Strategic MAnagement to Improve CRT Using Multi-Site Pacing
Post Approval Study

SMART MSP

CLINICAL INVESTIGATION PLAN

Protocol#: C1918

Sponsored By

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Revision History

<table>
<tr><th>Revision Number</th><th>Release Date</th><th>Template number and version</th><th>Section</th><th>Change</th><th>Reason for Change</th></tr>
<tr><td>Revision A</td><td>November 30, 2016</td><td>90702637 Rev/Ver AH</td><td>NA</td><td>Original Release</td><td>NA</td></tr>
<tr><td>Revision B</td><td>December 2, 2016</td><td>90702637 Rev/Ver AH</td><td>9.3

11.4.8, 11.5.9, 11.6.8, and 26.1

Multiple sections</td><td>Changed the order of how exclusion criteria are listed.

Clarified the electrical interval values to be measured from the ECG/EGM strip

Clarifications and corrections</td><td>Clarifications and corrections</td></tr>
<tr><td>Revision C</td><td>March 13, 2017</td><td>90702637 Rev/Ver AH</td><td colspan="3">
<table>
<tr><th>Section</th><th>Change</th><th>Reason for Change</th></tr>
<tr><td>2
8.1,
10.5</td><td>Update number of enrollment, number of US sites, and attrition percentage</td><td>Update due to change in study design per FDA request</td></tr>
<tr><td>11.5.1 and multiple sections</td><td>Use the term “HF event” to match its definition</td><td>Clarification</td></tr>
<tr><td>10.1,
10.4,
11.3</td><td>Clarify definition of enrollment</td><td>Consistency</td></tr>
<tr><td>11,
Table 11.1-1, all sub-sections of 11</td><td>Additional testing and data collection:
- Smart Delay interval test, ECG/EGM strip
- RVp-LVs interval test, ECG/EGM strip
- Sleep Incline Trend calibration</td><td>Data collection to support future feature and algorithm development</td></tr>
</table>
</td></tr>
</table>

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				- "Save All" device data	
			11, Table 11.1-1, all sub-sections of 11	Additional data collection: - Echo measurement value, if performed per standard of care - Charge Remaining	Per FDA request
			11.5.2, 11.6.2	Add blinded NYHA Class assessment	Per FDA request
			12.1.1	Update LV MSP feature relatedness categories, clarify method of analysis, and add sensitivity analysis	Correction
			12	Update sample size, power calculation, attrition estimate for primary effectiveness endpoint and overall study	Update due to change in study design per FDA request
			12.1.1.3	Clarify time-to-event analysis language for primary safety endpoint	Clarification
			12.2.1	Add ancillary assessment of Echo Measurements and CCS Response Status Outcomes in Non-Responders	Per FDA request
			19.3 and 19.6	Update risks of worsening HF; Update risks associated with participating in study	Update risk per FDA request Update to align with additional testing and clarification of study risks
			20.7	Update death reporting time period to 3 calendar days.	Correction
			22.2	Clarify roles and responsibilities of CEC in HF event adjudication and adjudication process.	Update per FDA request
			Multiple Sections	Minor clarification, modification, and correction	Minor clarification, modification, and correction
Revision D	May 16, 2017	90702637 Rev/Ver AH	26	Appendix Section removed. The recommended step-by-step guidance on	Modification

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
				testing will be provided in investigator and site training.	
			Figure 12.3-1	**Death is removed from the description of attrition between 6 and 12 month visit**	**Correction**
Revision E	**September 8, 2017**	**90702637 Rev/Ver AH**	**Synopsis and Section 9.3**	**Adding one exclusion criteria: Women of childbearing potential who are pregnant or plan to become pregnant over the course of the clinical trial.**	**Update**
			Table 11.1-1, Section 11.4.14, Section 11.5.18, Section 11.6.18	**Adding data collection on HeartLogic Alert assessment.**	**Update**
			Section 22.2	**Clarify that the CEC's role is to adjudicate heart failure event**	**Clarification**
			Section 11.5.5	**Clarify that both hospitalization and IV therapy event are used in CEC adjudication**	**Clarification**
			Section 11.5.9	**In the determination of 2 viable pacing vectors, clarify the original protocol language that could have led to different interpretation**	**Clarification**
Revision F	**November 15, 2017**	**90702637 Rev/Ver AH**	**Table 11.1- 1: Data Collection Schedule** **Section 11.5 and 11.6 6 Month Visit and 12 Month Visit list of data**	**Provide clarification regarding HeartLogic Alert feature data collection**	**Clarification**

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
			collection Section 11.5.18 and Section 11.6.18		

2. Protocol Synopsis

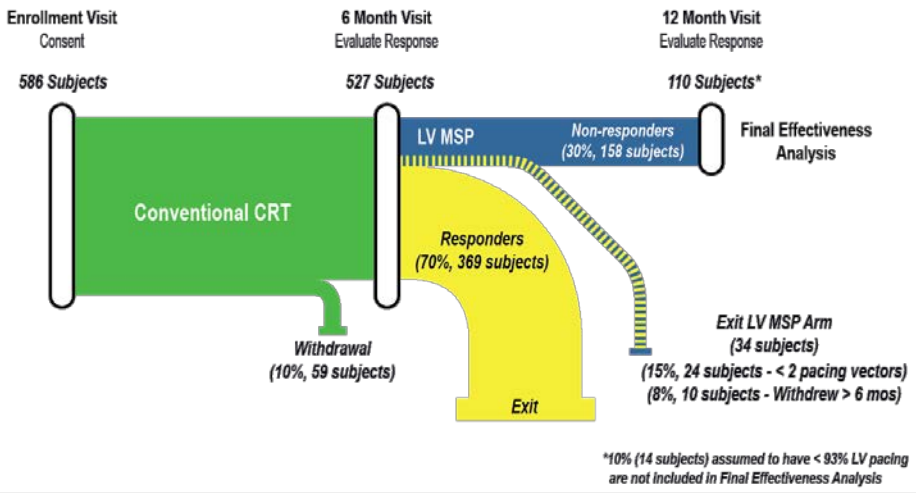
<table>
<tr><th colspan="2">SMART MSP
Post Approval Study</th></tr>
<tr><td>Study Objective(s)</td><td>Evaluate the effectiveness of Boston Scientific (BSC)'s LV MSP (Left Ventricular MultiSite Pacing) feature in the Resonate family of CRT-D devices[1] and confirm safety in a post approval study when used in accordance with its approved labeling.</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The BSC Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with heart failure who receive stable optimal pharmacologic therapy (OPT) for heart failure and who meet any one of the following classifications:
Moderate to severe heart failure (NYHA Class III-IV) with EF ≤ 35% and QRS duration ≥ 120 ms
Left bundle branch block (LBBB) with QRS duration ≥ 130 ms, EF ≤ 30%, and mild (NYHA Class II) ischemic or non-ischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure
The LV MSP is a feature of the BSC's Resonate family of CRT-D devices and is intended for use with subjects who are non-responders to conventional Biventricular (BiV) CRT-D therapy. The CRT-D device and the LV MSP feature will be used within the current BSC labeled indications for CRT-D therapy.</td></tr>
<tr><td>Description of Device under Evaluation</td><td>Eligible CRT-D Device models in the study – Resonate family of CRT-D devices
<table>
<tr><th>Resonate family of CRT-Ds
Device Name</th><th>US
Model Numbers</th><th>Description of Port
RV/ LV/ RA</th><th>Capable of
LV Only pacing?</th></tr>
<tr><td>RESONATE HF™</td><td>G548</td><td>DF1/IS4/IS1</td><td>Yes</td></tr>
<tr><td>RESONATE HF™</td><td>G547</td><td>DF4/IS4/IS1</td><td>Yes</td></tr>
<tr><td>RESONATE HF™</td><td>G528</td><td>DF1/IS4/IS1</td><td>No</td></tr>
<tr><td>RESONATE HF™</td><td>G537</td><td>DF4/IS4/IS1</td><td>No</td></tr>
<tr><td>RESONATE™ X4</td><td>G448</td><td>DF1/IS4/IS1</td><td>Yes</td></tr>
</table></td></tr>
</table>

[1] Resonate refers to all trademarked devices in this family of pulse generators, including RESONATE HF, RESONATE, VIGILANT, and MOMENTUM.

SMART MSP

Post Approval Study

	RESONATE™ X4 G447 DF4/IS4/IS1 Yes RESONATE™ X4 G428 DF1/IS4/IS1 No RESONATE™ X4 G437 DF4/IS4/IS1 No VIGILANT™ X4 G248 DF1/IS4/IS1 Yes VIGILANT™ X4 G247 DF4/IS4/IS1 Yes VIGILANT™ X4 G228 DF1/IS4/IS1 No VIGILANT™ X4 G237 DF4/IS4/IS1 No MOMENTUM™ X4 G138 DF1/IS4/IS1 Yes MOMENTUM™ X4 G128 DF1/IS4/IS1 No
Study Design	Prospective, multi-center, single arm, post approval study to be conducted in the United States.
Planned Number of Subjects	The study will enroll approximately 586 subjects.
Planned Number of Study Sites	Approximately 60 US sites.
Primary Safety Endpoint(s)	LV MSP feature-related complication-free rate between the 6 Month Visit and the 12 Month Visit in non-responders with the LV MSP turned on for any duration
Primary Effectiveness Endpoint(s)	Proportion of the LV MSP Group subjects with Improved Clinical Composite Score (CCS) from the 6 Month Visit through the 12 Month Visit
Ancillary Analyses	• Assessment of Echocardiographic Measurements and CCS Response Status Outcomes in Non-responders • Assessment of effectiveness of the LV MSP in SMART MSP PAS and SMART Registry • Assessment of Worsened LV MSP Group • Assessment of RV-LV electrical delay and response • Assessment of battery consumption

SMART MSP **Post Approval Study**	
	• Assessment of SmartDelay and SmartVector usage • Assessment of percentage of pacing • Additional descriptive statistics include but are not limited to: overall response rate at 6 Month Visit and percentage of LV MSP Group subjects with two viable vectors that are furthest apart
Method of Assigning Patients to Treatment	Subjects will be selected from the investigator's general population who receive a Boston Scientific Resonate family of CRT-D device in accordance with its labeled indication for use, as well as an ACUITY™ X4 coronary venous LV lead.
Follow-up Schedule	Study visits in clinic will occur at the following time periods: - Enrollment Visit: between 1 day and 21 days post-CRT-D implantation. - 6 Month Follow-up Visit: 183 days -30 days/+0 day after Enrollment Visit - 12 Month Follow-up Visit: 183 days -0 day/+30 days after 6 Month Visit  Subjects determined to be a responder at their 6 Month Visit will complete the study. Subjects in the Non-Responder Group, including those subjects who have no LV MSP turned on, will complete the study at their 12 Month Visit.
Study Duration	The study is expected to last approximately 36 months from the first enrollment to the study closure.

SMART MSP **Post Approval Study**	
Inclusion Criteria	1. Subjects who received de novo implantation of BSC's Resonate family of CRT-D devices with the LV MSP feature[2] and BSC's ACUITY™ X4 LV Quadripolar leads. A Resonate family of CRT-D device upgrade from previous single or dual chamber pacemaker or ICD implantation is allowed. 2. Subjects must meet BSC labeled indication for CRT-D implantation[3]. 3. Subjects must have a functional RA lead and RV lead implanted. 4. Subjects who are willing and capable of providing informed consent 5. Subjects who are willing and capable of participating in all testing/visits associated with this clinical study at an approved clinical study center and at the intervals defined by this protocol 6. Subjects who are age 18 and above, or of legal age to give informed consent specific to state and national law
Exclusion Criteria	1. Subjects who received LV pacing prior to receiving the Resonate family of CRT-D system implantation. 2. Subjects who received the LV MSP therapy post CRT-D implantation but prior to enrollment 3. Subjects with documented history of permanent AF 4. Subjects with documented permanent complete AV block 5. Subjects who are expected to receive a heart transplant during the 12 months course of the study 6. Subjects with documented life expectancy of less than 12 months 7. Women of childbearing potential who are pregnant or plan to become pregnant over the course of the clinical trial. *Note: For patients with uncertain pregnancy status, pregnancy tests should have been performed per site's standard clinical practice prior to CRT-D device implant.* 8. Subjects who enrolled in any other concurrent study or registry, with the exception of mandatory national or governmental

[2] Resonate refers to all trademarked devices in this family of pulse generators, including RESONATE HF, RESONATE, VIGILANT, and MOMENTUM.

[3] For BSC labeled indication for CRT-D implantation, see **Section 9.1.1**.

SMART MSP

Post Approval Study

<table>
<tr><td></td><td>registry, without prior written approval from BSC.</td></tr>
<tr><td colspan="2">Statistical Methods</td></tr>
<tr><td>Endpoint Hypotheses and Statistical Test Methods</td><td>
<table>
<tr><th>Endpoint</th><th>Hypothesis</th><th>Analysis Method</th></tr>
<tr><td>Primary Safety</td><td>LV MSP feature-related complication-free rate between 6 Month Visit and 12 Month Visit > 90%.</td><td>Kaplan-Meier methodology</td></tr>
<tr><td>Primary Effectiveness</td><td>Proportion of LV MSP Group with Improved CCS from 6 Month visit through 12 Month Visit > 5%</td><td>One-sided Exact Test for a Single Binomial Proportion</td></tr>
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</table>

3. Table of Contents

Table of Figures

Table of Tables

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 improve cardiac function for ICD patients with NYHA Class III-IV heart failure, reduced ejection fraction, and wide QRS duration in the CONTAK CD study[1]. Subsequently, the COMPANION study demonstrated additional benefits of CRT that included 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 ICD patients in NYHA Class I-II[3]. In addition to the benefits shown in previous studies, MADIT CRT also demonstrated significant reduction in left ventricular volumes and improvement in left ventricular ejection fraction (LVEF).

