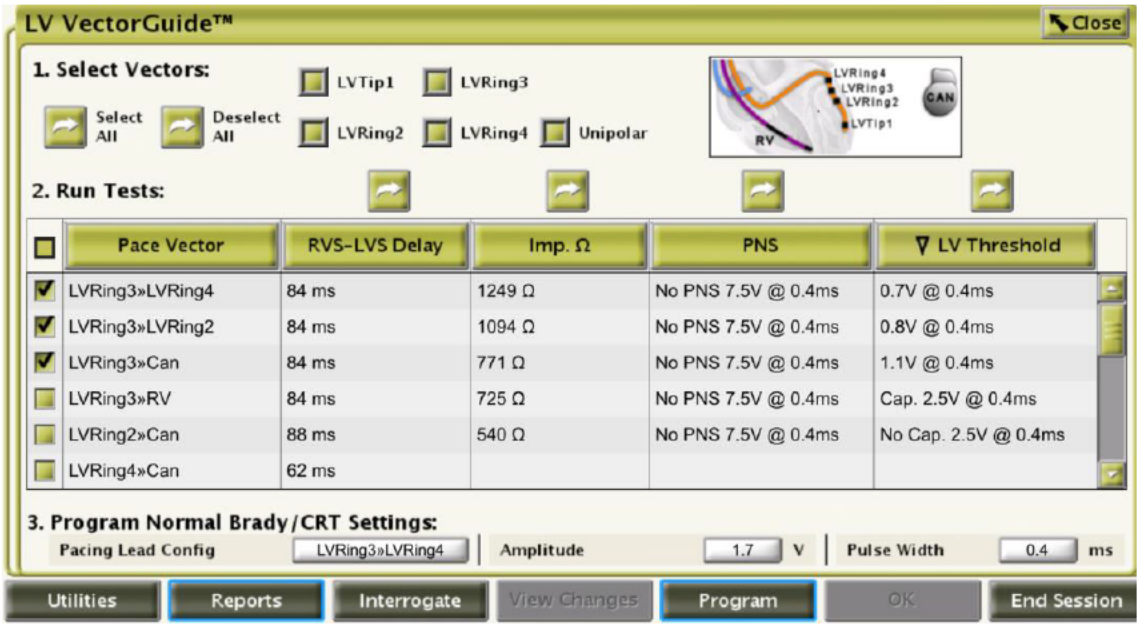

Figure 2: LV VectorGuide Screen Example

5.1.2. SmartDelay™

The SmartDelay optimization feature quickly (<2.5 minutes) provides recommended settings for programming paced and sensed AV Delay based on the measurement of intrinsic AV intervals. The objective of the feature is to recommend AV Delays that provide optimally timed CRT, which maximizes contractile function.

The SmartDelay optimization test evaluates right and left ventricular response to both atrial sensed and paced events to determine suggested settings for the following: Paced AV Delay (PAV), Sensed AV Delay (SAV), pacing chamber(s).

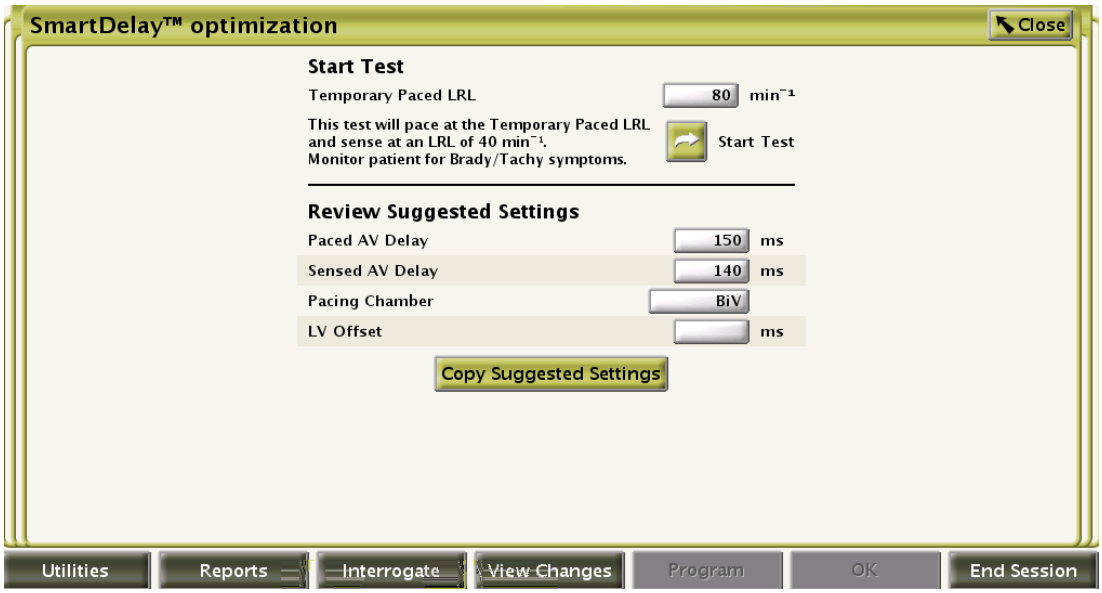

Figure 3: SmartDelay Screen Example

5.1.3. LV MultiSite Pacing

Among new features available in the NG4 CRT-D devices is the Left Ventricular MultiSite Pacing (LV MSP).

The LV MSP feature allows the clinician to program cardiac resynchronization therapy (CRT) to deliver two LV paces per cardiac cycle during Normal Brady operation which is different compared with traditional CRT with one LV pace per cardiac cycle. Each of the LV paces has its own independently programmable pacing vector and LV MSP provides the clinician the ability to control the timing between the ventricular paces.

The clinician can program Pacing Chamber so that the system delivers CRT pacing therapy to both ventricular chambers (BiV Pacing) or to just the left ventricular chamber (LV Only).

5.1.4. HeartLogic™ Index

Among new features available in some of the NG4 CRT-D devices is the HeartLogic™ Heart Failure Diagnostic Service (HeartLogic). HeartLogic is comprised of a composite trend called the HeartLogic Index, a configurable yellow Alert, and the device measured Heart Sounds trends. These alerts are all delivered via BSC LATITUDE™ NXT 5.0 System (LATITUDE) (or equivalent) remote monitoring system. The HeartLogic Index and Alert are a validated diagnostic tool to detect gradual worsening of heart failure (HF) over days or weeks using multiple physiologic measurements (accepted for publication).

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 and should not replace standard-of-care treatment.

The CRT-D device, along with its associated leads, constitutes the implantable portion of the system. The external portion of the system includes the commercially available LATITUDE System (or equivalent) and the Model 3120 Programmer Recorder Monitor (or equivalent). 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 system is shown in Figure 4. When the subject is near the LATITUDE communicator, data will automatically be uploaded and transmitted to the clinician for review. When the HeartLogic index is met or exceeded, a yellow alert is generated which triggers health care professional to review the data and contact the subject.

Figure 4: LATITUDE NXT 5.0 System

5.2. *Other Devices*

Any commercially available Right Atrial (RA) lead, Right Ventricular (RV) lead and quadripolar LV lead from any manufacturer is eligible in the study.

6. Study Objectives

The primary objective in this study is to learn in a general CRT-D population, which optimization techniques are used and how effective they are. It will compare 12-month response rates among different optimization methods and characterize which selected patient subgroups achieve better response than others.

A subset of SMART Registry subjects will contribute to the NG4 Post Market Clinical Follow-Up (PMCF) Cohort whose objective is collecting data on the NG4 CRT-D features and device usage in a real world setting and monitor long term safety associated with these devices to support CE Mark.

7. Study Endpoints

The primary endpoint will evaluate the CRT Response rate among Full Registry subjects at 12 months, defined by a Clinical Composite Score (CCS) consisting of:

- All-cause mortality
- Heart failure events
- NYHA Class
- Quality of life (patient Global Assessment instrument)

For the NG4 PMCF Cohort the primary endpoint will be NG4 PG related complication free rate at 36 months.

SMART Registry Entire Cohort

The Clinical Composite Score developed by Packer will be evaluated to determine CRT Response in the entire SMART Registry cohort and in selected subgroups[4, 17]. The CCS will be evaluated at 12 months and consists of all-cause mortality, heart failure events, NYHA class and quality of life as assessed by the patient Global Assessment instruction. CRT response status for each subject will be determined by the CCS, with CRT response classified as improved, unchanged or worsened.

NG4 PMCF Cohort

In the subjects included in the NG4 PMCF Cohort, the NG4 PG-related complication free rate (CFR) at 36 months will be evaluated. The PMCF Primary Endpoint will evaluate the safety of the NG4 device when LV MSP is enabled.

8. Study Design

This is a global, multicenter, prospective, observational, single-arm post market study (Registry), including the NG4 PMCF necessary to support NG4 CE Mark.

8.1. *Scale and Duration*

The study will be conducted at up to 200 sites globally. Approximately 2000 subjects will be enrolled in Europe, United States, Canada and Asia Pacific, and sites may continue to enroll subjects until notified of enrollment completion.

