Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy

SMART CRT

CLINICAL INVESTIGATION PLAN

Reference Number C2067

Sponsored By

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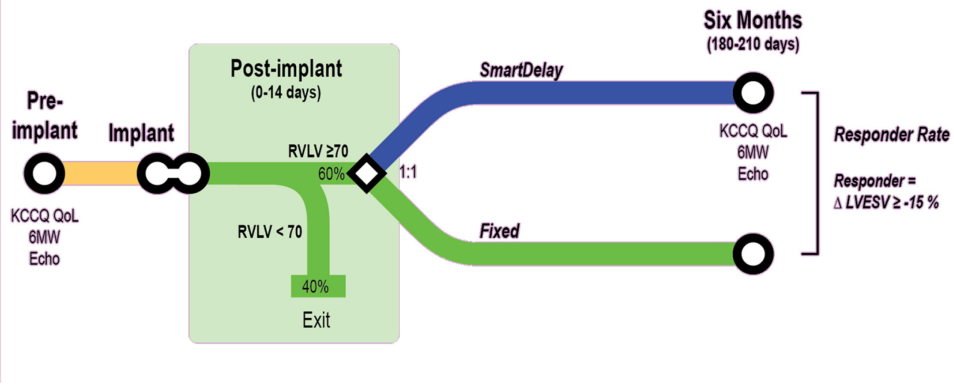
	Release Date	Template number and version	Section	Change	Reason for Change
A	**21 Dec 2016**	90702637 Rev./Ver. AH	N/A	Original Release	N/A
B	**25 Jan 2017**	90702637 Rev./Ver. AH	9.3 Exclusion criteria	Revised exclusion criteria to match the synopsis for pregnancy criterium	Correction: Was updated in the synopsis, but not in the body of the protocol
C	**28 Mar 2017**	90702637 Rev./Ver. AH	Current Version	Current Version was not updated to match Rev B release date	Correction: Updated Current Version to March 28, 2017
			11.4; 11.5.2.2	"Should" changed to "must"	Correction: Criteria is required for the study.
			11.4.2;	Updated: "Echocardiography will *be* used"	Correction: grammatical error
			11.6.2	Corrected format: "directed to the patient to address how well"	Correction: grammatical error
			11.5.1; 11.5.2.1; 11.6.1	Instructions for SmartDelay and VectorGuide printouts removed	Updated programmer software
			11.6	Device testing not required to be completed prior to other assessments.	Correction: Requirement removed.
D	**10 Apr 2017**	90702637 Rev./Ver. AH	N/A	Removal of redlines in version C.	New version required in order to remove redlines existing in previous document. No content change from version C.

2. Protocol Synopsis

Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy SMART CRT	
Study Objective(s)	The primary objective is to show the benefit of SmartDelay™ in patients with a prolonged RV-LV interval.
Planned Indication(s) for Use	All implanted devices will be used within the current labeled indications for use. Cardiac Resynchronization Therapy Defibrillators (CRT-D) are intended to provide cardiac resynchronization therapy and provide anti-tachycardia pacing and defibrillation therapy.
Device Description	All commercially approved Boston Scientific X4 quadripolar CRT-D devices and future generations of BSC X4 CRT-Ds approved by the appropriate regulatory bodies will be included in the trial in combination with a Boston Scientific ACUITY™ X4 quadripolar LV lead. CRT-D devices must be capable of providing SmartDelay recommendations for both biventricular pacing (BiV) and left ventricular (LV) only pacing. A list of approved ACUITY X4 LV leads and CRT-D models is available upon request.
Study Design	SMART CRT is a prospective, double-blind, multicenter, international, randomized controlled trial.
Planned Number of Subjects	[redacted]
Planned Number of Investigational Sites / Countries	The study will be conducted at up to 100 sites globally.
Primary Endpoint	The primary endpoint is comparing cardiac resynchronization therapy (CRT) response rates between AV Delay programming schemes defined by SmartDelay or a Fixed AV Delay of 120ms. CRT response is defined by a decrease in Left Ventricular End Systolic Volume (LVESV) ≥ 15% at 6 months compared to pre-implant baseline.

Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy SMART CRT	

Additional Analyses	Additional analyses include:
	• Clinical Composite Endpoint
	  • All-cause mortality
	  • Heart failure events
	  • NYHA Class
	  • Quality of Life (patient Global Assessment instrument)
	• Six-minute walk distance
	• Kansas City Cardiomyopathy Questionnaire
	• Left-ventricular ejection fraction (LVEF)

Method of Assigning Patients to Treatment	For all subjects enrolled and implanted with a BSC X4 CRT-D system, the RV-LV delay will be measured at the Post-Implant Assessment. For those subjects identified with an RV-LV delay ≥70ms, 1:1 randomization will occur in the electronic data capture (EDC) system. Subjects will be randomized to have an AV Delay determined by SmartDelay or by a Fixed AV Delay of 120ms. Those subjects identified with an RV-LV < 70ms will be exited from the study after 30 day contact to assess for any reportable safety events.
Follow-up Schedule	Study procedures or clinic visits will occur at the following time periods: • Enrollment Visit (<30 days prior to implant procedure) • Pre-Implant Visit (<30 days prior to implant procedure) • Post-Implant Assessment (0-14 days post-implant) and Randomization, if applicable • Six Month Follow-Up Visit (180 to 210 days after Randomization) 
Study Duration	The trial duration is estimated to be approximately 2.5 years from first enrollment to the last patient follow-up.

Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy SMART CRT	
Key Inclusion Criteria	• Subject must be indicated to receive a *de novo* quadripolar Boston Scientific Cardiac Resynchronization Therapy Defibrillator (CRT-D) in conjunction with an ACUITY X4 LV lead. This includes subjects who are indicated to receive an upgrade to a BSC X4 CRT-D from a previously implanted device. • In order to achieve a homogenous population for the study, qualifying subjects are those with heart failure who meet BSC US indications for use defined as those subjects who receive stable optimal pharmacologic therapy (OPT) for heart failure and who meet any one of the following classifications: o Moderate to severe heart failure (NYHA Class III-IV) with EF ≤ 35% and QRS duration ≥ 120 ms o Left bundle branch block (LBBB) with QRS duration ≥ 130 ms, EF ≤ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure • Subject is age 18 or above, or of legal age to give informed consent specific to each country and national laws • Subject is willing and capable of providing informed consent • Subject is willing and capable of complying with visits and procedures as defined by this protocol
Key Exclusion Criteria	• Subjects with documented permanent complete AV block • Subjects with permanent or chronic atrial fibrillation (AF) or in AF at the time of enrollment • Subjects who have previously received cardiac resynchronization therapy with pacing in the left ventricle • Subjects on the active heart transplant list or who has or is to receive ventricular assist device (VAD) • Life expectancy shorter than 12 months due to any medical condition (e.g., cancer, uremia, liver failure, etc…) • Subject with a known or suspected sensitivity to dexamethasone acetate (DXA) • Subject is enrolled in any other concurrent clinical study, with the exception of local mandatory governmental registries and observational studies/registries, without the written approval from Boston Scientific • Women of childbearing potential who are or plan to become pregnant during the course of the trial • Subjects currently requiring dialysis

Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy SMART CRT	
Statistical Methods	
Primary Statistical Hypothesis	The following set of hypotheses will be used to evaluate the Primary Endpoint: $H_o: p_{(SmartDelay)} \leq p_{(Fixed)}$ $H_1: p_{(SmartDelay)} > p_{(Fixed)}$ Where *p* represents the proportion of CRT responders. Response is defined as a >15% decrease LVESV ([$LVESV_{6M} - LVESV_{BL}$]/ $LVESV_{BL}$ < - 15%).
Statistical Test Method	A chi-square test will compare the proportion of responders between the groups.
Sample Size Parameters	[redacted] Our sample size parameters for patient enrollment were estimated based on experience from prior studies. These parameters will be re-evaluated while the study is in progress, and if necessary, adjustments may be made.

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4. Introduction

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

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

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

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

The benefits of CRT-D are not conferred on every 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 Endpoint (CCE) is the most widely used[4]. This endpoint combines four metrics: all-cause mortality, heart failure hospitalization, NYHA Class, and quality of life as measured with the patient global assessment instrument. When clinical metrics are used, the typical non-response rate cited is one-third of patients are non-responders. When echo-based measures are used, the non-response rate is somewhat higher.