The benefits of CRT-D are not conferred on every patient implanted with a device, however. Patients 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 around 30% of the patients. When echo-based measures are used, the non-response rate is higher and around 50%.

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

- Poor lead location
- Lack of baseline dyssynchrony
- Improper programming
- Irreversibly advanced heart failure
- Myocardial scar

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

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

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

V-V Timing: The InSync III Marquis Study[6] using the CCS, DECREASE HF Study[7] using a composite of peak VO_2 and LVESD, and RHYTHM ICD V-V Optimization Study[8] using peak VO_2 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[7] using a composite of peak VO_2 and LVESD and the B-LEFT HF Study[9] using the CCS demonstrated safety of LV pacing. The AdaptivCRT study[10], using the CCS, 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. Overall, the results from these studies showed that the LV only pacing is as effective as conventional BiV CRT pacing.

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[11] (which also included a V-V timing optimization algorithm), which used the CCS, and SMART-AV[12], which used LVESV to measure effectiveness of optimizing AV delay. Both studies showed that these methods were non-inferior to empiric programming. The RESPOND-CRT study[13], which evaluated a CRT system that employed a hemodynamic sensor to optimize both AV and VV timing, used a modified version of the CCS. This study also found that the sensor was non-inferior to echocardiographic optimization.

Multi-site Pacing: Left ventricular multi-site pacing (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 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[14-22]. Furthermore, acute studies on MSP have shown no ventricular arrhythmias or other adverse events during acute testing, implant and pre-discharge[18]. Among different 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 MPP Trial[23], 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 Left Ventricular Multi-Site Pacing (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. The objective of SMART MSP study is to demonstrate the effectiveness of the LV MSP feature to improve CRT non-response rate and confirm the safety of the feature in the post-market settings.

5. Device Description

5.1. *CRT-D Device*

Commercially approved Boston Scientific (BSC)'s Resonate family of CRT-Ds are eligible devices in this study. The LV MSP feature is available in the Resonate family of CRT-Ds, which includes RESONATE HF, RESONATE, VIGILANT, and MOMENTUM devices. These devices have quadripolar headers and accept LV quadripolar leads. See **Table 5.1-1** for a complete list of eligible CRT-D device models.

Table 5.1-1: Eligible CRT-D Device Models

Resonate family of CRT-Ds Device Name	US Model Numbers	Description of Port RV/ LV/ RA	Capable of LV Only pacing?
RESONATE HF™	G548	DF1/IS4/IS1	Yes
RESONATE HF™	G547	DF4/IS4/IS1	Yes
RESONATE HF™	G528	DF1/IS4/IS1	No
RESONATE HF™	G537	DF4/IS4/IS1	No
RESONATE™ X4	G448	DF1/IS4/IS1	Yes
RESONATE™ X4	G447	DF4/IS4/IS1	Yes
RESONATE™ X4	G428	DF1/IS4/IS1	No
RESONATE™ X4	G437	DF4/IS4/IS1	No
VIGILANT™ X4	G248	DF1/IS4/IS1	Yes
VIGILANT™ X4	G247	DF4/IS4/IS1	Yes
VIGILANT™ X4	G228	DF1/IS4/IS1	No
VIGILANT™ X4	G237	DF4/IS4/IS1	No
MOMENTUM™ X4	G138	DF1/IS4/IS1	Yes
MOMENTUM™ X4	G128	DF1/IS4/IS1	No

5.1.1. LV MSP

A new feature available in these CRT-D devices is the LV 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 compared to the one LV pace per cardiac cycle as done in conventional CRT with single-site LV

pacing. Each of the LV paces has its own independently programmable pacing vector and output (LVa vector and LVb vector). Depending on the pacing chamber selected, the LV MSP feature can deliver BiV MSP pacing or LV Only MSP pacing.

Two features associated with the LV MSP are described below:

5.1.1.1. SmartVector

The SmartVector feature provides recommendations for the LV MSP pacing sequence, LV pacing vectors and LV pacing characteristics (amplitude and pulse width) based on data gathered via the LV VectorGuide feature and on LV electrode spacing.

5.1.1.2. SmartOffset

The SmartOffset feature provides recommendations for the LV MSP programmed delays between the ventricular paces based on data gathered via the LV VectorGuide data and the current LV MSP pacing vectors.

5.1.2. LV Only Pacing

Another new feature available in these CRT-D devices is the LV only pacing feature. The clinician can program Pacing Chamber settings so that the system delivers CRT pacing therapy to both ventricular chambers (BiV Pacing) or just to the left ventricular chamber (LV Only).

5.1.3. LV VectorGuide™

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

- RV sense (RVs) to LV sense (LVs) timing
- LV lead impedance
- Phrenic Nerve Stimulation (PNS)
- LV pace threshold

The LV VectorGuide feature is available in previous generations of BSC CRT-D devices.

5.1.4. SmartDelay™

The SmartDelay optimization feature provides recommended settings for programming the 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 cardiac contractile function. The AV delay optimization provided by SmartDelay is expected to be applicable to the functioning of the LV MSP feature.

The SmartDelay feature is available in previous generations of BSC CRT-D devices.

5.2. *ACUITY™ X4 Quadripolar Coronary Venous LV Lead*

Boston Scientific's ACUITY™ X4 heart failure lead family for the Left Ventricle (LV) quadripolar leads is required in this study. The ACUITY™ X4 leads are intended for chronic left ventricular pacing and sensing. A variety of pace/sense configurations are possible with the four electrodes that can function as cathodes (all four electrodes) or anodes (all except E1, the most distal electrode) when used with a compatible pulse generator. ACUITY™ X4 leads are available in three tip configuration designs (straight tip, short tip spiral, long tip spiral)—intended to provide choices for a variety of patient anatomies.

The ACUITY™ X4 LV lead models are required to be used in this study but they are not under evaluation.

See **Figure 5.2-1** and **Figure 5.2-2** for images of the ACUITY™ X4 leads and the layout and spacing of the electrodes on the lead.

Figure 5.2-1: Three Types of ACUITY™ X4 LV Leads

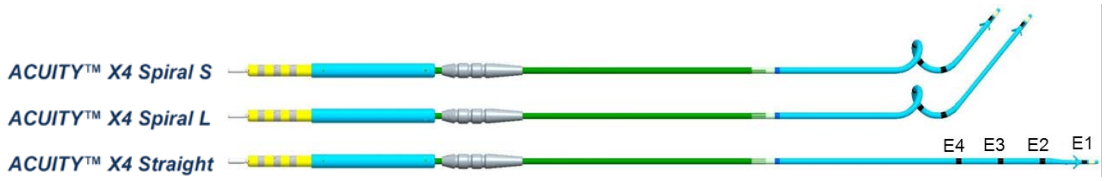
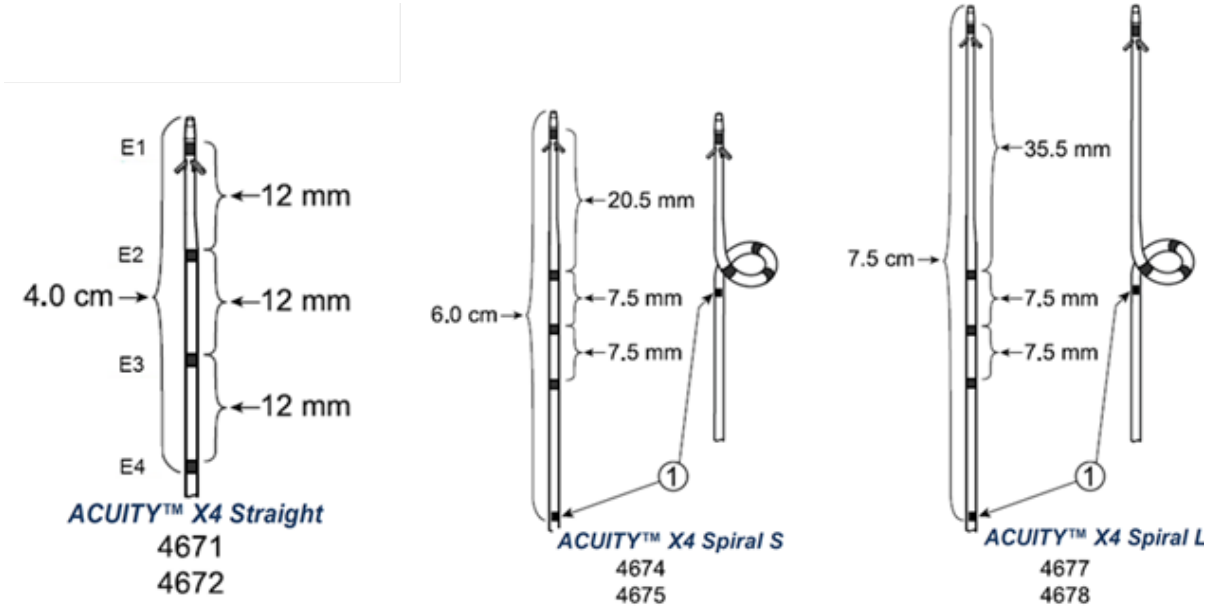


Figure 5.2-2: Electrode Layout and Spacing on ACUITY™ X4 LV Leads.



The nomenclature of the electrodes on the LV lead (E1, E2, E3, E4) is an industry standard. The corresponding nomenclature on the BSC PRM is as follows: LVTip1, LVRing2, LVRing3, and LVRing4.

E1: LV Tip 1	E3: LV Ring 3
E2: LV Ring 2	E4: LV Ring 4

Table 5.2-1: Electrode Spacing and Length of ACUITY™ X4 LV Lead Models

Tip Configuration	Electrode Spacing	Length	
		86cm	95cm
		Model Number	
Straight	Even	4671	4672
Spiral	Short tip	4674	4675
	Long tip	4677	4678

5.3. *Other Devices*

Commercially approved BSC Right Atrial (RA) lead and Right Ventricular (RV) lead are recommended to be included in this study, but any commercially available RA lead and RV lead from any manufacturer is eligible.

6. Study Objectives

The objective of the study is to evaluate the effectiveness of the Boston Scientific's LV MSP feature in the BSC's Resonate family of CRT-D devices, and confirm safety in a post approval study when used in accordance with its approved labeling.

7. Study Endpoints

7.1. *Primary Safety Endpoint*

- LV MSP feature-related complication-free rate between the 6 Month Visit and the 12 Month Visit in non-responders with the LV MSP on for any duration.

7.2. *Primary Effectiveness Endpoint*

- Proportion of the LV MSP Group subjects with Improved CCS from the 6 Month Visit through the 12 Month Visit.

8. Study Design

The SMART MSP study is designed as a prospective, single arm, multi-center, post-approval study to be conducted within the US.

8.1. *Scale and Duration*

The SMART MSP study's sample size is approximately 586 subjects. See **Section 8.2** and **Section 12.3** for further details on the sample size and attrition estimate. This study will be conducted in approximately 60 US sites. All study required visits will be completed as part of

the subject's regularly scheduled clinic follow-up visits. The subject participation is complete when the final actively enrolled subject in the Non-Responder Group completes the 12 Month Visit. Study completion is anticipated to be approximately 36 months after first enrollment.

8.2. *Treatment Assignment*

All enrolled subjects will be programmed to conventional CRT from the point of enrollment visit to the 6 Month Visit. At the 6 Month Visit, the clinical composite score (CCS) will be calculated for each subject to determine the subject's responder status to conventional CRT. Subjects who are responders will be in the Responder Group and complete the study at the 6 Month Visit, as shown in **Figure 8.2-1**.

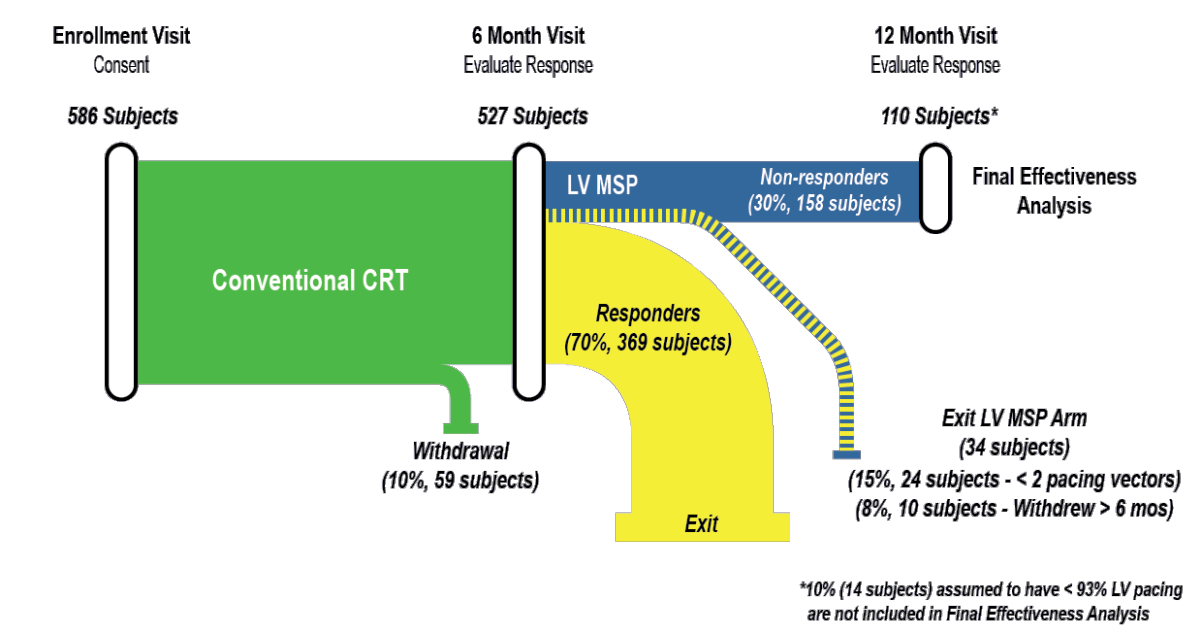
Subjects who are non-responders to conventional CRT based on the CCS calculation belong to the Non-Responder Group. The LV MSP feature will be enabled for these subjects from the 6 Month Visit through the 12 Month Visit. Those subjects who are able to receive the LV MSP therapy and achieve at least 93% of LV pacing are classified in the LV MSP Group, which is defined as meeting all of the following criteria:

- Subjects who have achieved at least 2 viable LV pacing vectors
- Subjects who have the LV MSP feature enabled
- Subjects who have achieved at least 93% of the LV MSP pacing

To determine whether an LV pacing vector is considered viable, the following criteria are recommended:

- The pacing impedance is not out-of-range per physician's programmed value
- No presence of PNS - the pacing capture threshold (PCT) plus 3V of safety margin should be less than PNS threshold
- LV PCT at ≤ 4.5V or demonstrated capture at ≤ 4.5V

Figure 8.2-1: Study Design Flowchart



8.3. *Justification for the Study Design*

This study is designed to evaluate the therapy benefit provided by multisite pacing to those patients who are non-responders to CRT with single site LV pacing based on a clinical evaluation using the CCS. The study's primary endpoint of the Clinical Composite Endpoint (CCS) measures multiple components related to the improvement of patient's clinical status, including Patient Global Assessment, NYHA class change, heart failure event, and mortality rate. See **Section 11.5.1** for the definition and calculation used in the study. These measures are well-understood and widely accepted by the medical community.