SMART Registry Entire Cohort

Enrollments are expected to occur over a period of approximately 28 months. Subjects enrolled in the SMART Registry will be followed for12 months.

NG4 Post-Market Clinical Follow-up Cohort

The NG4 PMCF subjects will be enrolling exclusively from European participating sites and will be followed for a minimum of 36 months.

The SMART Registry and NG4 PMCF Cohort are expected to be completed in approximately 6 years.

The subject follow-up schedule and study flow are shown in Figure 5.

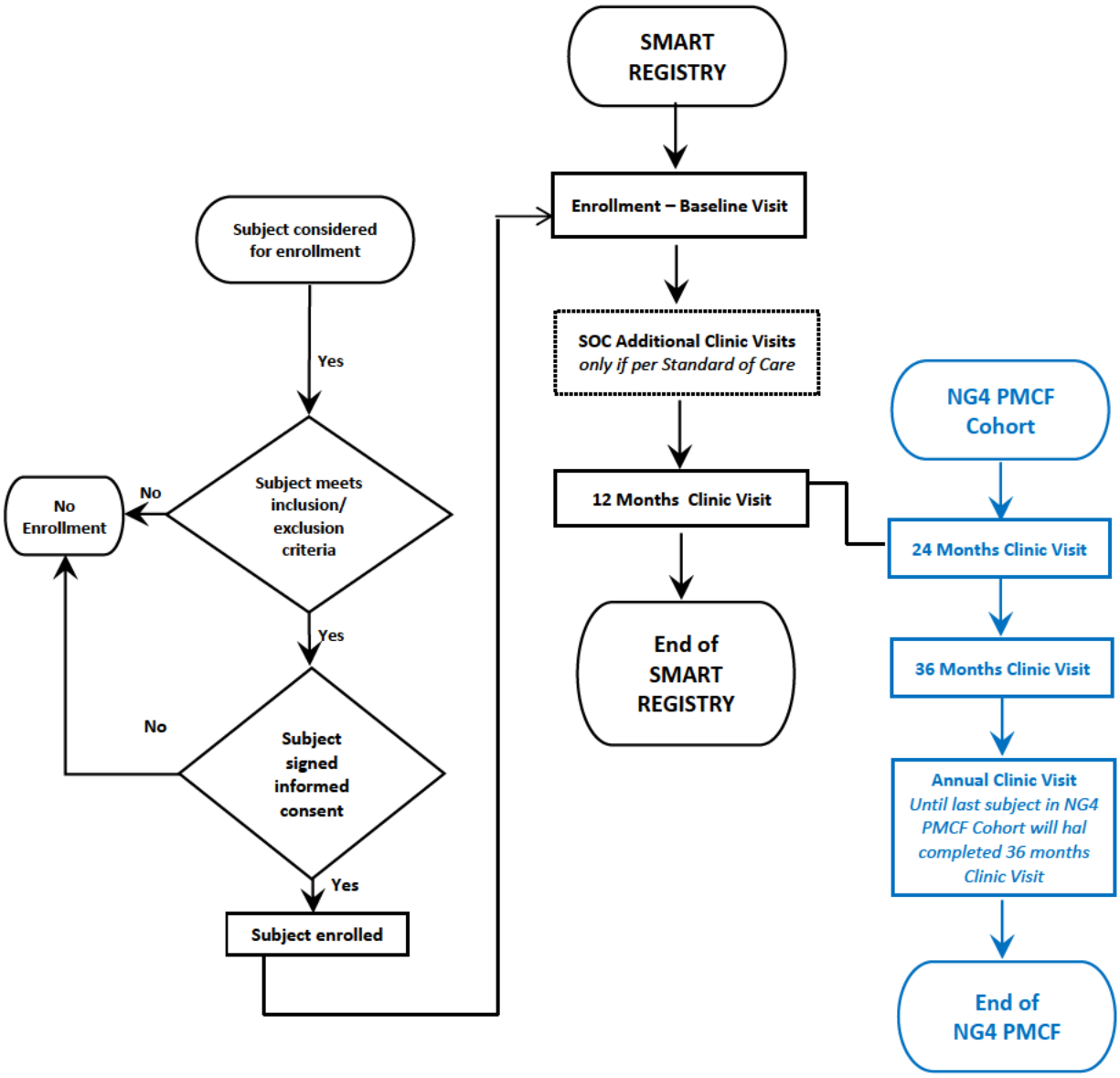

Figure 5: SMART Registry Study Flow Chart

8.2. *Treatment Assignment*

Potential study subjects will include "all-comers" who meet the enrollment criteria. Study Investigators are expected to approach all potentially eligible study subjects who have been implanted (between 1 and 21 calendar days post CRT-D device implant window) with an

eligible BSC CRT-D device and a compatible quadripolar LV lead according to their corresponding Physician Technical Manual

8.2.1. Treatment and Control

Subjects will not be randomized or blinded to treatment received. Any subject meeting all inclusion and no exclusion criteria is enrollment eligible for the SMART Registry. Subjects are considered enrolled in the study once the informed consent form (ICF) has been executed.

8.3. *Justification for the Study Design*

While a randomized study is considered the gold standard in many clinical research settings, considering the sample size and study objectives, a non-randomized, observational study with up to 2000 subjects is considered appropriate to meet the objectives of the study. In order to obtain a "real world" picture of the device use, inclusion and exclusion criteria and follow up schedule has been written generally enough to allow for study center specific standard of practice that should accurately capture the device use in a "standard" clinical setting.

Additionally by requiring the study centers to follow their specific standard of practice, risk to the subject is minimized because the treatment received by the subject will be similar to the treatment the subject would receive if not participating in the study.

The SMART Registry is a global, multicenter, prospective, observational, single-arm post market study (registry), including a European, multicenter, prospective, single-arm sub-study (NG4 PMCF). The objective of the SMART Registry is to characterize rates of CRT response in a general CRT-D population as well as in selected subgroups defined by device and subject characteristics.

It is desired to have a high degree of confidence in the CRT response rates obtained in the study. To obtain a two-sided 95% confidence interval width of the CRT response rate that does not exceed 5%, a total of 2000 subject enrollments are required. Additionally, it is expected that with a total of 2000 enrollments, each subgroup analysis will include approximately 50 subjects.

A minimum of 103 NG4 PMCF subjects are required to sufficiently power the PMCF endpoint.

The primary objective of the NG4 PMCF sub-study is to gather data to establish the chronic safety, performance and effectiveness of NG4 CRT-D devices.

9. Subject Selection

9.1. *Study Population and Eligibility*

Subjects included in the SMART Registry should be selected from the investigator's general patient population of subjects who are indicated for CRT-D implantation per BSC labeled

indication provided in **Section 9.2**. Investigators are responsible for screening all potential subjects and selecting those who meet the eligibility criteria for the study as described in **Sections 9.2** and **Section 9.3** below. Investigators are encouraged to include *consecutive* subjects in order to minimize selection biases.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 9.2-1) may be given consideration for inclusion in this Registry, provided no exclusion criterion (see Section 9.3) is met.

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	• Subject implanted or upgraded with an NG3 or NG4 CRT-D device based on BSC labelling for devices in specific geographies in conjunction with a quadripolar LV lead from any manufacturer • Subjects must be enrolled between 1 and 21 calendar days post CRT-D implantation procedure • Subject is age 18 or above, or of legal age and willing and capable to provide informed consent specific to each country and national laws • Subject is willing and capable of providing informed consent • Subject is willing and capable of complying with follow-up visits and procedures as defined by this protocol

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 9.3-1) will be excluded from this clinical study.

Table 9.3-1: Exclusion Criteria

Clinical Exclusion Criteria	• Subject with documented life expectancy of less than 12 months • Subject currently on the active heart transplant list or has a current Left Ventricular Assist Device or other assist device. • Subject who have had a pre-existing CRT device • Subject Enrolled in any other concurrent clinical trial without prior written approval from BSC Clinical Trial Manager • Women of childbearing potential who are or might be pregnant at time of study enrolment • Any contra-indication to receive a CRT-D device per local guidelines

10. Subject Accountability

10.1. *Point of Enrollment*

Investigators will select subjects who are appropriate for study inclusion as per eligibility criteria. Subjects who meet the eligibility criteria and agree to participate will be given written informed consent approved by the center's Institutional Review Board (IRB) / Ethics Review Committee (ERC).

All subjects who complete the informed consent process, sign and date the informed consent form (ICF) are considered enrolled in the SMART Registry. Subjects who have signed the informed consent but are found to not meet eligibility criteria at the time of enrollment are classified as consent ineligible. No study related procedures or data collection can take place until the ICF is executed. Screening tests that are part of Standard of Care (SOC) can be used to determine pre-eligibility. Subjects enrolled in this registry must be followed per this protocol.

Subjects will be enrolled at post implant (between 1 and 21 calendar days post CRT-D implantation procedure).

SMART Registry subject is considered as part of the NG4 PMCF Cohort when enrolled in a European site, has an NG4 device implanted and LV MSP feature is enabled.

10.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from this registry, the reason(s) shall be reported. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal include, but are not limited to:

- Subject found not to meet eligibility criteria
- Subject choice to withdraw consent
- PI decision to withdraw the subject
- Device explanted and not replaced with an NG3/NG4 CRT-D system
- Implanted system element not active (IPG, RA lead, RV lead and quadripolar LV lead)
- Use of epicardial lead
- Ventricular Assist Device insertion or heart transplant
- Lost to follow-up, despite best efforts to locate the subject;
    - Three documented attempts to contact the subject are required to declare a subject lost to follow up.
- Death (see Section 19.7 for reporting requirements)

If a subject withdraws from the clinical investigation, the reason(s) shall be reported on the corresponding eCRF of the EDC system. Data up to the point of withdrawal will be collected and may be used. All open adverse events should be closed or documented as chronic.

10.3. *Subject Status and Classification*

Enrolled Subjects will be classified in the study as follows:

- Consented and ineligible - A study subject who has signed informed consent form (ICF) but is found to not meet eligibility criteria will be considered a consent ineligible subject and will not count towards the enrollment ceiling. There are no follow-up or adverse event reporting requirements for consent ineligible subjects. The original signed ICF must be maintained in the center's administrative file.
- Actively Enrolled (Consented and eligible) - subjects who have signed the ICF, meet all inclusion criteria and do not meet any of the exclusion criteria. These subjects will be followed in accordance with Clinical Investigational Plan (CIP) follow up schedule and included in the future study analysis. The original signed ICF must be maintained in the center's administrative file. All applicable case report forms per the CIP must be completed.
- NG4 PMCF Cohort - will be a minimum of the first 103 European subjects identified by the Sponsor enrolled in the SMART Registry, implanted with an NG4 device and that had LV MultiSite feature enabled at any time during the initial 12 months follow up.

10.4. *Enrollment Controls*

Approximately 2000 subjects will be enrolled in the SMART Registry. Study sites will be notified when the enrollment is complete. No single site shall enroll more than 20% subjects to mitigate any bias from a single center in final study analysis without the prior written approval from BSC Clinical Trial Manager.

NG4 PMCF Cohort will be completed as soon as a minimum of the first 103 European subjects identified by the Sponsor enrolled in the SMART Registry, implanted with an NG4 device and that had LV MultiSite feature enabled at any time during the initial 12 months follow up.

Once the NG4 PMCF Cohort has been completed, a notification will be submitted to all European sites confirming that no additional subjects are required to be identified to be followed more than 12 months.

11. Study Methods

11.1. *Data Collection*

The data collection schedule is shown in Table 11.1-1.

SMART Registry subjects:

- Enrollment and consenting visit at Post-Implant (between 1 and 21 calendar days after CRT-D implantation procedure) *(Required)*
- 12 months Clinic Visit (330-390 calendar days from enrollment date) *(Required)*
- Additional Standard of Care (SOC) Visits

NG4 PMCF Cohort: Only for the identified NG4 PMCF Cohort:

In addition to complete all standard SMART Registry Clinic Visits stated above, NG4 PMCF subjects will have to complete the following Clinic Visits:

- 24 months Clinic Visit (690-750 calendar days from enrollment date) *(Required)*
- 36 months Clinic Visit (1050-1110 calendar days from enrollment date) *(Required)*
- Annual Follow-Up Visit after 36 months and until last PMCF subject will complete the 36 months Clinic Visit *(Required)*

Table 11.1-1: Data Collection Schedule						
	SMART Registry			**Only NG4 PMCF subjects** (in addition to the standard SMART Registry)		
Procedure/Assessment	**Enrollment visit** ***(Index Visit)*** (between 1 and 21 days post CRT-D implantation procedure)	**12 months Clinic Visit** (330 days - 390 days post-enrollment)	**Additional SOC Clinic Visit** (only if per site SOC)	**24 months Clinic Visit** (690 days - 750 days post-enrollment)	**36 months Clinic Visit** (1050 days - 1110 days post-enrollment)	**Annual Clinic Visit** (until last PMCF subject will achieve 36 months of follow up)
Informed consent process, including informed consent signature date	X	--	--	--	--	--
Inclusion/Exclusion	X	--	--	--	--	--
Demographics	X	--	--	--	--	--
Physical assessment	X	X	O	--	--	--
Medical history	X	--	--	--	--	--
Echo data post implant (if available)	X	X	O	--	--	--
NYHA Class	X	X	O	X	X	X
ECG Data (if available)	X	X	O	--	--	--
Patient & Physician Global Assessments (Global Assessment Tool)	--	X	--	--	--	--
Cardiac Medications	X	X*	O*	X*	X*	X*
Implanted system information	X	X**	X**	X**	X**	X**
Device Initial interrogation, settings and status and print of Combined Report and Settings Report	X	X	X	X	X	X
Leads measurements	X	X	O	X	X	X
Optimization information as per site SOC	X	X	X	X	X	X
Device Final Combined Report and Setting Report						
Adverse Event Assessment	X	X	X	X	X	X

X = required; **O** = optional; **--** = not required, *= Need to document changes to cardiac meds only (new, increase, decrease), ** = Need to document only if there is changes from implanted system
NYHA = New York Heart Association; ECG = Electrocardiogram; HF = Heart Failure, SOC – Standard of Care

11.2. *Study Candidate Screening*

After approval by the investigator's IRB/EC and the sponsor or delegated representative the investigator or designee is responsible for screening potential subjects and selecting those who meet all inclusion criteria and do not meet any of exclusion criteria. A formal screening log is not required to be maintained.

11.3. *Informed Consent*

Subjects who meet all of the inclusion criteria, none of the exclusion criteria, and undergo the informed consent process, sign, and date the informed consent form are considered enrolled in the study. No data collection, data entry, or study specific procedure shall be performed prior to having appropriately consented the subject.

11.4. *Enrollment Visit - Index Visit (Day 0)*

The Enrollment Visit may occur at pre-discharge of CRT-D implantation procedure but only between 1 and 21 calendar days post CRT-D implantation procedure. Enrollment cannot occur on the same day of the implantation procedure.

An overview of data to be collected at the Enrollment Visit is provided below, with further details followed in the sections below.

- Inclusion and Exclusion (including CRT-D indication verification according BSC labelling)
- Subject demographics
- Subject Physical Assessment
- Medical history
- NYHA Class Assessment
- Cardiac medications
- Implanted system information (CRT-D IPG, RA lead, RV lead and LV lead information including LV lead location)
- Device Initial Interrogation to capture current settings, programming and status (including battery consumption) at the beginning of the Clinic Visit
- Lead measurements
- BSC Optimization features data: SmartDelay test and value (if done), LV Vector Guide test and value (if done), LV MSP (if enabled), SmartVector and SmartOffset value (if done), HeartLogic information (if applicable) and other optimization methods as per site SOC

- Device Final Report to capture programming, settings, programming and status (including battery consumption) at the end of the Clinic Visit before subject will leave the site.
- Adverse event assessment

11.4.1. Inclusion and Exclusion Criteria

The following values from subject's medical record are required to demonstrate that the subjects meet the BSC's labeled indication for CRT-D implantation:

BSC approved labeling verification in US

- LVEF and date of measurement (*It is required that the LVEF value be measured no more than 6 months prior to the CRT-D implantation*).
- QRS duration
- Bundle Branch Block morphology (LBBB or non-LBBB)
- Heart failure etiology (ischemic or non-ischemic)
- NYHA class
- Cardiovascular medications

BSC approved labeling in Europe

Subjects who are at risk for sudden cardiac death caused by ventricular arrhythmias and who have heart failure (including asymptomatic [NYHA Class I] ischemic heart failure) with ventricular dyssynchrony.

11.4.2. Subjects Demographics

Subject's age and sex. Race/ethnicity are only required in US.

11.4.3. Medical History

Subject's history of cardiovascular diseases is required to be collected.

11.4.4. Subject Physical Assessment

Physical presentation will be used to provide an assessment of the subject's condition and changes in clinical symptoms. Evaluation includes:

- Resting heart rate
- 12-lead ECG (if available)
- Blood pressure
- Height/weight
- Presenting symptoms
- Echo post-implant data (if available)

11.4.5. NYHA Class Assessment

The subject's current New York Heart Association (NYHA) Class must be determined based on Table 11.4-1.

Table 11.4-1: NYHA Classifications

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

11.4.6. Cardiac Medications

Subject current cardiovascular medications uses are required. For study purposes, cardiac medications include: diuretics, ACE inhibitors/angiotensin receptor blockers, beta blockers, aldosterone antagonists, Neprilysin inhibitors, Class I/III antiarrhythmics, calcium channel blockers, anti-hypertensive drugs, and statins.

11.4.7. Implanted System Information

The following data are required to be collected from the implanted CRT-D device, RA lead, RV lead, and quadripolar LV lead:

- Manufacturer
- Model number
- Serial number (optional for non-BSC leads)
- Implant date
- Report if it was a *de novo* implant or a device upgrade (from pacemaker or ICD)
- Battery consumption data: Time to explant need to be collected

11.4.7.1. LV Lead Location

The coronary venous LV lead location data are required if such information is available from reviewing lead imaging documents including in-procedure fluoroscopy or pre-discharge

chest X-rays, or can be obtained from the implanter's dictation in the subject's medical record.