9. Subject Selection

9.1. *Study Population and Eligibility*

Subjects included in the SMART MSP Study should be selected from the investigator's general patient population who received BSC Resonate family of CRT-D devices, and were indicated for CRT-D implantation per BSC labeled indication provided in **Section 9.1.1**. 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.

9.1.1. BSC Labeled Indication for CRT-D Implantation

The BSC's CRT-Ds are indicated for patients with heart failure who receive stable optimal pharmacologic therapy (OPT) for heart failure and who meet any one of the following classifications:

- Moderate to severe heart failure (NYHA Class III-IV) with EF ≤ 35% and QRS duration ≥ 120 ms
- Left bundle branch block (LBBB) with QRS duration ≥ 130 ms, EF ≤ 30%, and mild (NYHA Class II) ischemic or non-ischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure

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 clinical investigation, provided no exclusion criterion (see **Section 9.3**) is met.

Table 9.2-1: Inclusion Criteria

Inclusion Criteria	1. Subjects who received de novo implantation of BSC's Resonate family of CRT-D devices with the LV MSP feature[4] and BSC's ACUITY™ X4 LV Quadripolar leads. A Resonate family of CRT-D device upgrade from previous single or dual chamber pacemaker or ICD implantation is allowed. 2. Subjects must meet BSC labeled indication for CRT-D implantation. 3. Subjects must have a functional RA lead and RV lead implanted 4. Subjects who are willing and capable of providing informed consent 5. Subjects who are willing and capable of participating in all testing/visits associated with this clinical study at an approved clinical study center and at the intervals defined by this protocol 6. Subjects who are age 18 and above, or of legal age to give informed consent specific to state and national law

9.3. *Exclusion Criteria*

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

[4] Resonate refers to all trademarked devices in this family of pulse generators, including RESONATE HF, RESONATE, VIGILANT, and MOMENTUM.

Table 9.3-1: Exclusion Criteria

Exclusion Criteria	1. Subjects who received LV pacing prior to receiving the Resonate family of CRT-D system implantation. 2. Subjects who received the LV MSP therapy post CRT-D implantation but prior to enrollment 3. Subjects with documented history of permanent AF 4. Subjects with documented permanent complete AV block 5. Subjects who are expected to receive a heart transplant during the 12 months course of the study 6. Subjects with documented life expectancy of less than 12 months 7. Women of childbearing potential who are pregnant or plan to become pregnant over the course of the clinical trial. *Note: For patients with uncertain pregnancy status, pregnancy tests should have been performed per site's standard clinical practice prior to CRT-D device implant.* 8. Subjects who enrolled in any other concurrent study or registry, with the exception of mandatory national or governmental registry, without prior written approval from BSC

10. Subject Accountability

10.1. *Point of Enrollment*

Subjects who meet all study eligibility criteria will be considered enrolled in the SMART MSP Study at the time of signing the informed consent form. All enrolled subjects meeting the eligibility criteria will be counted against the enrollment ceiling for the study. Any adverse event (AE) experienced post-enrollment by an actively enrolled subject that meets the protocol requirement for reporting must be recorded in the electronic case report form (eCRF) or alternative methods, if necessary. See **Section 20** for information on protocol requirements of AE reporting.

10.2. *Point of Study Exit*

All subjects enrolled in the clinical study shall be accounted for. An End of Study form is required for all study subjects and is completed following occurrence of any of these events:

- Subject completion of study participation
    - For subjects classified in the Responder Group, this is upon the completion of the 6 Month Visit.
    - For subjects classified in the Non-Responder Group, this is upon the completion of the 12 Month Visit.

- Subject withdrawal
- Subject death

10.3. *Study Withdrawal*

If a subject withdraws from the clinical study, the reason(s) shall be reported. If such withdrawal is due to problems related to the device safety or performance, the investigator shall ask for the subject's permission to follow the subject outside of the study.

Reasons for withdrawal may include but are not limited to:

- physician discretion
- subject choice to withdraw consent
- CRT-D device or LV lead explant
- lost to follow-up
- uncorrected LV lead dislodgment or undiscovered LV lead dislodgment until the 6 Month Visit
- LV lead revision prior to the 6 Month Visit

While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. All applicable eCRFs up to the point of subject withdrawal and an "End of Study" eCRF must be completed. For subjects who are "lost-to-follow-up", the investigator/center staff must have at least three documented attempts to contact the subject prior to completion of the "End of Study" eCRF. Additional data can no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, regardless of the reason. All data queries should be resolved and all open adverse events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used.

10.4. *Subject Status and Classification*

All patients who meet all study eligibility criteria, and sign and date an informed consent form are considered enrolled in the study.

Enrolled subjects will be classified as follows:

- Active enrolled - subject who completes the Informed Consent process, signs and dates the ICF and meets the eligibility criteria. Active enrolled subjects will be counted towards the enrollment ceiling.
- Consented and ineligible – subject who signs Informed Consent but does not meet the eligibility criteria.

10.5. *Enrollment Controls*

Approximately 586 subjects will be enrolled in the study. Study sites will be notified when the enrollment ceiling is close to being reached and once enrollment is complete. No single

site shall enroll more than 20% of the study subjects without the prior written approval from BSC.

11. Study Methods

11.1. *Data Collection*

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

Table 11.1-1: Data Collection Schedule

Procedure/Assessment	Enrollment Visit (between 1 day and 21 days post-CRT-D implantation)	Follow-up Visits		
		6 Month Office Visit (183 days post-enrollment -30 days/+0 day)	12 Month Office Visit (183 days post-6 Month Visit -0 day/+30 days)	Additional Visit
Informed consent process, including informed consent signature and date	X	--	--	--
Inclusion and exclusion	X	--	--	--
Demographics	X	--	--	--
Medical history and medication	X	--	--	--
NYHA Class	X	X	X	--
Patient Global Assessment (PGA), Physician Global Assessment (PhGA)	--	X	X	--
Adverse Events Assessment	X	X	X	X
HeartLogic Alert (required if the feature is enabled)	X	X	X	--
Echo measurement, required only if performed by standard of care	X	X	X	--
Device settings and status	X	X	X	X
Lead measurements (RA, RV, and LV*)	X	X	X	O
SmartDelay test and value, ECG/EGM	X	X	X	--
LV VectorGuide test and value	X**	X***	X****	--
RVp-LVs interval test, ECG/EGM	X	X	X	--
SmartVector test and value	--	X (Non-Responder Group with LV MSP on)	X (Non-Responder Group with LV MSP on)	--
SmartOffset test and value	--	X (Non-Responder Group with LV MSP on)	X (Non-Responder Group with LV MSP on)	--
Battery Consumption	X	X	X	--
LV lead location	X*****	--	--	--
Sleep Incline Trend calibration	X******	--	--	--

Procedure/Assessment	Enrollment Visit (between 1 day and 21 days post-CRT-D implantation)	Follow-up Visits		
		6 Month Office Visit (183 days post-enrollment -30 days/+0 day)	12 Month Office Visit (183 days post-6 Month Visit -0 day/+30 days)	Additional Visit
"Save all" device data	--	X*******	X*******	--

X = Required; -- = Not required/ Not applicable; O = Optional.
* The LV pacing configuration for lead measurements is per investigator discretion
** It is required to start the LV VectorGuide test at Enrollment Visit in order to measure the RV-LV intervals; however, it is not required to complete the LV VectorGuide test.
*** For subjects in the Responder Group, it is required to start the LV VectorGuide test at the 6 Month Visit in order to measure the RV-LV intervals; however, it is not required to complete the LV VectorGuide test. For subjects in the Non-Responder Group, LV VectorGuide test is required.
**** For subjects in the Non-Responder Group who did not receive LV MSP therapy, it is required to start the LV VectorGuide test at the 12 Month Visit in order to measure the RV-LV intervals; however, it is not required to complete the LV VectorGuide test. For subjects who received LV MSP therapy, LV VectorGuide test is required.
***** Required if the LV lead location information is available through imaging or patient's medical record.
****** Sleep Incline Trend calibration is not required if the Sleep Incline Sensor is initializing or if the trend is already calibrated prior to this visit.
******* "Save All" device data collection is only required for subjects not enrolled on LATITUDE Remote Monitoring System.

11.2. *Study Candidate Screening*

The investigator or designee is responsible for screening potential patients and selecting those who meet all inclusion criteria and do not meet any of exclusion criteria.

11.3. *Informed Consent*

Subjects who meet all of the inclusion criteria, none of the exclusion criteria, and sign and date the informed consent form are considered enrolled in the study.

11.4. *Enrollment Visit*

The Enrollment Visit may occur at the pre-discharge visit, and must be between 1 day and 21 days after the CRT-D implantation procedure. Enrollment cannot occur on the same day of the implantation procedure. A list of the data to be collected at the Enrollment Visit is provided below, with further details included in the sections below.

- CRT-D indication verification
- Echo measurement
- Subject demographics
- Medical history and medications
- NYHA class assessment
- Device and lead information
- Current device settings and status
- Lead measurements
- SmartDelay test and value
- Asense to Vsense and Apace to Vsense intervals
- LV VectorGuide test and value
- RVp-LVs interval test
- LV lead location (if available)
- Battery consumption
- Sleep Incline Trend calibration
- Final device settings and status
- Adverse event assessment

11.4.1. CRT-D Indication Verification

The following values from the subject's medical record are required to demonstrate that each subject met BSC's labeled indications prior to their CRT-D implantation:

- Most recent Echo measurement of 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.
    - The following measurement will be collected per site's standard of care practice: LVESV, LVEDV, Aortic VTI, and Mitral valve regurgitation.
- QRS duration
- Bundle Branch Block morphology (LBBB or non-LBBB)
- Heart failure etiology (ischemic or non-ischemic)
- NYHA class value
- Cardiovascular medications

11.4.2. Subject Demographics

Subject's age, sex, and race/ethnicity are required.

11.4.3. Medical History and Medication

Subject's history of cardiovascular diseases and current cardiovascular medications use are required to be collected.

11.4.4. NYHA Class Assessment

Obtain the subject's most recent NYHA Class assessment prior to the CRT-D implantation per the definition shown in **Table 11.4-1**.

Table 11.4-1: NYHA Classifications[5]

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.

[5] NYHA Heart Failure Classification by American Heart Association, updated September 28, 2016. http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp#.WLWhqlUrKpo

11.4.5. Device Information

The following are required for the implanted CRT-D device, RA lead, RV lead, and LV lead:

- Manufacturer
- Model and serial number
- Implant date

11.4.6. Current Device Settings and Status

Print a copy of the Quick Notes Report from the PRM to document current device settings and status prior to conducting any test and changing the programming settings.

11.4.7. Lead Measurements

The following lead measurements are required to be collected for the RA lead, RV lead, and LV lead:

- Intrinsic amplitude (mV)
- Pacing capture threshold (PCT in V; the recommended pulse width is 0.4 ms)
- Pacing lead impedance (Ω)
- Shocking lead impedance (Ω, RV lead).

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

- Print a copy of the Quick Notes Report from the PRM

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

It is recommended that the PCT measurements be collected in the following fashion:

- At least 3 cardiac cycles at a given voltage level are obtained before stepping down to the next voltage level.
- A count of two non-capture beats at a given voltage level is reached before declaring a loss of capture (LOC) for any of these tests.
- The pacing configurations used in the LV lead measurement testing are per the investigator discretion. At least one configuration must be tested for the LV lead, and it is recommended that the tested configuration be the configuration planned for final programming.

It is recommended that the threshold 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 CRF.

11.4.8. SmartDelay Test

It is required to perform the SmartDelay test for all subjects to obtain programming recommendations for the AV Delay and Pacing Chamber. It is per the investigator discretion whether to follow the programming recommendations. However, the Pacing Chamber that is selected for a subject at the Enrollment Visit must be used for that subject through the 6 Month Visit (for all subjects) and through the 12 Month Visit (for non-responders).

The LV offset is required to be set at 0 ms prior to running the SmartDelay test.

The SmartDelay test nominal Temporary Paced Lower Rate Limit (LRL) is set at 80 bpm. It is recommended to set the LRL at 10 to 15 bpm above the subject's intrinsic heart rate before conducting the SmartDelay test.

The following values from the SmartDelay test are required to be collected:

- SAV (sensed AV delay) and PAV (paced AV delay), both the recommended and final programmed values.
- Pacing Chamber (BiV or LV Only), both the recommended and final programmed values.
- Rationale if the SmartDelay recommendations are not followed.

The following documents from the SmartDelay test are required:

- Set EGM channels to RA, RV, and LV. Obtain ECG/EGM strips at the paper speed of 100 mm/s for approximately 3-5 representative beats during the Atrial Sense test and Atrial Pace test, respectively. The following values are required to be measured from the ECG/EGM strips:
    - Asense-RVsense, Asense-LVsense, Apace-RVsense, and Apace-LVsense intervals for each of the representative beats
    - Calculate the mean value for each of the 4 intervals from these representative beats

  Record the Subject ID and visit information (Enrollment, 6 Month, or 12 Month) on each ECG/EGM strip. Copies of all ECG/EGM strip should be submitted to BSC quarterly or more frequently, and before study ends. The data collected in this test will be used for future product feature enhancement or development, and are not associated with the primary and ancillary objectives. A deviation is not required if the ECG/EGM strips are not sent to BSC.
- Print a copy of the Settings Changes Report from the PRM 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.

If the SmartDelay test fails to complete, re-perform the test to obtain the recommended value. If the SmartDelay test was complete but not successful, the SmartDelay will display the nominal value as the recommended value. The SmartDelay test should be limited to two attempts in total.

11.4.9. LV VectorGuide Test

It is required that the RV-LV interval value be measured from all 4 electrodes as cathode (LVTip1, LVRing2, LVRing3, and LVRing4) by starting the LV VectorGuide Test; however, it is not required to complete all steps of the LV VectorGuide test once the RV-LV intervals are collected. If the LV VectorGuide test is completed, provide the number of viable pacing vectors (See **Section 8.2** for definition of viable pacing vectors).

Subjects must have RV and LV sensed beats for test to be successful. If the subject does not tolerate a low intrinsic heart rate, stop the test and provide the rationale for not completing the required test (e.g. subject needs RV pacing support).

The following values are required to be collected:

- Select the unipolar vectors and run the RV-LV Delay test for all 4 unipolar vectors to obtain RV-LV delay values.

The following values are required to be collected only if the LV VectorGuide test is completed:

- Number of viable pacing vectors (See definition in **Section 8.2**)

The following document is required:

- Print a copy of the LV VectorGuide Report from the PRM.

11.4.10. RVp-LVs Interval Test

The data collected in this section will be used for future product feature enhancement or development, and are not associated with the primary and ancillary objectives. A deviation is not required if the test is not performed or the ECG/EGM strips are not sent to BSC.

Set the EGM channels to RA, RV and LV, pacing mode to VVI, LRL to 10 to 15 beats above the subject's intrinsic rate and ventricular pacing chamber to RV Only. Obtain the ECG/EGM strips at the paper speed of 100 mm/s for approximately 3-5 representative beats in two LV sense vector configurations: LVTip1 to Can and LVRing2 to Can, respectively. Record the Subject ID, visit information (Enrollment, 6 Month, or 12 Month), and the cathode of the LV sensing configuration (LVTip1 or LVRing2) on each ECG/EGM strip. Copies of all ECG/EGM strip should be submitted to BSC quarterly or more frequently, and before study ends.

11.4.11. LV Lead Location

The coronary venous LV lead location is required to be collected if the location information is available; such information would typically be available by reviewing lead imaging documents including in-procedure fluoroscopy or pre-discharge chest X-rays, or obtained from the subject's medical record.

The LV lead location is required to be classified and recorded in the eCRF as follows:

- Anterior, anterolateral, lateral, posterolateral, or posterior

and

- Basal, Middle, or Apical

11.4.12. Battery Consumption

The following values are required to be collected:

- Time to explant
- Charge Remaining

11.4.13. Sleep Incline Trend Calibration

The Sleep Incline Trend of the CRT-D device will be calibrated at Enrollment Visit. Calibration is not required if the Sleep Incline Sensor is initializing or if the trend is already calibrated prior to this visit. The data collected in this section will be used for future product feature enhancement or development, and are not associated with the primary and ancillary objectives. A deviation is not required if the calibration is not performed.

11.4.14. Final Device Settings and Status

Print a copy of the Device Settings Report from the PRM for all subjects at the Enrollment Visit and clear the device counters as the final step. Record whether the HeartLogic feature (Heart Failure Sensor Suite) is enabled in the CRT-D device and whether the HeartLogic Alert is programmed ON via the LATITUDE system. All subjects at the Enrollment Visit are required to receive conventional CRT therapy and have the LV MSP feature programmed off. All other programming settings are per investigator discretion.

11.4.15. Adverse Event Assessment

Study required adverse event data will be collected and assessed for each subject after signing of the informed consent. See **Section 20** for Adverse Event collection and reporting requirements.

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

Table 11.4-2: Source Documentation Required at Enrollment Visit

Source Documentation Requirement	Disposition
Informed consent form and process, including informed consent signature and date	Retain at study site
Inclusion and exclusion criteria	
Cardiovascular disease history and medication	
NYHA class assessment	
Device and lead information	
Adverse event assessment	
Device Settings Report, Quick Notes Report, LV VectorGuide Report, Settings Changes Report	
Echo measurement, if performed per standard of care	
Manually recorded Charge Remaining	
ECG/EGM Strips from the SmartDelay test	Retain at study site Submit 1 copy to BSC
ECG/EGM Strips from the RVp-LVs interval test	

11.5. *6 Month Visit*

The 6 Month Visit must be performed in office at 183 -30 days/+0 day post-Enrollment Visit. A list of the data to be collected at the 6 Month Visit is provided below, with further details included in the sections below.

- NYHA class assessment
- Patient Global Assessment
- Physician Global Assessment
- HF event
- Response status determination
- Echo measurement
- Current device setting and status
- Lead measurements
- LV VectorGuide test and value
- RVp-LVs interval test
- SmartDelay test and value

- Asense to Vsense and Apace to Vsense intervals
- SmartVector and SmartOffset value
- Battery consumption
- Final device settings and status
- Adverse event assessment
- HeartLogic Alert
- "Save All" device data

11.5.1. Definition and Components of the Clinical Composite Score

The CCS will be calculated for all subjects at the 6 Month Visit. The CCS consists of the following components:

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

11.5.1.1. HF Event Definition

For the purpose of the CCS calculation, HF event is defined as an adverse 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.

11.5.1.2. PGA Classification

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

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

Per CCS definition, a little better and a little worse are considered placebo effect and are treated as no change in PGA status.

The investigator will use the subject's response to the PGA and classify response of "a little better", "no change", or "a little worse" to the category of "no change". Subsequently, the investigator will use "very much better", "much better", "no change", "much worse", and "very much worse" to determine the status of PGA changes.

See **Table 11.5-1** for a detailed description of the PGA assessment tool.

11.5.1.3. NYHA Class Assessment

See Section 11.4.4 for a detailed description of performing NYHA Class assessment.

11.5.1.4. CCS Status Classification

Subjects will be classified as improved, unchanged, or worsened by comparing their clinical response in the current visit to their last visit. At the 6 Month Visit, subjects' status will be compared to their status immediately prior to receiving the CRT-D implantation. 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 event 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 event 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.

11.5.2. NYHA Class

NYHA Class assessment shall be performed by a site staff who is blinded to the study design, subject's clinical status in the study, and the programmed device settings. The subject's current NYHA Class must be determined based on **Table 11.4-1**.

11.5.3. Patient Global Assessment

The current PGA must be filled out by the subject, as specified in the assessment tool in **Table 11.5-1**.

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**.

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

Patient Global Assessment: Check the response which best describes how you feel today compared to prior to the CRT-D implantation (asked at the 6 Month Visit) or compared to the 6 Month Visit (asked at the 12 Month Visit).

- Very much better
- Much better
- A little better
- No change
- A little worse
- Much worse
- Very much worse

Physician Global Assessment: How is the patient's clinical status today compared to his or her status at prior to the CRT-D implantation (assessed as the 6 Month Visit) or compared to the 6 Month Visit (assessed at the 12 Month Visit).

- Markedly improved
- Moderately improved
- Mildly improved
- No change
- Mildly worse
- Moderately worse
- Markedly worse

11.5.5. Response Status Determination

Based on subject's vital status, NYHA class, PGA, and occurrence of HF event, the investigator/delegated site staff will classify each subject to either responder or non-responder per the following criteria:

- Responder: subjects with an Improved CCS score
- Non-Responder: subjects with a Worsened or unchanged CCS score

The PhGA will not be used in classifying the subject response status. Responders will complete the study at the end of their 6 Month Visit based on the CCS status collected on the 6 Month Visit eCRF.

All reported hospitalizations and events that meet the definition of HF events will be adjudicated by the Clinical Events Committee (CEC) for relatedness to the heart failure. A subject with any hospitalization or IV therapy reported in the first 6 months will continue to be followed as a non-responder, regardless of the CCS. If the CEC determines that the event is not an HF event and the subject belongs to the Responder Group, the subject will be exited prior to the 12 Month Visit and excluded from the analysis for the non-responders.

Non-responders will continue to be followed in the study via the Non-Responder Group.

11.5.6. Echocardiography Measurement

If an echocardiography was performed by the standard of care since last visit, collect the subject's most recently obtained echo values and the date of measurement.

- LVEF
- LVESV
- LVEDV
- Aortic VTI
- Mitral Valve Regurgitation

11.5.7. Current Device Settings and Status

Print a copy of the Quick Notes Report from the PRM 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 settings, percent of pacing (%RA paced, % RV paced, %LV paced), and percent of AT/AF (%AT/AF) are required to be collected.

11.5.8. Lead Measurements

The following lead measurements are required to be collected for the RA lead, RV lead, and LV lead:

- Intrinsic amplitude (mV)
- Pacing capture threshold (PCT in V; the recommended pulse width is 0.4 ms)
- Pacing lead impedance (Ω)
- Shocking lead impedance (Ω, RV lead)

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

- Print a copy of the Quick Notes Report from the PRM.

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

It is recommended that the PCT measurements be collected in the following fashion:

- At least 3 cardiac cycles at a given voltage level are obtained before stepping down to the next voltage level.
- A count of two non-capture beats at a given voltage level is reached before declaring a loss of capture (LOC) for any of these tests.

It is recommended that the threshold 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 CRF.

11.5.9. LV VectorGuide Test

At the 6 Month Visit, the VectorGuide test should be performed prior to performing the SmartDelay test by selecting the VectorGuide test under the Test tab from the main programmer screen.

Responder Group

For subjects classified in the Responder Group, it is required that the RV-LV interval value be measured from all 4 electrodes as cathode (LVTip1, LVRing2, LVRing3, and LVRing4) by starting the LV VectorGuide test; however, it is not required to complete all steps of the LV VectorGuide test once the RV-LV intervals are collected. If the LV VectorGuide test is completed, also provide the number of viable pacing vectors.

Subjects must have RV and LV sensed beats for the test to be successful. If the subject does not tolerate a low intrinsic heart rate, stop the test and provide the rationale for not completing the required test (e.g. subject needs RV pacing support).

The following values are required to be collected in the Responder Group:

- Select the unipolar vectors and run the RV-LV Delay test for all 4 unipolar vectors to obtain RV-LV delay values.

The following values are required to be collected only if the LV VectorGuide test is completed:

- Number of viable pacing vectors (See definition in **Section 8.2**)

The following document is required in the Responder Group:

- Print a copy of the LV VectorGuide Report from the PRM.

Non-Responder Group

For subjects classified in the Non-Responder Group, it is required to use the LV VectorGuide to assess viable LV pacing vectors from all 17 pacing vectors.

For all 17 pacing vectors, the following values are required to be collected for subjects in the Non-Responder Group:

- RV-LV delay
- LV pacing impedance
- PNS test results
- LV Quick Capture threshold test
- Number of viable pacing vectors (See definition in **Section 8.2**)

The following document is required for subjects in the Non-Responder Group:

- Print a copy of the LV VectorGuide Report from the PRM.

For subjects classified in the Non-Responder Group, the LV pacing vectors will be recommended by the required SmartVector test; however, since it is not required to follow

the recommendation from the SmartVector, final pacing vectors are per the investigator discretion.

LV MSP Status in Non-Responder Group

Subjects who have at least 2 viable pacing vectors identified using the LV VectorGuide test or determined by the investigator will have the LV MSP feature turned on.

Subjects who do not have at least 2 viable pacing vectors identified will continue to be followed in the study but will not have the LV MSP feature turned on due to lacking of 2 viable pacing vectors.

11.5.10. RVp-LVs Interval Test

The data collected in this section will be used for future product feature enhancement or development, and are not associated with the primary and ancillary objectives. A deviation is not required if the test is not performed or the ECG/EGM strips are not sent to BSC.

Set the EGM channels to RA, RV and LV, pacing mode to VVI, LRL to 10 to 15 beats above the subject's intrinsic rate and ventricular pacing chamber to RV Only. Obtain the ECG/EGM strips at the paper speed of 100 mm/s for approximately 3-5 representative beats in two LV sense vector configurations: LVTip1 to Can and LVRing2 to Can, respectively. Record the Subject ID, visit information (Enrollment, 6 Month, or 12 Month), and the cathode of the LV sensing configuration (LVTip1 or LVRing2) on each ECG/EGM strip. Copies of all ECG/EGM strip should be submitted to BSC quarterly or more frequently, and before study ends.