The LV lead location will be classified and recorded in eCRF as follows:

- Anterior, anterolateral, lateral, posterolateral, or posterior

And

- Basal, Middle, and Apical

11.4.8. Current Device Setting and Status

After initial device interrogation, print a copy of the Combined Report and Settings Report to document current device settings and status prior to conducting any test and changing the programming settings.

11.4.9. Battery Consumption

The following values are required to be collected:

- Time to explant

11.4.10. Lead Measurements

The following lead measurements are required for RA lead, RV lead, and LV lead:

- Intrinsic amplitude (mV)
- Pacing capture threshold (PCT in V/ms; the recommended pulse width is 0.4ms)
- Pacing lead impedance (Ω)
- Shocking lead impedance (Ω, RV lead)
- Phrenic Nerve Stimulation (PNS) Threshold (V LV lead)

The following document is required for RA lead, RV lead, and LV lead measurements:

- Device follow-up report

Lead measurement testing is required unless a rationale is provided. For example, the measurement is prohibited by a subject's condition.

- The pacing configurations used in the LV lead measurement testing are per the investigator's discretion. It is recommended that at least one configuration must be tested for the LV lead, and it is recommended that it be the configuration that is planned for the final programming.

The threshold should be defined as one voltage level above the level where two non-captured beats are observed. If multiple PCT tests were performed, only the final measurement is required to be entered on the eCRF.

11.4.11. Optimization features information

Each site should be using Optimization features or any other method as per their site SOC.

11.4.11.1. SmartDelay Feature Data

If the SmartDelay test is done per site SOC to obtain programming recommendations for the AV Delay and Pacing Chamber. It is per the investigator's discretion whether to follow the programming recommendations.

If SmartDelay test is done, the following values are recommended to be obtained:

- Sensed AV delay (SAV) and Paced AV delay (PAV), both recommended and final programmed value (Print a copy of Settings Changes Report. This report will display recommended SAV, PAV and Pacing Chamber). Keep this printed report at the Subject File.
- Pacing Chamber (BiV or LV Only), both recommended and final programmed values.
- Rationale if the SmartDelay recommendations are not followed.
- A sense to RV sense interval, A sense to LV sense interval, A pace to RV sense interval and A pace to LV sense interval

If the SmartDelay test is done, the following document is required:

- Print a copy of the Settings Changes Report immediately after running the SmartDelay test and before any other changes in settings are made and programmed. This report will display the recommended changes to the SAV, PAV, and Pacing Chamber at pending status.

For a step-by-step guidance on performing the SmartDelay test, see Appendix 0.

11.4.11.2. LV VectorGuide feature Data

If LV VectorGuide test is done per site SOC and completed, provide the number of viable pacing vectors.

Subjects must have LV and RV sensed beats for test to be successful. If the subject does not tolerate low rate RV pacing, stop the test and provide the rationale of not completing the test.

The following values are recommended to be obtained when VectorGuide is performed:

- Number of viable pacing vectors.
- RV-LV delay (Is RV-LV test run? If Yes, capture the values)
- Impedance (Is Impedance test run? If Yes, out of bounds? Yes or No)
- PNS (Is PNS test run? If Yes, at which tested threshold and Is PNS present)
- Pacing Capture Threshold (Is Quick Capture test run?

- if Yes, capture the tested threshold and whether it is captured or not;
- If No, Is Auto or Manual threshold test run? If yes, capture the pacing capture threshold)

If the LV VectorGuide test is done, the following document is required:

- Print a copy of the VectorGuide Report

For a step-by-step guidance on performing the LV VectorGuide test, see Appendix 26.2.

11.4.11.3. LV MSP feature Data

For subjects with LV MSP feature enabled, it is required to use VectorGuide to assess viable LV pacing vectors from all tested pacing vectors. It is recommended to use the pacing vectors recommended by SmartVector test; however, final selection of the pacing vectors is per investigator's discretion.

The following values are required for subjects with LV MSP enabled:

- RV-LV delay value for all 4 electrodes as cathode: E1-Tip1, E2-Ring2, E3-Ring3, E4-Ring4

- LV pacing impedance for all tested vectors
- Phrenic Nerve Stimulation (PNS) test results for all tested vectors
- LV Quick Capture threshold test
- Number of viable pacing vectors

For subjects with LV MSP feature enabled, the LV pacing vectors will be recommended by the required SmartVector test; however, since it is not required to follow the recommendation from SmartVector, final pacing configurations for PCT measurement are per the investigator's discretion.

Investigator rationale is required commended if investigator not following LV MSP final pacing configuration feature recommendations.

MSP SmartVector Test (only for subjects with MSP turned on)

- LVa and LVb, both the recommended and final programmed values.
- Rationale if the LVa and LVb recommendations are not followed.

For a step-by-step guidance on performing SmartVector operation, see Appendix 26.3

MSP SmartOffset Test (only for subjects with MSP turned on)

- SmartOffset values, both the recommended and final programmed values.
- Rationale if the SmartOffset recommendations are not followed.

For a step-by-step guidance on performing SmartOffset operation, see Appendix 26.4

11.4.11.4. HeartLogic feature Data

HeartLogic alerts only can be available via the LATITUDE Remote Monitoring System.

For subjects with HeartLogic feature enabled, data may be collected via LATITUDE. HeartLogic feature usage throughout the follow-up period will be collected along with changes to alert thresholds and review of sensor trends with the data collected via LATITUDE system. The following data are to be collected in the eCRFs:

- HeartLogic alert programming: On or Off
- Any change in subjects' treatment plan based on the HeartLogic alerts (if available)

11.4.11.5. Other optimization methods information

Data about any other method used to optimize subject A-V delay need to be collected in this section: Echo optimization, Fixed A-V delay programming, etc.

11.4.12. Final Device Settings and Status

Print a copy of the Combined Report and Settings Report for all subjects at the end of the visit and clear the device counters as the final step.

11.4.13. Adverse Events Assessment

Study required adverse event will be collected and assessed for each eligible subject after signing of the informed consent. See Section 19.1 for Adverse Event collection and reporting requirement.

A summary of the source documentation required at Enrollment Clinic Visit is described in **Table 11.4-2**.

Table 11.4-2: Source Documentation Required at Enrollment Visit

Data Collection Requirement	Retention of Original Source Documentation
• Informed consent form and process, including informed consent signature and date • Inclusion and exclusion criteria • Cardiovascular Medical History • NYHA Class assessment • Physical Assessment • Cardiac Medication • Reportable Adverse Events, Device Deficiencies (if applicable)	Study Center
• Echocardiogram post implant data (if available)	Study Center
• 12-lead ECG (if available)	Study Center
• Device and leads information • Device Settings Report (at the beginning and at the end of the visit)	Printed reports will remain at Study Center

• Device features used report (if applicable) • Device Combined Report (at the beginning and at the end of the visit)	

11.5. *12 months Clinic Visit*

The 12 months Clinic Visit is must be performed at 330-390 calendar days post Enrollment Visit *(Required)*

Subjects with LATITUDE remote monitoring system may have their device performance and diagnostic data downloaded remotely from the LATITUDE BSC team during these visits timeframe. The device data transmission via LATITUDE will not be replacing the Clinic Visit.

An overview of data to be collected at 12 months Clinic Visit is provided below, with further details followed in the sections below:

- Subject Physical Assessment
- Cardiac Medication Changes
- NYHA class assessment
- Patient Global Assessment (PGA)
- Physician Global Assessment (PhGA)
- HF hospitalization information
- Device Initial Interrogation to capture current settings, programming and status (including battery consumption) at the beginning of the Clinic Visit
- Changes in programming or features since the last Clinic Visit
- Lead measurements
- BSC Optimization features data: SmartDelay test and value (if done), LV Vector Guide test and value (if done), LV MSP (if enabled), SmartVector and SmartOffset value (if done), HeartLogic information (if applicable) and other optimization methods as per site SOC
- Final device programming, settings and status (including battery consumption) at the end of the Clinic Visit before subject will leave the site.
- Adverse Events Assessment

11.5.1. Subject Physical assessment

Physical presentation will be used to provide an assessment of the subject's condition and changes in clinical symptoms following instructions from Section 11.4.4.

11.5.2. Cardiac Medication Changes

Subject current cardiovascular medications changes only from their last study visit (increase, decrease, new or removed). Medications collected include: diuretics, ACE inhibitors/angiotensin receptor blockers, beta blockers, aldosterone antagonists, Neprilysin inhibitors, Class I/III antiarrhythmics, calcium channel blockers, anti-hypertensive drugs, and statins.

11.5.3. NYHA Class Assessment

The subject's current NYHA Class must be determined based on Table 11.4-1.

11.5.4. Physician Global Assessment

The current Physician Global Assessment (PhGA) will be filled out by the investigator/delegated site staff based on the evaluation of the subject's status from multiple clinical aspects. A comparison of the assessment tool for the PGA and PhGA is shown in **Table 11.5-1: Global Assessment Tool: Physician Global Assessment (PhGA) and Patient Global Assessment (PGA)**Table 11.5-1**Error! Reference source not found.**.

11.5.5. Patient Global Assessment

The current PGA must be filled out by the subject, as specified in the Assessment Tool in Table 11.5-1**Error! Reference source not found.**.

Table 11.5-1: Global Assessment Tool: Physician Global Assessment (PhGA) and Patient Global Assessment (PGA)

Physician Global Assessment (PhGA)	Patient Global Assessment (PGA)
How is the patient's clinical status today compared to his or her status at the time of baseline? • Markedly improved • Moderately improved • Mildly improved • No change • Mildly worse • Moderately worse • Markedly worse	How do you feel today compared to how you felt when you started the study? • Very much better • Much better • A little better • No change • A little worse • Much worse • Very much worse

11.5.6. Definition and Components of the Clinical Composite Score

The Clinical Composite Score (CCS) will be calculated for all subjects at the 12 Month Visit. The CCS consists of the following components:

- All-cause mortality
- Heart Failure (HF) hospitalization
- Patient Global Assessment (PGA)
- NYHA class

11.5.6.1. HF Hospitalization Definition

For the purpose of the CCS calculation, HF hospitalization is defined as an HF event with a primary cause of HF and either of the conditions below is met:

- Subject is admitted and discharged with a calendar date change.
- Subject is not hospitalized but received one or more IV medications including diuretics, inotropes, vasodilators, other parenteral therapy, or aquapheresis

11.5.6.2. PGA Classification

Interpretation of no change status in PGA is defined as the following:

- A little better, no change, and a little worse.

A little better and a little worse are considered placebo effect and are treated as no change in PGA status. See for a detailed description of the PGA assessment tool Table 11.5-1

11.5.6.3. CCS Status Classification

Subjects will be classified as improved, unchanged, or worsened by comparing their clinical response in the current visit to their enrollment visit. At the 12 months Clinic Visit, subjects' status will be compared to their status at enrollment. The following criteria will be used:

- Improved: Subjects are considered improved if they experienced a favorable change in at least one NYHA functional class or in the PGA (or both) while remaining alive and free of HF hospitalization comparing to their status in the Enrollment Visit. See Table 11.5-1 on selecting improved PGA status.

- Worsened: Subjects are considered worsened if any of the followings occurs:
    - died (from any cause) or
    - experienced an HF hospitalization or
    - reported worsening of at least one NYHA functional class or
    - reported worsening of the PGA comparing to their status immediately prior to receiving the CRT-D implantation. See Table 11.5-1 on selecting worsened PGA status.

- Unchanged: Subjects are considered unchanged if they are neither improved nor worsened.

11.5.7. Current Device Settings and Status

After initial device interrogation, print a copy of the Combined Report and Settings Report to document current device settings and status prior to conducting any test and changing the programming settings.

11.5.8. Changes in programming since the last Clinic Visit

Collect changes done in programming since the last Clinic Visit:

- Parameters modified and Features enabled/disabled
- Who made the change (investigator, device check facility, emergency services, other)
- Date of the change
- Impact of the change.

11.5.9. SmartDelay test and value

If SmartDelay test done please follow instructions from Section 11.4.11.1

11.5.10. LV VectorGuide test and value

If LV Vector Guide test done, please follow instructions from Section 11.4.11.2

11.5.11. SmartVector and SmartOffset value

If SmartVector and Smart Offset tests done, please follow instructions from Section 11.4.11.3

11.5.12. Current device setting and status

Print a copy of the Quick Notes Report to document current device settings and status prior to conducting any test and changing the programming settings. A list of settings and status, including but not limited to the SmartDelay, Vector Guide, LV MSP and HeartLogic settings, percent of pacing (% RV pacing, %LV pacing), and percent of AT/AF are recommended to be collected (if applicable).

11.5.13. Battery Consumption

The following values are required to be collected:

- Time to explant

11.5.14. Lead Measurements

The lead measurements are recommended to be collected for RA lead, RV lead, and LV lead. Please follow instructions in Section 11.4.10.

11.5.15. Optimization information

Each site should be using Optimization features or any other method to optimize their subjects as per their site SOC. BSC Optimization Features Data (SmartDelay, LV VectorGuide, LV MSP, HeartLogic) need to be collected if they are used as any other optimization method used following instructions in Section 11.4.11.

11.5.16. Final Device Settings and Status

Print a copy of the Combined Report and Settings Report for all subjects at the end of the visit and clear the device counters as the final step.

11.5.17. Adverse Events Assessment

Study required adverse event will be collected and assessed for each eligible subject after signing of the informed consent. See Section 19.1 for Adverse Event data collection and reporting requirements.

A summary of the source documentation required at 12 months Clinic Visit is described in Table 11.5-2.

Table 11.5-2: Source Documentation required at 12 months Clinic Visit

Data Collection Requirement	Retention of Original Source Documentation
• NYHA Class assessment • Physical Assessment • Cardiac Medication Changes • Patient Global Assessment • Physician Global Assessment • Reportable Adverse Events, HF hospitalizations and Device Deficiencies (if applicable)	Study Center
• Echocardiogram data (if available)	Study Center
• 12-lead ECG (if available)	Study Center
• Device and leads information • Device Settings Report (at the beginning and at the end of the visit) • Device features used report (if applicable) • Device Combined Report (at the beginning and at the end of the visit)	Printed reports will remain at Study Center

11.6. *Additional SOC Clinic Visits*

An Additional SOC Visit is recommended to be completed when:

- The Clinic Visit is done within the site SOC for this HF subject population and
- The device is interrogated and any of the programming settings have been permanently changed. A rationale for the setting changes may be collected

The level of data collection during this Additional Clinic Visits will remain as per each site SOC, however the minimum will be to collect device Settings/Features data and Programming. Save a print out of the interrogation, and complete Adverse Event Assessment and report if applicable.

A summary of the source documentation required at Additional SOC Clinic Visit is described in Table 11.6-1.

Table 11.6-1: Source Documentation Required at Additional SOC Clinic Visits

Data Collection	Retention of Original Source Documentation
• NYHA Class assessment (if applicable) • Physical Assessment (if applicable) • Cardiac Medication Changes (if applicable) • Reportable Adverse Events, HF hospitalizations and Device Deficiencies (if applicable)	Study Center
• Device and leads information • Device Settings Report (at the beginning and at the end of the visit) • Device features used report (if applicable) • Device Combined Report (at the beginning and at the end of the visit)	Printed reports will remain at Study Center

11.7. *24 months Clinic Visit, 36 months Clinic Visit and Annual Clinic Visits*

For only those subjects belonging to the NG4 PMCF Cohort, the 24 months Clinic Visit, 36 months Clinic Visit and Annual Clinic Visit will have to be performed as per each site SOC. The same procedures and data collection will apply to all visits.

- The 24 months Clinic Visit must be performed at 690-750 calendar days post Enrollment Visit *(Required)*
- The 36 months Clinic Visit must be performed at 1050-1110 calendar days post Enrollment Visit *(Required)*
- Annual Clinic Visit must be performed for all NG4 PMCF subjects until last subject from the PMCF cohort will have complete the 36 months Clinic Visit *(Required)*

Subjects with LATITUDE remote monitoring system may have their device performance and diagnostic data downloaded remotely from the LATITUDE BSC team during these visits timeframe. The device data transmission via LATTITUDE will not be replacing the Clinic Visit.

An overview of data to be collected at 24, 36 months Clinic Visit and Annual Visit is provided below, with further details followed in the sections below.

- NYHA class assessment
- Cardiac Medications Changes
- Current device setting and status
- Lead measurements
- LV MSP feature use and programming (if applicable)
- HeartLogic feature data (if applicable)
- Battery consumption
- Final device settings and status
- Adverse Events Assessment

11.7.1. NYHA Class Assessment

The subject's current NYHA Class must be determined based on Table 11.4-1.

11.7.2. Cardiac Medication Changes

Subject current cardiovascular medications changes from their last study visit (increase, decrease, new or removed). Medications collected include: diuretics, ACE inhibitors/angiotensin receptor blockers, beta blockers, aldosterone antagonists, Neprilysin inhibitors, Class I/III antiarrhythmics, calcium channel blockers, anti-hypertensive drugs, and statins.

11.7.3. Current device setting and status

After initial device interrogation, print a copy of the Combined Report and Settings Report to document current device settings and status prior to conducting any test and changing the programming settings.

11.7.4. Changes in programming since the last Study Clinic Visit

Collect changes done in programming since the last Clinic Visit

- Parameters modified and Features enabled/disabled
- Who made the change (investigator, device check facility, emergency services, other)
- Date of the change
- Impact of the change

11.7.5. Battery Consumption

The following values are required to be collected:

- Time to explant

11.7.6. Lead Measurements

The lead measurements are recommended to be collected for RA lead, RV lead, and LV lead. Please follow instructions in Section 11.4.10.