11.5.11. SmartDelay Test

It is required to perform the SmartDelay test for all subjects to obtain programming recommendations for the AV Delay and Pacing Chamber. It is per the investigator discretion whether to follow the programming recommendations. However, the Pacing Chamber that is selected for a subject at the Enrollment Visit must be used for that subject through the 6 Month Visit (all subjects) or through the 12 Month Visits (for non-responders). For subjects in the Responder Group, there is no requirement to keep the same Pacing Chamber as these subjects are completing the study at the end of the 6 Month Visit.

The LV offset is required to be set at 0 ms prior to running the SmartDelay test. For non-responders, it is recommended that the LV pacing vector is set to a viable vector (from the LV VectorGuide test) with the longest RV-LV delay before running the SmartDelay test.

The SmartDelay test nominal Temporary Paced Lower Rate Limit (LRL) is set at 80 bpm. It is recommended to set the LRL at 10 to 15 bpm above the subject's intrinsic heart rate before conducting the SmartDelay test.

The following values from the SmartDelay test are required to be collected:

- SAV and PAV, both the recommended and final programmed values.
- Pacing Chamber (BiV or LV Only), both the recommended and final programmed values.

- Rationale if the SmartDelay recommendations are not followed.

The following documents from the SmartDelay test are required:

- Set EGM channels to RA, RV, and LV. Obtain ECG/EGM strips at the paper speed of 100 mm/s for approximately 3-5 representative beats during the Atrial Sense test and Atrial Pace test, respectively. The following values are required to be measured from the ECG/EGM strips:
    - Asense-RVsense, Asense-LVsense, Apace-RVsense, and Apace-LVsense intervals for each of the representative beats
    - Calculate the mean value for each of the 4 intervals from these representative beats

  Record the Subject ID and visit information (Enrollment, 6 Month, or 12 Month) on each ECG/EGM strip. Copies of all ECG/EGM strip should be submitted to BSC quarterly or more frequently, and before study ends. The data collected in this test will be used for future product feature enhancement or development, and are not associated with the primary and ancillary objectives. A deviation is not required if the ECG/EGM strips are not sent to BSC.
- Print a copy of the Settings Changes Report from the PRM immediately after running the SmartDelay test and before any other setting changes are made and programmed. This report will display the recommended changes to the SAV, PAV, and Pacing Chamber at pending status.

If the SmartDelay test fails to complete, re-perform the test to obtain the recommended value. If the SmartDelay test was complete but not successful, the recommended value will be the nominal value used by SmartDelay. The SmartDelay test should be limited to two attempts in total.

11.5.12. SmartVector Operation (Non-Responders with LV MSP on)

For subjects who will receive the LV MSP therapy, it is required to use SmartVector to obtain recommendations for LVa and LVb pacing vectors after performing the LV VectorGuide tests. It is recommended to use the pacing vectors recommended by the SmartVector test; however, final selection of the 2 pacing vectors is per investigator discretion.

The following values are required to be collected for subjects who have the LV MSP turned on:

- The pacing configuration of LVa and LVb, both the recommended and final programmed vectors.
- Rationale if the SmartVector recommendations are not followed.

The following document is required for subjects who have the LV MSP on:

- Print a copy of the Settings Changes Report from the PRM before setting changes are made and programmed to show the recommended changes to the LVa and LVb vectors.

11.5.13. SmartOffset Operation (Non-Responders with LV MSP on)

For subjects who will receive the LV MSP therapy, it is required to use SmartOffset to obtain recommendations for the offset value between LVa, LVb, and RV. It is recommended to use the offset provided by the SmartVector operation; however, the final programmed offset is per investigator's discretion.

The following values are required to be collected for Non-Responders with the LV MSP turned on:

- Offset from LVa to LVb to RV, both recommended and final programmed.
- Offset from LVa to LVb if LV only pacing is programmed, both recommended and final programmed.
- Rationale if the SmartOffset recommendations are not followed.

The following document is required to be collected for Non-Responders with the LV MSP turned on:

- Print a copy of the Settings Changes Report from the PRM before setting changes are made and programmed to show the recommended changes to the offset.

11.5.14. LV MSP Settings Programming

Complete the programming of the LV MSP settings for subjects in the Non-Responder Group who have the LV MSP on. It is required that the LV MSP feature be turned on from the 6 Month Visit to the 12 Month Visit. The investigator may consider turning off the LV MSP feature if a subject experiences worsening symptoms. The subject may continue to receive conventional CRT. A rationale and study deviation are required if the LV MSP feature is turned off.

11.5.15. Battery Consumption

The following values are required to be collected:

- Time to explant
- Charge Remaining

11.5.16. Final device settings and status

Print a copy of the Device Settings Report from the PRM for all subjects at the 6 Month Visit and clear the device counters as the final step. For non-responder subjects with at least 2 viable LV pacing vectors, it is required to turn on the LV MSP feature. The pacing chamber (BiV or LV only) is required to be the same as determined at the Enrollment Visit. All other programming settings are per investigator discretion.

11.5.17. Adverse Event Assessment

Study required adverse event data will be collected and assessed for each subject. Hospitalization records are required to be sent to BSC. See **Section 20** for Adverse Event collection and reporting requirements.

11.5.18. HeartLogic Alert

The HeartLogic Alert feature is newly available in the Resonate family of devices. If the HeartLogic Alert feature is turned on, then the HeartLogic Alert(s) that resulted in a change in the subject's medical treatment will be collected.

11.5.19. "Save All" Device Data

Device data is required to be downloaded on a USB disk using "Save All" method if the subject is not enrolled in the LATITUDE Remote Monitoring System. Downloading the data requires ending the PRM session with the device. Hence, it is recommended to complete all other study activities that require PRM-device communication prior to this step. For subjects enrolled in the LATITUDE Remote Monitoring System, device data will be transmitted to BSC automatically on a regular basis and do not require manual download.

The original USB disk will be retained at the site and a copy of the disk should be submitted to BSC quarterly or more frequently. Label the Subject ID and visit information (6 Month or 12 Month) on both USB disks. The data collected in this section will be used for future product feature enhancement or development, and are not associated with the primary and ancillary objectives. A deviation is not required if the "Save All" USB disk is not performed or submitted to BSC.

A summary of the source documentation required at the 6 Month Visit is described in **Table 11.5-2**.

Table 11.5-2: Source Documentation Requirement at the 6 Month Visit

Source Documentation Requirement	Disposition
NYHA class assessment	Retain at study site
Patient Global Assessment	
Physician Global Assessment	
Adverse event assessment	
Device Settings Report, Settings Changes Report, Quick Notes Report, LV VectorGuide Report	
Hospitalization record	
Echo measurement, if performed per standard of care	
Manually recorded Charge Remaining	

Source Documentation Requirement	Disposition
ECG/EGM Strips from the SmartDelay test	Retain at study site Submit 1 copy to BSC
ECG/EGM Strips from the RVp-LVs interval test	
"Save All" device data on USB disk, if applicable	

11.6. *12 Month Visit*

The 12 Month Visit must be performed in office at 183 -0 day/+30 days post-6 Month Visit for subjects who were classified in the Non-Responder Group at the 6 Month Visit. A list of the data to be collected at the 12 Month Visit is provided below, with further details included in the sections below.

- NYHA class assessment
- Patient Global Assessment
- Physician Global Assessment
- HF Event
- Response status determination
- Echo measurement
- Current device setting and status
- Lead measurements
- SmartDelay test and value
- Asense to Vsense and Apace to Vsense intervals
- LV VectorGuide test and value
- RVp-LVs interval test
- SmartVector and SmartOffset value
- Battery consumption
- Final device settings and status
- Adverse event assessment
- HeartLogic Alert
- "Save All" device data

11.6.1. Definition and Components of the Clinical Composite Score

The 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) event
- Patient Global Assessment (PGA)
- NYHA class

11.6.1.1. HF Event Definition

For the purpose of the CCS calculation, HF event is defined as an adverse 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.

11.6.1.2. PGA Classification

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

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

Per CCS definition, a little better and a little worse are considered as placebo effect and are treated as no change.

The investigator will use the subject's response to the PGA and classify response of "a little better", "no change", or "a little worse" to the category of "no change". Subsequently, the investigator will use "very much better", "much better", "no change", "much worse", and "very much worse" to determine the status of PGA changes.

11.6.1.3. NYHA Class Assessment

See Section 11.4.4 for a detailed description of performing NYHA Class assessment.

11.6.1.4. CCS Status Classification

Subjects will be classified as improved, unchanged, or worsened by comparing their clinical response in the current visit to their last visit. At the 12 Month Visit, subjects' status will be compared to their status at the 6 Month Visit. 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 event comparing to their status in the 6 Month 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 a HF event or
    - reported worsening of at least one NYHA functional class or

- reported worsening of the PGA comparing to their status in the 6 Month Visit. See **Table 11.5-1** on selecting worsened PGA status.

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

11.6.2. NYHA Class

NYHA Class assessment shall be performed by a site staff who is blinded to the study design, subject's clinical status in the study, and the programmed device settings. The subject's current NYHA Class must be determined based on **Table 11.4-1**.

11.6.3. Patient Global Assessment

The current PGA must be filled out by the subject, as specified in the assessment tool in **Table 11.5-1**.

11.6.4. 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**.

11.6.5. Response Status Determination

Based on the subject's vital status, NYHA class, PGA, and occurrence of HF event, the investigator/delegated site staff will classify each subject in the Non-Responder Group to be either a responder or a non-responder per the following criteria:

- Responder: subjects with an Improved CCS score
- Non-Responder: subjects with a Worsened or unchanged CCS score

The PhGA will not be used in classifying the subject response status. All subjects in the Non-Responder Group will complete the study at the end of their 12 Month Visit.

All reported hospitalization and events that meet the definition of HF event will be adjudicated by the Clinical Events Committee (CEC) for relatedness to the heart failure.

11.6.6. Echocardiography Measurement

If an echocardiography was performed by the standard of care since last visit, collect the subject's most recently obtained echo values and the date of measurement.

- LVEF
- LVESV
- LVEDV
- Aortic VTI

- Mitral Valve Regurgitation

11.6.7. Current Device Settings and Status

Print a copy of the Quick Notes Report from the PRM 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 settings, percent of pacing (%RA paced, % RV paced, %LVa paced, and %LVb paced), and percent of AT/AF (%AT/AF) are required to be collected.

The investigator may have turned off the LV MSP feature if a subject experienced worsening symptoms prior to the 12 Month Visit. A rationale and study deviation are required if the LV MSP feature is turned off prior to the 12 Month Visit.

11.6.8. Lead Measurements

The following lead measurements are required to be collected for the RA lead, RV lead, and LV lead:

- Intrinsic amplitude (mV)
- Pacing capture threshold (PCT in V; the recommended pulse width is 0.4 ms)
- Pacing lead impedance (Ω)
- Shocking lead impedance (Ω, RV lead)

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

- Print a copy of the Quick Notes Report from the PRM.

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

It is recommended that the PCT measurements be collected in the following fashion:

- At least 3 cardiac cycles at a given voltage level are obtained before stepping down to the next voltage level.
- A count of two non-capture beats at a given voltage level is reached before declaring a loss of capture (LOC) for any of these tests.

It is recommended that the threshold 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 CRF.

11.6.9. SmartDelay Test

It is required to perform the SmartDelay test for all subjects to obtain programming recommendations for the AV Delay and Pacing Chamber. It is per the investigator discretion whether to follow the programming recommendations. The pacing chamber is selected for the subject at the Enrollment Visit. There is no requirement to keep the same pacing chamber

at the end of the 12 Month Visit as all subjects in the Non-Responder Group will complete the study at their 12 Month Visit.

The LV offset is required to be set at 0 ms prior to running the SmartDelay test.

The SmartDelay test nominal Temporary Paced Lower Rate Limit (LRL) is set at 80 bpm. It is recommended to set the LRL at 10 to 15 bpm above the subject's intrinsic heart rate before conducting the SmartDelay test.

The following values from the SmartDelay test are required to be collected:

- SAV and PAV, both the recommended and final programmed values.
- Pacing Chamber (BiV or LV Only), both the recommended and final programmed values.
- Rationale if the SmartDelay recommendations are not followed

The following documents from the SmartDelay test are required:

- Set EGM channels to RA, RV, and LV. Obtain ECG/EGM strips at the paper speed of 100 mm/s for approximately 3-5 representative beats during the Atrial Sense test and Atrial Pace test, respectively. The following values are required to be measured from the ECG/EGM strips:
    - Asense-RVsense, Asense-LVsense, Apace-RVsense, and Apace-LVsense intervals for each of the representative beats
    - Calculate the mean value for each of the 4 intervals from these representative beats

  Record the Subject ID and visit information (Enrollment, 6 Month, or 12 Month) on each ECG/EGM strip. Copies of all ECG/EGM strip should be submitted to BSC quarterly or more frequently, and before study ends. The data collected in this test will be used for future product feature enhancement or development, and are not associated with the primary and ancillary objectives. A deviation is not required if the ECG/EGM strips are not sent to BSC.
- Print a copy of the Settings Changes Report from the PRM immediately after running the SmartDelay test and before any other setting changes are made and programmed. This report will display the recommended changes to the SAV, PAV, and Pacing Chamber at pending status.

If the SmartDelay test fails to complete, re-perform the test to obtain the recommended value. If the SmartDelay test was complete but not successful, the recommended value will be the nominal value used by SmartDelay. The SmartDelay test should be limited to two attempts in total.

11.6.10. LV VectorGuide Test

Non-Responder Group with No LV MSP

For Non-Responder Group subjects who did not receive the LV MSP therapy, it is required that the RV-LV interval value be measured from all 4 electrodes as cathode (LVTip1,

LVRing2, LVRing3, and LVRing4) by starting the LV VectorGuide test; however, it is not required to complete all steps of the LV VectorGuide test once the RV-LV intervals are collected. If the LV VectorGuide test is completed, also provide the number of viable pacing vectors.

Subjects must have RV and LV sensed beats for the test to be successful. If the subject does not tolerate a low intrinsic heart rate, stop the test and provide the rationale for not completing the required test (e.g. subject needs RV pacing support).

The following values are required to be collected in the Non-Responder Group:

- Select the unipolar vectors and run the RV-LV Delay test for all 4 unipolar vectors to obtain RV-LV delay values.

The following values are required to be collected only if the LV VectorGuide test is completed:

- Number of viable pacing vectors (See definition in **Section 8.2**)

The following document is required in the Non-Responder Group:

- Print a copy of the LV VectorGuide Report from the PRM.

Non-Responder Group with LV MSP on

For subjects with the LV MSP turned on, it is required to use the LV VectorGuide test to assess viable LV pacing vectors from all 17 pacing vectors.

For all 17 pacing vectors, the following values are required to be collected for subjects in the Non-Responder Group:

- RV-LV delay
- LV pacing impedance
- PNS test results
- LV Quick Capture threshold test
- Number of viable pacing vectors (See definition in **Section 8.2**)

The following document is required for subjects with the LV MSP on:

- Print a copy of the LV VectorGuide Report from the PRM.

11.6.11. RVp-LVs Interval Test

The data collected in this section will be used for future product feature enhancement or development, and are not associated with the primary and ancillary objectives. A deviation is not required if the test is not performed or the ECG/EGM strips are not sent to BSC.

Set the EGM channels to RA, RV and LV, pacing mode to VVI, LRL to 10 to 15 beats above the subject's intrinsic rate and ventricular pacing chamber to RV Only. Obtain the ECG/EGM strips at the paper speed of 100 mm/s for approximately 3-5 representative beats in two LV sense vector configurations: LVTip1 to Can and LVRing2 to Can, respectively. Record the Subject ID, visit information (Enrollment, 6 Month, or 12 Month), and the

cathode of the LV sensing configuration (LVTip1 or LVRing2) on each ECG/EGM strip. Copies of all ECG/EGM strip should be submitted to BSC quarterly or more frequently, and before study ends.

11.6.12. SmartVector Operation

For subjects who receive the LV MSP therapy, it is required to use SmartVector to obtain recommendations for the LVa and the LVb pacing vectors after performing the LV VectorGuide tests. It is recommended to use the pacing vectors recommended by SmartVector test; however, final selection of the 2 pacing vectors is per investigator discretion.

The following values are required to be collected for subjects who have the LV MSP turned on:

- The pacing configuration of LVa and LVb, both recommended and final programmed vectors.
- Rationale if the SmartVector recommendations are not followed

The following document is required to be collected for subjects who have the LV MSP turned on:

- Print a copy of the Settings Changes Report from the PRM before setting changes are made and programmed to show the recommended changes to the LVa and LVb vector.

11.6.13. SmartOffset Operation

For subjects who receive the LV MSP therapy, it is required to use SmartOffset to obtain recommendations for the offset value between LVa, LVb, and RV. It is recommended to use the offset recommended by the SmartVector operation; however, the final programmed offset is per investigator discretion.

The following values are required to be collected for subjects who have the LV MSP turned on:

- Offset from LVa to LVb to RV, both recommended and final programmed.
- Offset from LVa to LVb if LV only pacing is programmed, both recommended and final programmed.
- Rationale if the SmartOffset recommendations are not followed

The following document is required to be collected for subjects who have the LV MSP turned on:

- Print a copy of the Settings Changes Report from the PRM before setting changes are made and programmed to show the recommended changes to the offset.

11.6.14. LV MSP Settings Programming

At the end of the 12 Month Visit, programming the device to the LV MSP feature for all subjects is per investigator discretion.

11.6.15. Battery Consumption

The following values are required to be collected:

- Time to explant
- Charge Remaining

11.6.16. Final device settings and status

Print a copy of the Device Settings Report from the PRM for all subjects at the 12 Month Visit. Final programming at the 12 Month Visit is per investigator discretion.

11.6.17. Adverse Event Assessment

Study required adverse event data will be collected and assessed for each subject. Hospitalization records are required to be sent to BSC. See **Section 20** for Adverse Event collection and reporting requirements.

11.6.18. HeartLogic Alert

The HeartLogic Alert feature is newly available in the Resonate family of devices. If the HeartLogic Alert feature is turned on, then the HeartLogic Alert(s) that resulted in a change in the subject's medical treatment will be collected.

11.6.19. "Save All" Device Data

Device data is required to be downloaded on a USB disk using "Save All" method if the subject is not enrolled in the LATITUDE Remote Monitoring System. Downloading the data requires ending the PRM session with the device. Hence, it is recommended to complete all other study activities that require PRM-device communication prior to this step. For subjects enrolled in the LATITUDE Remote Monitoring System, device data will be transmitted to BSC automatically on a regular basis and do not require manual download.

The original USB disk will be retained at the site and a copy of the disk should be submitted to BSC quarterly or more frequently. Label the Subject ID and visit information (6 Month or 12 Month) on both USB disks. The data collected in this section will be used for future product feature enhancement or development, and are not associated with the primary and ancillary objectives. A deviation is not required if the "Save All" USB disk is not performed or submitted to BSC.

A summary of the source documentation required at the 12 Month Visit is described in **Table 11.6-1.**

Table 11.6-1: Source Documentation Requirement at the 12 Month Visit

Source Documentation Requirement	Disposition
NYHA class assessment	Retain at study site
Patient Global Assessment	
Physician Global Assessment	
Adverse event assessment	
Device Settings Report, Settings Changes Report, Quick Notes Report, LV VectorGuide Report	
Hospitalization record	
Echo measurement, if performed per standard of care	
Manually recorded Charge Remaining	
ECG/EGM Strips from the SmartDelay test	Retain at study site Submit 1 copy to BSC
ECG/EGM Strips from the RVp-LVs interval test	
"Save All" device data USB disk, if applicable	

11.7. *Additional Visit*

An Additional Visit is required to be completed when the device is interrogated and any of the following programming settings have been permanently changed:

- Any time the device counter is reset
    - Date the counter is reset
    - Percent of LV pacing prior to resetting the counter in subjects receiving either conventional CRT or LV MSP pacing.
- AV delay
- Pacing chamber (BiV pacing or LV only pacing)
- LV Offsets
- The LV pacing configuration selected at the Enrollment Visit
- The 2 pacing vectors selected for the LV MSP at the 6 Month Visit
- SmartOffset
- Pacing mode (e.g. DDD, VVI)
- LRL

- LV MSP programming change (On or Off)

A rationale for the setting changes is required. A deviation is required if the changes in programming settings are not per the protocol requirement.

The following documents are required:

- Print a copy of the Settings Changes Report from the PRM.
- Print a copy of the Device Settings Report from the PRM.

Lead measurement is optional at this visit.

11.7.1. Adverse Event Assessment

Study required adverse event data will be collected and assessed for each subject. Hospitalization records are required to be sent to BSC. See **Section 20** for Adverse Event collection and reporting requirements.

A summary of the source documentation required at the Additional Visit is described in **Table 11.7-1.**

Table 11.7-1: Source Documentation Requirement at Additional Visit

Source Documentation Requirement	Disposition
Settings Changes Report, Device Settings Report	Retain at study site
Adverse event assessment	

11.8. *Study Completion*

All subjects will be followed until the completion of their required last visit, death, or withdrawal if it occurs prior to the last required visit. For subjects in the Responder Group, their last visit is the 6 Month Visit; for subjects in the Non-Responder Group, their last visit is the 12 Month Visit, regardless if the LV MSP feature was turned on or not. Upon completion of participation in the study, subjects will be followed per normal standard of care.

12. Statistical Considerations

12.1. *SMART MSP Study Endpoints*

12.1.1. Primary Safety Endpoint: LV MSP feature-related complication-free rate

The primary safety endpoint will be assessed for all non-responder subjects with the LV MSP on for any duration between the 6 Month Visit and the 12 Month Visit.

Safety will be confirmed by evaluating the LV MSP feature-related complication-free rate (CFR) between the 6 Month Visit and 12 Month Visit. For the purpose of this endpoint, an LV MSP feature-related complication will be defined as those complications that are

determined as "yes, related" or "possibly related" to the LV MSP feature and will count against this endpoint. These may include but are not limited to:

- Ventricular Tachyarrhythmia/Ventricular Fibrillation (VT/VF)
- Loss of Capture (LOC)
- Phrenic Nerve Stimulation (PNS)
- Worsening HF

12.1.1.1. Hypotheses

The following hypotheses will be used to evaluate the Primary Safety Endpoint:

H_0: LV MSP feature-related complication-free rate between 6 Month Visit and 12 Month Visit ≤ 90%

H_A: LV MSP feature-related complication-free rate between 6 Month Visit and 12 Month Visit > 90%.

The performance goal is set at 90%, which is consistent with other product features undergoing FDA evaluation[6].

12.1.1.2. Sample Size

The overall study sample size of 586 subjects is driven by the primary effectiveness endpoint. For further details on overall sample size and attrition see **Section 12.3**. The sample size of 61 subjects is required to evaluate the Primary Safety Endpoint. Since a power calculation cannot be directly calculated for a one group Kaplan-Meier analysis, an exact test was used. A power calculation using a sample size of 61 subjects as the non-responders with the LV MSP on was calculated based on a one-sided exact test for a single binomial proportion, using SAS Version 9.4 with the following assumptions:

- Performance goal = 90%
- Expected LV MSP feature-related CFR rate between 6 and 12 Month Visit = 98%
- Significance level = 5%
- Power = 80%

12.1.1.3. Statistical Methods

Data from subjects who are deemed as a non-responder at the 6 Month Visit with LV MSP turned on for any duration of time from 6 Month Visit onward will be eligible for inclusion in the endpoint analysis. The LV MSP feature-related CFR between the 6 Month Visit and the 12 Month Visit will be calculated using Kaplan-Meier methodology. The evaluation period for each subject will begin at the time LV MSP was turned on (at or after the 6 Month Visit) and will continue through 180 days post-LV MSP being turned on.

[6] BSC's Enable MRI Clinical Study (IDE # G150181); performance goal for MR Scan related complication-free rate.

The 95% one-sided lower pointwise confidence limit of the LV MSP feature-related complication-free rate will be calculated via log-log methodology and compared to the performance goal of 90%. If the lower confidence limit exceeds 90%, the null hypothesis will be rejected.

Each subject's exact follow-up time in the period between the 6 Month Visit when the LV MSP is turned on through 180 days after the LV MSP is turned on will be included in the analysis due to the rate being calculated via Kaplan-Meier methodology. The subjects that reach the 6 Month Visit and have the LV MSP turned on but fail to reach 180 days of follow-up after the LV MSP was turned on (without experiencing an endpoint event prior to their end of follow-up in the period) will be censored at the time of their end of follow-up in the period. Because non-informative censoring cannot be assumed for these subjects, a tipping point analysis will be performed to determine the potential effects these censored subjects could have on the results if full information on each subject was present. The tipping point analysis will assign each subject that was censored between the 6 and 12 Month Visit as either having or not having an LV MSP feature-related complication. The tipping point will be determined by the point at which the endpoint results turn from passing (null hypothesis) to failing (null hypothesis rejected). An exact binomial test will be performed for the tipping point analysis.

In addition, a sensitivity analysis on the impact of "Unknown" related to the LV MSP feature will be performed. Subjects with a complication determined as "yes, related", "possibly related" or "Unknown" related to the LV MSP feature will be included as a LV MSP feature-related complication.

12.1.2. Primary Effectiveness Endpoints: Proportion of LV MSP Group with an Improved CCS

The effectiveness endpoint for SMART MSP PAS is the proportion of the LV MSP Group with an Improved CCS. Details regarding the CCS are provided in **Section 11.5.1**. For this endpoint, those subjects in the LV MSP Group that become responders will be defined as having an Improved CCS as discussed in **Section 11.5.1**. This endpoint will be evaluated at the 12 Month Visit to determine if the LV MSP Group subjects improved from their 6 Month Visit.

12.1.2.1. Hypotheses

The following hypotheses will be used to evaluate the Primary Effectiveness Endpoint:

H_0: Proportion of LV MSP Group subjects with Improved CCS from 6 Month Visit through 12 Month Visit $\leq 5\%$

H_A: Proportion of LV MSP Group subjects with Improved CCS from 6 Month Visit through 12 Month Visit $> 5\%$

12.1.2.2. Sample Size

The sample size of 110 subjects with paired CCS calculation from the 6 Month Visit through 12 Month Visit is required to evaluate the Primary Effectiveness Endpoint. For further details on overall sample size and attrition see **Figure 12.3-1**. The overall study sample size is

driven by the primary effectiveness endpoint. This sample size was calculated based on a one-sided exact test for a single binomial proportion, using SAS Version 9.4 with the following assumptions:

- Performance goal = 5%
- Expected performance = 15%
- One-sided significance level = 5%
- Power = 95%

The performance goal was established based on the evaluation of clinical response data previously reported for similar features under investigation, and based on clinical input from the study's National Principal Investigator and the Steering Committee that an improvement of at least 5% would be clinically meaningful given the subject's non-responder status as determined after 6 months of conventional CRT with single-site LV pacing.