11.7.7. LV MSP feature Data

Collect information about the LV MSP feature. Please follow instructions from Section 11.4.11.3.

11.7.8. HeartLogic feature Data

For subjects with HeartLogic feature, its usage throughout the follow-up period will be documented along with changes to alert thresholds and review of sensor trends. Please follow instructions from Section HeartLogic feature Data11.4.11.4.

11.7.9. Final Device Settings and Status

Print a copy of the Combined Report and Settings Report for all subjects at the end of the visit and clear the device counters as the final step.

11.7.10. Adverse Events Assessment

Study required adverse event will be collected and assessed for each eligible subject after signing of the informed consent. See Section 19.1 for Adverse Event data collection and reporting requirements.

A summary of the source documentation required at 24, 36 months and Annual Clinic Visits is described in Table 11.7-1.

Table 11.7-1: Source Documentation Required at 24, 36 months and Annual Clinic Visit

Data Collection Requirement	Retention of Original Source Documentation
• NYHA Class • Medication changes • LV MSP and HeartLogic features data (if applicable) • Reportable Adverse Events, HF hospitalizations and Device Deficiencies (if applicable)	Study Center
• Device and leads information • Device Settings Report (at the beginning and at the	Printed reports will remain at Study Center

end of the visit) • Device features used report (if applicable) • Device Combined Report (at the beginning and at the end of the visit)	

11.8. *Study Completion*

Subjects enrolled in SMART Registry only will conclude study participation once the 12 months visit will be performed. However all subjects enrolled also in NG4 PMCF Cohort will complete study participation only when the last enrolled subject in the PMCF will have completed the 36 months Clinic Visit. Sites will continue to follow subjects until notified of follow-up completion. Sites will be notified when subject follow-up at their site is complete for the study.

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. Primary Endpoint

CRT Response rates will be determined in the entire SMART Registry and in selected subgroups. No formal hypotheses will be evaluated for this analysis. To fulfill post-approval requirements related to the NG4 family of devices, the NG4 PG-related complication free rate (CFR) at 36 months will be evaluated in the subjects included in the NG4 PMCF Cohort. Details of the SMART Registry Primary Objective and the NG4 PMCF Cohort Primary Endpoint are provided in the following sections.

12.1.2. SMART Registry Primary Endpoint

12.1.2.1. Hypotheses

There are no formal hypotheses to be tested for the SMART Registry Primary Objective.

12.1.2.2. Sample Size

Due to a lack of hypotheses for this objective, the sample size cannot be determined through traditional statistical powering techniques. It is, however, desired to have a high degree of confidence in the CRT Response rates obtained in the study. In order to obtain a two-sided 95% confidence interval width of the overall SMART Registry CRT Response rate that does not exceed 5%, a total of 2000 subject enrollments are required. Additionally, it is expected that with a total of 2000 enrollments, each subgroup analysis will include a sufficient sample of approximately 50 subjects.

12.1.2.3. Statistical Methods

The Clinical Composite Score allows for three levels of CRT Response: Improved, Unchanged or Worsened. The number and percent of SMART Registry subjects contributing to each level of CRT Response will be calculated.

CRT Response rates will be compared between selected subgroups. Due to the ordinal nature of the three CRT response levels defined by the Clinical Composite Score, statistical tests accounting for ordinality of response will be used, when appropriate. In analyses comparing two subgroups, a Cochran-Armitage test for trend will be employed. If more than two subgroups will be compared, a cumulative logit model or some other appropriate test will be used.

12.1.3. NG4 PMCF Endpoint

12.1.3.1. Hypotheses

The NG4 PMCF Primary Endpoint was designed to evaluate the safety of the NG4 device when LV MSP is enabled. In the subjects included in the NG4 PMCF Cohort, the NG4 PG-related complication free rate (CFR) at 36 months will be used to evaluate the PMCF Primary Endpoint.

A PG-related Complication will be defined as those detectable adverse events that resulted in:

- Death
- Serious injury
- Correction of PG failure requiring invasive intervention
- Permanent loss of PG device function. Permanent loss of device function is defined as any Pulse Generator (PG) that reverts to Safety Core or any PG rendered unable to deliver pacing or shocks

Complications that are determined to be associated with the PG will be considered PG-related complications (PG) and count against the PMCF endpoint. Complications related to the LV, RV, RA leads will not be counted against the PMCF endpoint.

12.1.3.2. Hypotheses

The following hypotheses will be evaluated to evaluate the safety of the NG4 device:

H_0: PG-related CFR at 36 months $\leq 88.5\%$

H_A: PG-related CFR at 36 months $> 88.5\%$

To ensure that the safety of the NG4 devices with LV MSP enabled is acceptable, the performance goal for this endpoint was based on the observed safety of prior approved Boston Scientific devices in the following studies: CAPTIVATE, LSS of 4-SITE, MADIT CRT, MultiSENSE, NAVIGATE X4. Prior devices in these studies have shown a PG-related complication-free rate of 98.5% through 36 months of follow-up. The performance goal of 88.5% was derived from the prior performance of 98.5% minus 10% to account for variability in the estimate. Expected performance of the NG4 device was based on the observed rate of prior devices.

12.1.3.3. Sample Size

A minimum of 63 subjects are required to sufficiently power the NG4 PMCF Primary Endpoint. An additional requirement is follow-up of a minimum of 60 subjects with usage of the LV MSP feature. Therefore, follow-up of 63 subjects with LV MSP enabled will satisfy both requirements. To account for the expected 15% annual attrition, a minimum of 103 subjects with LV MSP usage will be followed to achieve 63 subjects at 36 months. A minimum of the first 103 subjects identified with LV MSP usage will be included in the NG4 PMCF Cohort.

12.1.3.4. Statistical Methods

The Primary Endpoint will be calculated using Kaplan-Meier methodology. The 95% one-sided pointwise log-log confidence limit of the PG-related complication-free rate at 36 months will be compared to the performance goal of 88.5%. If the lower confidence limit exceeds 88.5%, the null hypothesis will be rejected.

12.2. *General Statistical Methods*

12.2.1. Analysis Sets

All subjects with complete Clinical Composite Score data at 12 months will contribute to the analyses evaluating CRT Response rates. All subjects in the NG4 PMCF Cohort will contribute data to the PMCF Primary Endpoint.

12.2.2. Control of Systematic Error/Bias

Several subgroups, multivariate and other analyses are planned to evaluate the primary objective of the SMART Registry. No adjustments to the significance level (i.e., alpha) due to these multiple tests will be made. Rather, interpretation of all results will consider the biological plausibility of the findings as well as the consistency with other results obtained in this study and from other external sources.

The type I error rate for the PMCF Primary Endpoint will be contained at 5% by use of a one-sided 5% alpha in the analysis.

12.2.3. Number of Subjects per Investigative Site

Sites will be allowed to enroll a maximum of 200 subjects, equal to 10% of the SMART Registry expected enrollment.

12.3. *Data Analyses*

12.3.1. Other Endpoints/Measurements

Additional analyses may be performed to assist in the evaluation of the Primary Objective:

- CRT Response in the overall cohort and in subgroups using groupings of the three levels of the Clinical Composite Score:
    - Improved vs. Unchanged/Worsened
    - Improved/Unchanged vs. Worsened
- Evaluation of the components of the Clinical Composite Score in the overall cohort and in subgroups:
    - All-cause mortality
    - Heart failure events
    - NYHA Class
    - Quality of life (patient Global Assessment instrument)

Utilization patterns of device features and diagnostics will also be calculated, if available:

- MultiSite Pacing (MSP)
    - Number and percent of subjects with MSP usage overall and throughout follow-up
    - Physician rationale for utilizing MSP
    - Programming parameters (i.e., vectors) associated with MSP usage
- HeartLogic use (if available)
    - Number and percent of subjects with HeartLogic usage overall and throughout follow-up
    - Physician rationale for utilizing HeartLogic
    - Physician response to HeartLogic alerts
- SmartDelay
    - Number and percent of subjects with SmartDelay usage
- Vector Guide
    - Number and percent of subjects with Vector Guide usage
- Programming of pacing vectors
    - Rationale for selection of pacing vector (e.g., lowest pacing capture threshold without extracardiac stimulation, longest RV-LV delay, etc.)

12.3.2. Interim Analyses

No formal interim analyses are planned for stopping for superiority or futility. Interim analyses may be performed to support publications. Analysis of each endpoint will be performed when all applicable data for that endpoint has been collected.

12.3.3. Subgroup Analyses

The list of baseline covariates (with applicable subgroups in parentheses) includes, but is not necessarily limited to:

- Ischemic Etiology (Ischemic vs Non-Ischemic)
- Bundle Branch Block morphology (LBBB vs Non-LBBB)
- NYHA class (I/II vs III/IV)
- Presence of atrial fibrillation (Yes or No)
- Diabetes (Yes vs. No)
- Sex (Male vs. Female)
- Age < 65 years vs. ≥ 65 years
- RV-LV electrical delay (< 70 ms vs. ≥ 70 ms)
- QRS-LV at the implantation site
- QRS width (< 150 ms vs. ≥ 150 ms)

CRT Response rates (Full Registry) and PG-related complication-free rates (NG PMCF Cohort) will be compared between the two subgroups for each covariate. A Cochran-Armitage test for trend will be performed to compare CRT Response rates across subgroups. A log-rank test will be used to compare PG-related complication-free rates across subgroups. Additional cutpoints may be evaluated for continuous covariates, based on the data and/or clinical determination.