12.1.2.3. Statistical Methods

The SMART MSP PAS study's Primary Effectiveness Endpoint will be analyzed when the last 12 Month Visit is completed by the subjects in the LV MSP Group. Subjects eligible for this analysis include all non-responder subjects who meet the definition of the LV MSP Group. The LV MSP Group subjects' CCS data (NYHA class, HF event, all-cause mortality, and patient global assessment) will be collected at the 6 and 12 Month Visit and contribute to the endpoint analysis. The LV MSP Group subjects with the LV MSP on for less than 6 month duration will be included in the analysis.

The 95% one-sided lower pointwise confidence limit of the response rate will be calculated using the one-sided exact methodology for a single binomial proportion and compared to the performance goal of 5%. If the lower confidence limit exceeds the performance goal, then the null hypothesis will be rejected.

Subjects that do not have complete paired CCS data regarding NYHA class, HF event, all-cause mortality, and patient global assessment collected at the 6 and 12 month follow-up visit will be considered to have missing data. A tipping point analysis will be used to determine the potential effects subjects with missing data could have had on the results. The tipping point analysis will consider a range of possible responder rates in the subjects with missing data. The tipping point will be determined by the point at which the endpoint results turn from passing (null hypothesis rejected) to failing (null hypothesis not rejected).

12.2. *Ancillary Assessments*

The ancillary assessments are not formal endpoints and are not statistically powered.

12.2.1. Assessment of Echocardiographic Measurements and CCS Response Status Outcomes in Non-responders

Subjects with echo measurements (such as LVEF and LVESV) at Enrollment, 6, and 12 Month Visit will be reported. In addition, data available (response outcome of CCS and echo

measurements) for these subjects will be reported with summary descriptive statistics and listings. Additional analyses may be explored.

12.2.2. Assessment of Effectiveness of LV MSP in the SMART MSP PAS and SMART Registry

A supplemental analysis of the primary effectiveness endpoint and subgroups will be performed and include a subset of data collected from the SMART Registry, a post market study assessing the LV MSP feature in a similar patient population to fulfill the requirement of an European regulatory body.

12.2.3. Assessment of Worsened LV MSP Group

The percentage of subjects in the LV MSP Group that worsened from the 6 Month Visit through 12 Month Visit will be reported. For this assessment, the CCS will define worsened as "Worsened" only and will not include subjects with a CCS of "No change."

12.2.4. Assessment of RV-LV Electrical Delay and Response

Available data on RV-LV electrical delay will be collected to determine whether an electrical delay is a predictor of responder status in the overall population.

12.2.5. Assessment of Battery Consumption

In order to understand the impact of MSP on battery longevity, the following time durations will be summarized using descriptive statistics:

- BiV related battery consumption from enrollment to 6 months
- LV MSP related battery consumption from 6 to 12 months
- The average battery life in years for subjects with the LV MSP On at 12 Month Visit

12.2.6. Assessment of SmartDelay and SmartVector Usage

In order to understand the usage of features such as SmartVector and SmartDelay, the following will be summarized using descriptive statistics:

- Percent success using the SmartVector
- Percent use of SmartDelay
- Percent of subjects with SmartDelay value (AV delay and paced chamber) changed between Enrollment Visit and 6 Month Visit and 6 to 12 Month Visit

12.2.7. Assessment of Percentage of Pacing

The following data on percentage of pacing will be summarized using descriptive statistics:

- Percent of BiV pacing at 6 Month Visit
- Percent of LV only pacing (if programmed) at 6 Month Visit

- Percent of LVa and LVb for LV MSP pacing at 12 Month Visit

12.2.8. Assessment of Additional Data Collection

Additional data collection and descriptive statistics will be collected and reported but is not limited to the following data:

- Overall response rate at 6 Month Visit
- Percent of the LV MSP Group subjects with furthest apart two viable vectors

12.3. *Sample Size Summary and Attrition*

The overall sample size of 586 subjects for the required LV MSP Group is based on the Primary Effectiveness endpoint. This sample size accounts for the overall study attrition. Below are the sources of attrition at different stages of this study:

- LV pacing less than 93%[7]: 10%
- Subject exiting the study prior to the 6 Month Visit[8]: 10%
- Responder rate [9]: 70%
- Percent of subjects who cannot achieve 2 viable pacing vectors[10]: 15%
- Subject exiting the study between the 6 and 12 Month Visit[11]: 8%

Figure 12.3-1 indicates the sample size at different time points throughout the study. The overall attrition for this study is 81%.

[7] Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? J Am Coll Cardiol. 2009 Jan 27;53(4):355-60.

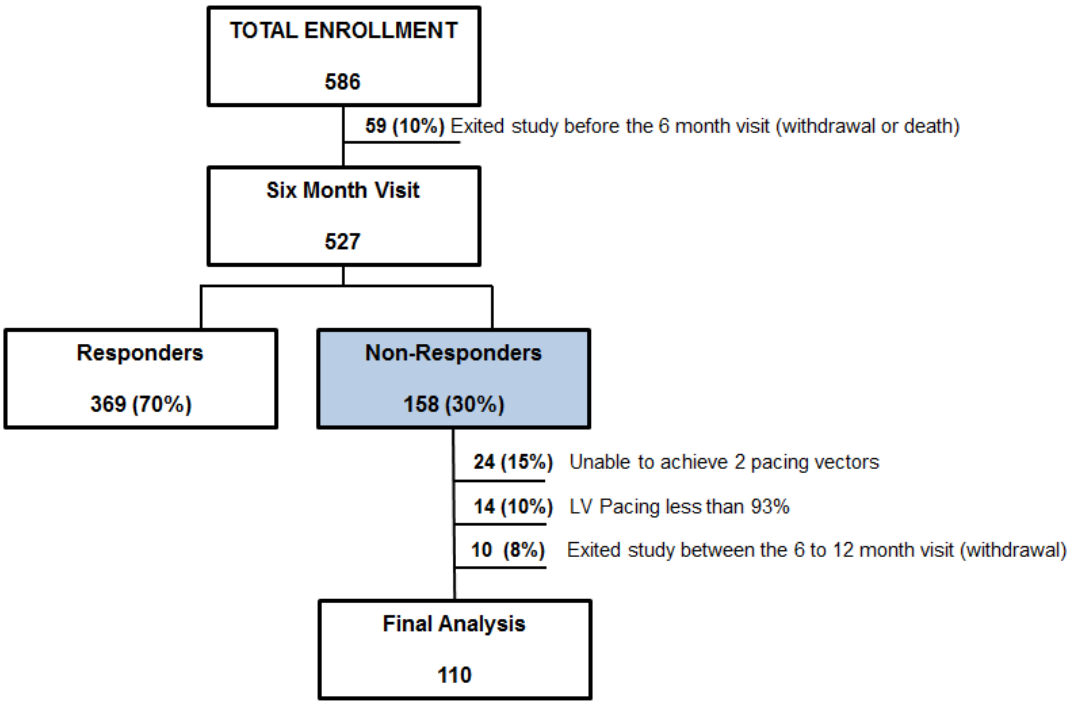
[8] Based on an estimate from BSC SMART AV Clinical Study and NAVIGATE X4 Clinical Study.

[9] Based on an evaluation of a set of previous clinical studies reporting clinical response rate to conventional CRT therapy and feedback from the physicians of the study's Steering Committee.

[10] Based on an estimate from BSC NAVIGATE X4 Clinical Study and Rally X4 Clinical Study.

[11] Based on an estimate from BSC SMART AV Clinical Study and NAVIGATE X4 Clinical Study.

Figure 12.3-1: Subject Flowchart with Estimated Attrition



12.4. *General Statistical Methods*

12.4.1. Study Success Criteria

The study will be considered successful if all primary endpoints (safety and effectiveness) are passed.

12.4.2. Analysis Sets

The analysis sets that will be used for each endpoint is shown in **Table 12.4-1**.

Table 12.4-1: Analysis Sets for Each Primary Endpoint

Endpoint	Analysis Sets
SMART MSP PAS Primary Safety Endpoint	All subjects who are non-responders with the LV MSP on for any duration from the 6 to the 12 month visit
SMART MSP PAS Primary Effectiveness Endpoint	All subjects who meet the LV MSP group criteria

12.4.3. Control of Systematic Error/Bias

Selection of patients will be made from the Investigator's usual patient population. All patients meeting the eligibility criteria and having signed the ICF will be enrolled in the study. To control for inter-observer variability among sites, an independent Clinical Events Committee (CEC) will adjudicate the reported HF event to be used as the component of the CCS to assess the Primary Effectiveness Endpoint.

12.4.4. Control of Type I Error

Each primary endpoint can be tested at the significance level of 5% while still maintaining the overall type I error level at no greater than 5%. This follows the methodology of the Intersection-Union Test (IUT).

12.4.5. Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to enroll more than 20% of the study subjects.

12.5. *Data Analyses*

In addition to the study endpoint analysis discussed in **Section 12.1** and **Section 12.2**, the following data analyses are planned for the SMART MSP Study.

12.5.1. Interim Analyses

No formal interim analyses are planned for the purpose of stopping the study early for declaring effectiveness or for futility. Analysis of each endpoint will be performed when all applicable data for that endpoint has been collected.

12.5.2. Pooling Analysis

Assessment of Pooling Across Investigational Centers

The poolability of data by center will be tested. This analysis will be performed to determine whether there are differences from center-to-center.

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

Investigational 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.

12.5.3. Subgroup Analyses

Analyses will be performed for the primary effectiveness endpoint to determine whether significant differences exist in endpoint results between subgroups of the LV MSP Group. The list of baseline covariates (with applicable subgroups in parentheses) includes, but is not necessarily limited to:

Categorical variables:

- Ischemic Etiology (Ischemic vs Non-Ischemic)
- Bundle Branch Block morphology (LBBB vs Non-LBBB)
- NYHA class (I/II vs III/IV)

- LV MSP Pacing chamber (BiV MSP vs. LV ONLY MSP)[12]
- Presence of atrial fibrillation (Yes or No)
- Diabetes (Yes vs. No)
- Sex (Male vs. Female)
- Spiral LV lead length (Short vs. Long)
- LV lead shape (Spiral vs. Straight)

Continuous Variables:

- RV-LV electrical delay
- Electrode spacing between the two LV pacing vectors[13]
- QRS width

For categorical variables, the subgroup variable will be added to a logistic univariate regression model. In addition, continuous variables will be determined as binary or continuous by linearity characteristics and/or clinical determination. If deemed as continuous, the subgroup variable will be added to a logistic univariate regression model.

In addition to subgroup analyses, descriptive statistics of patient demographic and baseline characteristics will be presented for each subgroup listed in this section. Descriptive statistics will also be presented for the overall study population.

12.5.4. Multivariable Analyses

As stated in the subgroup analysis in **Section 12.5.3**, the number of events in the LV MSP Group is limited. Therefore, multivariate analyses will be deemed exploratory. The various baseline covariates and their relationship to effectiveness endpoint are outlined in **Section 12.5.3**. For the effectiveness endpoint and subgroup analyses, all baseline characteristics found to be significantly associated with the response status will be included as covariates, in a multivariate regression model. The impact of each baseline characteristic's subgroups will be presented along with the multivariate model results.

12.5.5. 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.

[12] LV MSP pacing chamber is only collected at the 6 Month Visit when the LV MSP feature is turned on.

[13] Electrode spacing between the two LV pacing vectors is only collected at the 6 Month Visit when the LV MSP feature is turned on.

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 Investigator or his/her designee or the Investigational site will maintain at the investigative site all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the study has been formally closed. These documents will be retained in compliance with other local regulations. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator 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.

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/FDA) 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 per local reporting guidelines of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using the EDC eCRF system. Sites may also be required to report deviations to the IRB, per local guidelines and government regulations.

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

16. Device/Equipment Accountability

Devices used within the SMART MSP Study are commercially available and are not investigational.

17. Compliance

17.1. *Statement of Compliance*

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

17.2. *Investigator Responsibilities*

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

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

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of

interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency per **Section 20.**
- 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 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, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor or sponsor representatives 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 when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with

identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).

- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

17.2.1. 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. No study related tasks can be performed prior to completing the appropriate study training. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their IRB 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 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 approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB requirements. Copies of the Investigator's reports and the IRB continuance of approval must be provided to the sponsor.

17.4. *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.

17.4.1. 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.
- 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 technical source form.
- Print out programming reports directly from the 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.

18. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor from BSC or BSC designees 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 and/or their institution guarantee 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.

19. Potential Risks and Benefits

19.1. *Anticipated Adverse Events*

Subjects participating in this study are subject to the same risks shared by all patients undergoing implantation of a CRT-D system. Based on the literature and on pulse generator and/or lead implant experience, an alphabetical list of the possible adverse events is provided in the Resonate family of CRT-D physician's technical manual as follows:

- Air embolism
- Allergic reaction
- Bleeding
- Bradycardia
- Cardiac tamponade
- Chronic nerve damage
- Component failure
- Conductor coil fracture
- Death
- Electrolyte imbalance/ dehydration
- Elevated thresholds
- Erosion
- Excessive fibrotic tissue growth

- Extracardiac stimulation (muscle/ nerve stimulation)
- Failure to convert an induced arrhythmia
- Fluid accumulation
- Foreign body rejection phenomena
- Formation of hematomas or seromas
- Heart block
- Inability to defibrillate or pace
- Inappropriate therapy (e.g., shocks, and antitachycardia pacing [ATP] where applicable, pacing)
- Incisional pain
- Incomplete lead connection with pulse generator
- Infection including endocarditis
- Insulating myocardium during defibrillation with internal or external paddles
- Lead dislodgment
- Lead fracture
- Lead insulation breakage or abrasion
- Lead perforation
- Lead tip deformation and / or breakage
- Local tissue reaction
- Loss of capture
- Myocardial infarction (MI)
- Myocardial necrosis
- Myocardial trauma (e.g., tissue damage, valve damage)
- Myopotential sensing
- Oversensing / undersensing
- Pacemaker-mediated tachycardia (PMT)
- Pericardial rub, effusion
- Pneumothorax
- Pulse generator migration
- Shunting current during defibrillation with internal or external paddles
- Syncope
- Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
- Thrombus, thromboemboli
- Valve damage
- Vasovagal response
- Venous occlusion
- Venous trauma (e.g. perforation, dissection, erosion)

- Worsening heart failure

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

Additionally, potential adverse events associated with the implantation of a coronary venous lead system include:

- Allergic reaction to contrast media
- Breakage/failure of implant instruments
- Prolonged exposure to fluoroscopic radiation
- Renal failure from contract media used to visualize coronary veins.

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

There are no additional risks associated with the study devices beyond those already described for BSC commercially approved and market available CRT-D devices with the LV MSP feature.

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

All subjects have previously received a CRT-D device implantation as part of standard of care treatment. The study procedure starts at the Enrollment Visit, which is after device implant, and at the regularly scheduled standard of care follow-up visits.

In the SMART MSP study, a subset of the subjects in the Non-Responder Group (approximately 110 subjects) will receive the LV MSP therapy from the 6 Month Visit to the 12 Month Visit. The LV MSP feature may increase the device battery consumption. It is anticipated that the impact to the battery consumption during the study may average 6 weeks but may be as long as 4.8 months.

Additionally, there may be a temporary increase in the subject's heart rate and loss of AV synchrony due to VVI pacing during the Smart Delay test and RVp-LVs interval test. In rare cases, subjects may experience temporary symptoms of fatigue, chest discomfort, dyspnea, cough, confusion, presyncope, or syncope during these tests. The investigator may stop the test if the subject does not tolerate the testing procedure.

19.4. *Risk Minimization Actions*

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.

19.5. *Anticipated Benefits*

There may be no benefit to the subject. However, subjects participating in clinical studies may have better outcomes than the general population. The subject may benefit from closer device follow up due to the clinical protocol schedule. Subjects may be followed more carefully and their status, as well as their device and lead status, is checked by various study personnel and systems: investigators, data coordinators, monitors and automatic warning systems in the clinical study database set to monitor the data as it is submitted to Boston Scientific.

19.6. *Risk to Benefit Rationale*

The risks involved with subject participation in this study are the same as those for patients not participating in the study. The LV MSP feature will only be turned on in the study for subjects who are determined to be non-responders to conventional CRT therapy as defined in the protocol and may be turned off per physician discretion. Physicians should consider turning the LV MSP feature off if a subject's HF condition worsens. This study is designed to evaluate whether the LV MSP feature can improve clinical response to CRT in subjects who are not responders to conventional CRT.

20. Safety Reporting

20.1. *Reportable Events by Investigational Site to BSC*

The communication requirements for reporting adverse events, device deficiencies, failures, malfunctions, and product nonconformities to BSC are listed in **Table 20.4-1**. Adverse events must always be reported through the eDC system for SMART MSP Study. However, in cases where the eDC is not available, report the adverse event to BSC using SMARTMSP.Safety@bsci.com. It is the responsibility of the investigator to assess and report all reportable events in the following categories:

- All Serious Adverse Events
- All Heart Failure and Cardiac related Adverse Events requiring IV or invasive therapy, including new onset of cardiac events, or worsening in severity or frequency of pre-existing condition(s)
- 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 (such events include ATR, PMT, etc.)

  - All arrhythmias which received inappropriate therapy (i.e. inappropriate shock) must be reported
  - Include adverse events related to any part of the implanted CRT-D system
- All Device Deficiencies
- All Adverse Events related to the protocol required testing, excluding PNS during lead testing.
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects

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 event 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.

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

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or testing 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 must be recorded in the eCRF.

Death should not be recorded as an AE, but should only be reflected as an outcome of one (1) specific SAE (see **Section 20.2** for AE definitions).

Refer to **Section 19** for the known risks associated with the study device(s).

20.2. *Definitions and Classification*

Adverse event definitions are provided in **Table 20.2-1** Events to be reported in the clinical study are listed in **Section 20.1**.

Table 20.2-1: Safety Term Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or any

Table 20.2-1: Safety Term Definitions

Term	Definition
Ref: ISO 14155-2011 *Ref: MEDDEV 2.7/3 -2015*	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 14155-2011* *Ref: MEDDEV 2.7/3 -2015*	Adverse event related to the use of an investigational medical device NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 -2015*	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 -2011* *Ref: MEDDEV 2.7/3 -2015*	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.

Table 20.2-1: Safety Term Definitions

Term	Definition
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155 -2011* *Ref: MEDDEV 2.7/3 -2015*	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 -2011* *Ref: MEDDEV 2.7/3 -2015*	An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.
The following categories may be used by BSC for classification of events.	
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*	Not related to the investigational device(s), system component(s), or labeling, but would not have occurred in the absence of the investigational

Table 20.2-1: Safety Term Definitions

Term	Definition
Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions	device(s) and/or system component(s). This includes clinical events related to commercially released devices that are used in conjunction with investigational device(s) or protocol procedures.
Type IV *Ref: FDA Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions*	Related to a change in patient's condition.
Type V *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: IRB=Institutional Review Board

20.3. *Relationship to Study Device(s) and/or Study Testing*

The Investigator must assess the relationship of the AE to the study device or study testing procedure. See criteria in **Table 20.3-1.**

Table 20.3-1: 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

Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

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

20.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 20.4-1.**

Table 20.4-1: Investigator Reporting Requirement

Event Classification	**Communication Method**	**Communication Timeline post-market studies****
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	a) Within 1 business day of first becoming aware of the event. b) Terminating at the end of the study
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	c) Within 10 business days after becoming aware of the event or as per local/regional regulations. Reporting required through end of study
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	d) Within 60 calendar days of reported event
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	e) Within 2 business days of first becoming aware of the event or as per local/regional regulations. Reporting required through the end of the study
	Provide all complete, relevant source documentation (unidentified) for reported event	f) Send complete source documentation within 60 calendar days of becoming aware of the event
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities)	Complete device deficiency CRF with all available new and updated information.	g) 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.	h) In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information. Reporting required through completion of study

20.5. *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 in the eDC system 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.

20.6. *Reporting to Regulatory Authorities / IRBs / 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, and regulatory authorities of UADE and SAE as required by local/regional regulations.

20.7. *Subject Death Reporting*

A subject death during the study should be reported to Boston Scientific as soon as possible and, in any event, within 3 calendar days or per local regulations (per **Section 20.4**) of site notification via eDC system. An Adverse Event eCRF, with a death outcome must be completed, as well as an End of Study form. The site's IRB must be notified of any deaths in accordance with that site's IRB policies and procedures.

Boston Scientific may request additional information regarding subject deaths. These requests may include requests for source documentation, in order for BSC to understand the circumstances surrounding the death. Source documentation may include, but is not limited to: hospital records (H&P, consultations, diagnostics, etc.); last available device interrogation, last available office visit, etc. The following data should be provided:

- Date and time of death
- Immediate cause of death
- Rhythm at the time of death, if known (include any available documentation)
- Whether the death was related to the pulse generator, lead/catheter, clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Device status and/or activity at the time of death
- Whether the patient 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.

In addition, if the patient expired in the hospital:

- A copy of the medical records for that admission (e.g., H & P, consults, test results, operative reports, and/or progress notes from the hospital chart)
- Death certificate (if available)
- Autopsy report (if applicable)

If the patient expired outside of the hospital (e.g., home):

- A copy of the most recent clinic visit (if not already submitted to BSC)
- Death certificate (if available)

Whenever possible, the pulse generator (IPG) should be interrogated. The leads and the related BSC Rhythm Management system components (e.g., IPG) should be removed intact and returned promptly to BSC Rhythm Management for analysis.

20.8. *Source Documents for CEC Adjudication*

All post-enrollment hospitalizations except the hospitalization in which the existing device implant is performed will be adjudicated by the CEC per **Section 22.2**. Source documents required for adjudication include, but are not limited to: admission note, history and physical, consultation notes, medication lists and discharge summary.

21. Informed Consent

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

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, any applicable national regulations, and local IRB 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, 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. 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 approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

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

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

The ICF shall always be signed and personally dated by the subject and by the investigator and/or an authorized designee responsible for conducting the informed consent process. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB), 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. The new version of the ICF must be approved by the IRB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB. The IRB will determine the subject population to be re-consented.

22. Committees

22.1. *Safety Monitoring Process*

To promote early detection of safety issues, BSC Safety Trial Operation group will conduct the initial evaluations of all safety events and provide the evaluations to BSC Medical Safety group. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information. The BSC Medical Safety group includes physicians with expertise in heart failure and CRT device/therapy and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

22.2. *Clinical Events Committee*

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that reviews and adjudicates the following events, as a component used in determining the Primary Effectiveness Endpoint, as reported by study investigators:

- All hospitalizations
- Any event where a study subject is not hospitalized but received one or more IV medications including diuretics, inotropes, vasodilators, other parenteral therapy, or aquapheresis.
- Other events at the discretion of BSC

The CEC will review a safety event dossier, which may include copies of subject source documents provided by the study sites, for all applicable events. Investigative sites are requested to send source documents related to the event to SMARTMSP.Safety@bsci.com.

Committee members will include a minimum of three practitioners with training in Electrophysiology (EP), and/ or Cardiology with the necessary therapeutic and subject matter expertise to adjudicate heart failure event. CEC responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

23. Suspension or Termination

23.1. *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.

23.1.1 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.
- Reaching study futility.

23.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB Approval*

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

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

23.4. *Criteria for Suspending/Terminating a Study Site*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 6 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions. The IRB and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed per patient's standard of care. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

24. 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.

25. Abbreviations and Definitions

25.1. *Abbreviations*

Table 25.1-1: Study Abbreviation

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
Apace	Atrial Pace Marker
Asense	Atrial Sense Marker
AV	AtrioVentricular
BiV	Biventricular
BSC	Boston Scientific Corporation
CCS	Clinical Composite Score (Packer CCS)
CEC	Clinical Events Committee
CFR	Complication-free rate – within the endpoint sections
CFR	Code of Federal Regulations – excluding the endpoint sections
CRF	Case Report Form
CRO	Clinical Research Organization
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy – Defibrillator
CRT-P	Cardiac Resynchronization Therapy- Pacemaker
CS	Coronary Sinus
DD	Device Deficiency
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGM	Electrogram
FCS	Field Clinical Specialist
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare Provider
HF	Heart Failure
ICF	Informed Consent Form

Abbreviation	Term
ICH	International Conference on Harmonization
ICD	Implantable Cardioverter Defibrillator
IPG	Implantable Pulse Generator
IQRMP	Integrated Quality Risk Management Plan
IRB	Institutional Review Board
IV	Intravenous
LBBB	Left Bundle Branch Block
LOC	Loss of Capture
LRL	Lower Rate Limit
LV	Left Ventricle
LVED	Left Ventricular End Diastolic
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
LV MSP	Left Ventricular Multi-Site Pacing
ms	Millisecond
mV	millivolts
NYHA	New York Heart Association
Ω	Ohms
OPT	Optimal Pharmacologic Therapy
PA	Paced Atrium
PAS	Post Approval Study
PAV	Paced AV Delay
PCT	Pacing Capture Threshold
PG	Pulse Generator
PGA	Patient Global Assessment
PhGA	Physician Global Assessment
PI	Principal Investigator
PNS	Phrenic Nerve Stimulation
PRM	Reference to BSC Programmer
QLV	Q-Left Ventricular
RA	Right Atrium/ Atrial
RM	Rhythm Management
RV	Right Ventricle/ Ventricular

Abbreviation	Term
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 Delay
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
Vsense	Ventricular Sense Marker
VT	Ventricular Tachycardia

25.2. *Definitions*

Terms are defined in **Table 25.2-1**.

Table 25.2-1: Definitions

Term	Definition
Clinical Composite Score (CCS)	A method for evaluating heart therapies that unifies four outcomes of primary importance to clinicians: all-cause mortality, HF event, Patient Global Assessment, and New York Heart Association (NYHA) class.
Resonate family of CRT-D devices	As the next generation of BSC's CRT-D devices, Resonate refers to all trademarked devices in this family of pulse generators, including RESONATE HF, RESONATE, VIGILANT, and MOMENTUM.
LV MSP feature related Complication	The LV MSP feature related adverse events will include, but are not limited to the following: • Ventricular Tachyarrhythmia/Ventricular Fibrillation (VT/VF) • Loss of Capture • Phrenic Nerve Stimulation (PNS)

Table 25.2-1: Definitions

Term	Definition
	• Worsening HF
Conventional CRT	CRT with single-site LV pacing
Responder Group	Subjects with Improved CCS score at the 6 Month Visit.
Non-Responder Group	Subjects with Unchanged or Worsened CCS scores at the 6 Month Visit.
LV MSP Group	Subjects who have achieved at least 2 viable LV pacing vectors, have the LV MSP feature enabled, and with the percent of LV MSP pacing threshold of at least 93%
LV MSP Pacing	BiV pacing with the LV MSP On
LV MSP LV Only Pacing	LV only pacing with the LV MSP On
Viable LV Pacing Vector	To determine if an LV pacing vector is considered viable, the following criteria are recommended: • The pacing impedance is not out-of-range per physician's programmed value • No presence of PNS - the pacing capture threshold (PCT) plus 3V of safety margin should be less than PNS threshold • LV PCT at ≤ 4.5V or demonstrated capture at ≤ 4.5V

26. References

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