12.3.4. Justification of Pooling

The poolability of data by center will be tested among the NG4 PMCF Cohort. This analysis will be performed to determine whether there are NG4 PMCF endopoint differences from center-to-center.

Center-to-center heterogeneity will be assessed by performing random effects logistic regression analysis.

Participating center will be added into the model as a random effect. Centers will be deemed to be heterogeneous if the variance of the random center effect is found to significantly differ from zero. A significance level of 15% will be used for each test.

12.3.5. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in a Statistical Analysis Plan approved prior to performing the analyses.

Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

13. Data Management

13.1. *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.

13.2. *Data Retention*

The Principal Investigator or his/her designee or participating 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 registry. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other country/regional/local regulations.

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

14. Amendments

If a protocol revision is necessary 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.

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC of any deviation from the protocol 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 protocol, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC. 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 IRB/EC notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

16. Compliance

16.1. *Statement of Compliance*

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

16.2. *Investigator Responsibilities*

The Principal Investigator of an participating 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 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.
- 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 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 registry are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from registry while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the registry.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the registry is appropriately performed and documented, where applicable.

16.2.1. 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.

16.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the participating 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. 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.

16.4. *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.

16.4.1. Role of Boston Scientific Representatives

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

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 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
- Entering technical data on technical source form as long as the responsible investigator verifies and signs the completed worksheet
- 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

16.5. *Insurance*

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

17. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. 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 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.

18. Potential Risks and Benefits

18.1. *Anticipated Adverse Events*

The following anticipated adverse events (AE) for the SMART Registry subjects are the same as any other subject implanted with a CRT-D system and not participating in any study.

Table 18.1-1: Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System	
Air embolism	Lead dislodgment
Allergic reaction	Lead fracture
Bleeding	Lead insulation breakage or abrasion
Bradycardia	Lead perforation
Cardiac tamponade	Lead tip deformation and / or breakage
Chronic nerve damage	Local tissue reaction
Component failure	Loss of capture
Conductor coil fracture	Myocardial Infarction (MI)
Death	Myocardial necrosis
Elevated thresholds	Myocardial trauma (e.g., tissue damage, valve damage)
Erosion	Myopotential sensing
Excessive fibrotic tissue growth	Oversensing / undersensing
Extracardiac stimulation (muscle/ nerve stimulation)	Pacemaker-mediated tachycardia (PMT) (Applies to dual-chamber devices only.)
Failure to convert an induced arrhythmia	Pericardial rub, effusion
Fluid accumulation	Pneumothorax
Foreign body rejection phenomena	Pulse generator migration
Formation of hematomas or seromas	Shunting current during defibrillation with internal or external paddles
Heart block	Syncope
Heart failure following chronic RV apical pacing	Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
Inability to defibrillate or pace	Thrombus, thromboemboli
Inappropriate therapy (e.g., shocks, and antitachycardia pacing [ATP] where applicable, pacing)	Valve damage
Incisional pain	Vasovagal response
Incomplete lead connection with pulse generator	Venous occlusion
Infection including endocarditis	Venous trauma (e.g. perforation, dissection, erosion)
Insulating myocardium during defibrillation with internal or external paddles	Worsening heart failure

Please refer to the specific CRT-D device Physician's Technical Manual for additional information.

Subjects may develop psychological intolerance to a pulse generator system and may experience the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost
- Imagined shocking
- Fear of device malfunction

18.2. *Anticipated Adverse Device Effects*

Adverse Device Effects that are part of the listing in the previous18.1 section are to be considered Anticipated Device Effects.

18.3. *Risks Associated with the Study Device(s)*

There are no additional risks associated with the study devices that are above those of BSC commercially approved and market available CRT-D devices.

18.4. *Risks associated with Participation in the Clinical Study*

There are no additional risks that are associated with participation to the present study beyond those listed above, and all the visits associated to this protocol are performed as part of standard clinical practice.

18.5. *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.

18.6. *Anticipated Benefits*

There may be no benefit to the subject. However, medical science and future subjects may benefit from their participation in this registry.

18.7. *Risk to Benefit Rationale*

The implantable CRT-D systems and accessories used for this Registry will be commercially available and are considered to be SOC for subjects indicated for such implants. The risks

involved with subject participation in this study are essentially the same as those for subjects not participating in the study.

19. Safety Reporting

19.1. *Reportable Events by investigational site to Boston Scientific*

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

- All Serious Adverse Events
- All Adverse Device Effects
    - Events listed in the arrhythmia logbook, should be reported only if determined to be clinically significant by the investigator and/or delegated site staff (i.e. ATR, PMT, etc.)
    - Any new onset/diagnosis of VT/VF requiring anti-arrhythmic therapy, or per the PI, clinically worsening VT/VF requiring Therapy. (Appropriate VT therapy that is not considered clinically worsening per the PI is not to be reported).
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- All Heart Failure (HF) and All Cardiac related adverse events requiring IV or invasive therapy, including new onset cardiac events, or worsening in severity or frequency of pre-existing conditions.

An adverse event is deemed as a HF Event if the primary cause is HF and either of following conditions is met:

- In-patient hospitalization ≥ 24 hours
- No hospitalization but received one or more IV medications including diuretics, inotropes, vasodilators, other parenteral therapy, or aquapheresis.

Adverse event collection begins after the subject signs the informed consent. Events which occur prior to the signing of the informed consent form, and per the investigator/delegated site staff are a result of the device implant procedure should not be reported. Even if such event requires a treatment that is executed after the informed consent is signed. (e.g. hematoma that requires intervention is not an adverse event as long as it does not worsen after consenting; infection at the incision site is not an adverse event as long as it does not worsen after consenting; planned medical procedure or lead revisions are not adverse events as long as the event is identified prior to the consent). These are considered preexisting conditions and are not reportable. If the event worsens after consenting and meets criteria for a reportable event then they must be reported (e.g. hematoma that is worsened and requires intervention; a new infection at the incision site or an infection that is worsened and requires

intervention). If the study subject is consented while still hospitalized from the initial device implant, and an event occurs which meets the definition of an SAE, the event must be reported.

The medical diagnosis should be reported for reported events. In case the diagnosis is not available, individual symptoms can be reported to fulfill reporting timelines. If a diagnosis becomes available at a later date, it should be added to the reported event.

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

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

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be reported as an SAE, but should be reported as an outcome of an SAE and only one SAE should have the outcome documented as fatal (see Table 19.2-1 for AE definitions).

Refer to Section 18.3 for the known risks associated with the study device(s).

19.2. *Definitions and Classification*

Adverse event definitions are provided in Table 19.2-1. Administrative edits were made on the definition of serious adverse event from ISO 14155and MEDDEV 2.7/3 for clarification purposes. Reportable events are defined in Table 19.2-1. Administrative edits were made on the definition of serious adverse event from ISO 14155and MEDDEV 2.7/3 for clarification purposes.

Table 19.2-1: 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. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events 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.

Table 19.2-1: Safety Definitions

Term	Definition
	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 as defined by 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* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	A 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.

Table 19.2-1: Safety Definitions

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

Table 19.2-1: Safety Definitions

Term	Definition
Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions	
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

19.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in Table 19.3-1:

Table 19.3-1: Criteria for 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;

Table 19.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
	- 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; - 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.

19.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 19.4-1.

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

SmartRegistry.Safety@bsci.com

Table 19.4-1: 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) Reporting required through the end of study
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	h) When documentation is available
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	i) Within 2 business days of first becoming aware of the event or as per local/regional regulations. j) Reporting required through the end of

Table 19.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline post-market studies** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
		the study
	Provide all relevant source documentation (unidentified) for reported event	k) When documentation is available
Device Deficiencies (including but not 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.	Complete Device Deficiency eCRF with all available new and updated information.	l) Within 2 business days of first becoming aware of the event. Reporting 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.	m) In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information n) Reporting required through the end of study

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

19.5. *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. 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.

19.6. *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..

19.7. *Subject Death Reporting*

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

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

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

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

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to any 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 or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. 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.

21. Committees

21.1. *Safety Monitoring Process*

To promote early detection of safety issues, the BSC Safety Trials Operations group will provide the initial evaluations of safety events to the BSC Medical Safety group. The BSC Medical Safety Group includes physicians with knowledge in the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information.

21.2. *Steering Committee*

The Steering Committee is independent of Boston Scientific and is responsible for the overall conduct of the study with regard to protocol development, study progress, subject safety, and overall data quality and integrity.

22. Suspension or Termination

22.1 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.

22.1.1 Criteria for Premature Termination of the Study

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

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

- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

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

Any investigator, or IRB/ EC in the SMART Registry 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.

22.3 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 to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.4 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.

In the event of termination of site participation, 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 as per standard of care. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the participating site otherwise.

23. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination

of the study. Boston Scientific Corporation adheres to the 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.

24. Reimbursement and Compensation for Subjects

24.1. *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.

24.2. *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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26. Appendix Detailed Information on Running Features Testing

Only as guidance, if needed below details on the different features.

26.1. *Detailed steps on obtaining the data from the SmartDelay test*

Step 1. Navigate to the SmartDelay Optimization screen

- From the programmer (PRM) main screen, choose the *Settings* tab.
- From the *Settings tab*, choose *Settings – Normal Brady/CRT*,
- From the *Settings – Normal Brady/CRT* screen, choose *SmartDelay Optimization*.

Step 2. Run the SmartDelay test

- From the SmartDelay Optimization screen, choose *Start Test.* The test typically lasts up to 2.5 minutes.
- Set the *LRL* at 10 to 15 beats above the subject's intrinsic heart rate.
- Set EGM channels to RA, RV, and LV. Obtain ECG/EGM strips at the paper speed of 100 mm/s for approximately 5-10 representative beats in both the Atrial Sense test and Atrial Pace test. Measure values for Asense-RVsense, Asense-LVsense, Apace-RVsense, and Apace-LVsense intervals from the ECG/EGM strips

- SmartDelay will recommend *AV delay* and *Pacing Chamber* (*BiV* or *LV Only*).
- If the SmartDelay test fails, the nominal value will be displayed.

Step 3. Program AV Delays and Pacing Chambers

- If following the recommended *AV Delay* and *Pacing Chamber* value determined by the SmartDelay, choose *Copy Suggested Settings* and select the *Program* button to program the device.
- If not following the recommended *AV Delay* and *Pacing Chamber* value determined by SmartDelay,
    - Manually record the SmartDelay recommendation before exiting the test screen. Print a copy of the Settings Changes Report before any changes are made and programmed to document the recommended values from the SmartDelay test
    - Manually enter the desired values in the *Settings – Normal Brady/CRT* screen, and select the *Program* button to program the device.

Step 4. Record the recommended and programmed value

- Record in the corresponding Clinic Visit eCRFs both the SmartDelay recommendation and final programmed value for *AV Delay* and *Pacing Chamber*.

26.2. *Detailed steps on obtaining the data from the LV VectorGuide test*

Step 1. Navigate to the LV VectorGuide Screen

- From the programmer (PRM) summary tab: choose *TESTs.*
- From the *TESTs* screen: choose *Lead Tests*.
- From the *Lead Tests* screen: choose *LV VectorGuide.*

Or (for MSP)

- From the programmer (PRM) summary tab: choose *Settings Summary.*
- From the *Settings Summary* screen: choose *Normal Brady/CRT* screen.
- From the *Normal Brady/CRT* screen: choose *LV MultiSite Pacing.*
- From the *LV MultiSite Pacing* screen: choose *Run LV VectorGuide.*

Step 2. Select the vectors to be tested with LV VectorGuide

Step 3. Run the RVS-LVS delay test for the selected vectors.

- Subjects must have LV and RV sensed beats for test to be successful. If the subject does not tolerate a low intrinsic heart rate, stop the test.

Step 4. Run the lead impedance test for the selected vectors.

- The range of out-of-range pacing impedance value is programmable.

Step 5. Run the PNS test for the selected vectors (the pacing voltage and pulse width are at physician's discretion).

Step 6. Run the LV Threshold Test for the selected vectors

- There are 3 methods available to test the LV Threshold – *Quick Capture*, *Auto Amplitude*, or *Amplitude* Test.
- The nominal setting to test the LV threshold is 2.5V @ 0.4 ms; however, it can be reprogrammed at physician's discretion.

Step 7. Print LV VectorGuide Report to record test results.

- Navigate to the Report screen by choosing *Report* button at the bottom of the LV VectorGuide screen.
- Select *LV VectorGuide Report.*
- Select both *Print Selected Report* and *Save Report* for later retrieval of the report.
- Record test results in the Post Implant and follow-up eCRFs.

26.3. *Detailed steps on running SmartVector test*

Step 1. After running LV VectorGuide, navigate back to *Settings – LV Multisite Pacing Configuration* screen

Step 2. Run the SmartVector function:

- Under *Set LV Multisite Pacing Value*, select *Pacing Order* button and choose either LVa to LVb to RV for LV MSP BiV pacing or LVa to LVb for LV MSP LV Only Pacing.
- Under *Set LV Multisite Pacing Value*, choose the SmartVector button.
- The SmartVector function will recommend LVa and LVb pacing vectors.
- Print a copy of the Setting Changes Report before setting changes are made and programmed to show the recommended LVa and LVb vectors.
- If not following SmartVector recommendation, investigator may enter LVa and LVb vectors manually.

Step 3. Record both SmartVector recommended vectors and final programmed vectors.

- Record the values in the follow-up eCRFs. If not following SmartVector recommendation, record the rationale.

26.4. *Detailed steps on running SmartOffset test*

Step 1. Run the SmartOffset function:

- From the Settings – *LV MultiSite Pacing* screen, select the SmartOffset button.

- The SmartOffest function will recommend pacing offset values between LVa, LVb, and RV paces (or just between LVa and LVb if programmed to LV Only).
    - Print a copy of the Setting Changes Report before setting changes are made and programmed to show the recommended offset.
    - If not following SmartOffset recommendation, investigator may enter the offsets manually.

Step 2. Record SmartOffset value

- Record in the follow-up eCRFs the SmartOffset recommended values and the final programmed offsets for LVa to LVb and LVb to RV (or just LVa to LVb if programmed to LV Only).

Print a copy of the Device Settings Report for all subjects at Post Implant and follow up visits to capture the programmed settings (AV delays, pace chamber, LV pace vector (for MSP, LVa and LVb, and offset values), etc).

27. Abbreviations and Definitions

27.1. *Abbreviations*

Abbreviations are shown in Table 27.1-1.

Table 27.1-1: Abbreviations

Abbreviation	Term
A	Atrial
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AV	AtrioVentricular
BiV	Biventricular
BSC	Boston Scientific Corporation
CCE	Clinical Composite Endpoint
CCS	Clinical Composite Score
CEC	Clinical Events Committee
CFR	Code of Federal Regulations – excluding the endpoint sections
CRO	Clinical Research Organization
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy – Defibrillator

Table 27.1-1: Abbreviations

Abbreviation	Term
DD	Device Deficiency
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FCS	Field Clinical Specialist
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare Provider
HF	Heart Failure
ICF	Informed Consent Form
ICD	Implantable Cardioverter Defibrillator
IQRMP	Integrated Quality Risk Management Plan
IRB	Institutional Review Board
IV	Intravenous
LBBB	Left Bundle Branch Block
LRL	Lower Rate Limit
LV	Left Ventricle
LVED	Left Ventricular End Diastolic
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
ms	Millisecond
MPP	MultiPoint Pacing
MSP	MultiSite Pacing
mV	millivolts
NYHA	New York Heart Association
Ω	Ohms
OPT	Optimal Pharmacologic Therapy
PA	Paced Atrium
PAV	Paced AtrioVentricular
PCT	Pacing Capture Threshold
PG	Pulse Generator

Table 27.1-1: Abbreviations

Abbreviation	Term
PI	Principal Investigator
PNS	Phrenic Nerve Stimulation
QLV	Q-Left Ventricular
RA	Right Atrium/ Atrial
RM	Rhythm Management
RV	Right Ventricle/ Ventricular
RV-LV	Right Ventricle-Left Ventricle
RVs-LVs	Right Ventricle sense-Left Ventricle sense
SA	Sensed Atrium
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SAV	Sensed AV
US	United States of America
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
UADE	Unanticipated Adverse Device Effect
V	Volts
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

27.2. *Definitions*

Terms are defined in Table 27.2-1.

Table 27.2-1: Definitions

Term	Definition
Clinical Composite Score	A method for evaluating heart therapies that unifies four outcomes of primary importance to clinicians: all-cause mortality, HF hospitalization, Patient Global Assessment, and New York Heart Association (NYHA) class.

Table 27.2-1: Definitions

Term	Definition
NG3 family of CRT-D devices	Current generation of BSC's CRT-D devices, It refers to all trademarked devices in this family of pulse generators, including AUTOGEN, DYNAGEN and INOGEN
NG4 family of CRT-D devices	As the next generation of BSC's CRT-D devices, It refers to all trademarked devices in this family of pulse generators, including RESONATE HF, RESONATE, MOMENTUM, VIGILANT and CHARISMA.
NG4 PMCF Cohort	It will be constituted by a minimum of the first 103 European subjects identified by the Sponsor enrolled in the SMART Registry, implanted with an NG4 device and that had LV MultiSite feature enabled at any time during the initial 12 months follow up. The actual belonging to the NG4 PMCF study cohort will be based on sponsor's becoming aware date of the MSP feature being enabled, therefore following a chronological order.