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

- Poor lead location

- Lack of baseline electrical 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
- Multi-site pacing
- LV-only CRT

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

V-V Timing: The InSync III Marquis Study[6] using the CCE, DECREASE HF Study[7] using a composite of peak VO2 and LVESD, and RHYTHM ICD V-V Optimization Study[8] using peak VO2 all demonstrated the safety of this feature and non-inferiority to conventional sequential biventricular pacing, but none showed superiority.

LV Only CRT: The DECREASE HF Study[7] using a composite of peak VO2 and LVESD and the B-LEFT HF Study[9] using the CCE demonstrated safety of LV pacing but neither showed that LV Only CRT was superior to conventional biventricular CRT. The AdaptivCRT study, using the CCE, evaluated an algorithm that provided either LV or biventricular pacing depending on AV conduction while also periodically adjusting AV delay and V-V timing. This algorithm was found to be non-inferior to echocardiographic-guided optimization[10].

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) and used the CCE and SMART-AV[12] which used LVESV, which showed these methods were non-inferior to empiric programming. The RESPOND-CRT study, which evaluated a CRT system that employed a hemodynamic sensor to optimize both AV and VV timing, used a modified version of the CCE. This study as well found that the sensor was non-inferior to echocardiographic optimization[13].

Multi-site Pacing: To date, results from only one randomized clinical trial on multi-site pacing has been presented. The MPP Trial, using a modified version of the CCE, evaluated a CRT-D system that paced the left ventricle from two distinct sites using a quadripolar lead[14]. The study had a 3 month run-in phase that identified non-responders who were then randomized to MPP or conventional CRT. MPP was found to be non-inferior to conventional CRT in converting non-responders to responders.

Given that no major randomized trial has prospectively shown superiority to conventional methods of delivering CRT, emphasis has shifted to tailoring CRT to a given patient's intrinsic electrophysiologic characteristics. Left ventricular electrical delay (LVED), which is a measure of the difference in time between an intrinsic ventricular depolarization being

detected at the right ventricular lead and that of the left ventricular lead, has been examined as a way of identifying candidates for optimization. Longer LVEDs would be indicative of both underlying baseline dyssynchrony and good lead position and provide a better foundation for CRT optimization.

The SMART AV[12] study was reexamined in this light by Gold et al[15] and the results of the fixed AV delay and SMART AV-determined AV delay arms were divided into quartiles based on the LVED as measured at the time of implant using the Q-wave from the surface lead II ECG as one timing reference and appearance of unpaced ventricular depolarization on the left ventricular lead as the other. In this retrospective analysis that used reduction in LVESV as its primary endpoint, prolonged values of QLV were significantly associated with progressively greater degrees of reverse remodeling. The role of interventricular delay was examined again by Gold et al[16], but this time using data from the implanted CRT-D device instead of external hardware. For this analysis, interventricular delay was measured as the elasped time between unpaced ventricular depolarization detected on the right ventricular lead and the left ventricular lead (RV-LV). The same relationship was observed with RV-LV based subgroups that was previously observed with QLV, namely, that progressively larger values of RV-LV were significantly associated with greater reductions in left ventricular volumes and improvement in left ventricular ejection fraction and quality of life.
This retrospective observation that SmartDelay was more effective with prolonged RV-LV is the basis for the SMART CRT study. The objective of the SMART CRT study is to confirm this finding prospectively.

5. Device Description

5.1. *Medical Equipment Description*

Commercially approved quadripolar Boston Scientific (BSC) Cardiac Resynchronization Therapy Defibrillator (CRT-D) devices and future generations of BSC X4 CRT-D devices approved by the appropriate regulatory bodies will be included in the trial. All devices utilized in the study will include SmartDelay™ (5.1.2) and must be capable of providing SmartDelay recommendations for both biventricular pacing (BiV) and Left Ventricular (LV) only pacing. Additionally, all CRT-D devices will utilize LV VectorGuide™ (5.1.3). A list of approved CRT-D models is available upon request.

A 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 are eligible. Boston Scientific's ACUITY™ X4 IS4 heart failure lead family for the LV lead (5.1.1) will be required.

5.1.1. Boston Scientific's ACUITY X4 Quadripolar LV Lead and Accessories

Boston Scientific's ACUITY™ X4 IS4 heart failure lead family for the Left Ventricle (LV) leads are required in this study (Figure 5-1: ACUITY X4 Leads and Electrode Placement). The ACUITY X4 leads are intended for chronic left ventricular pacing and sensing. A variety

of pace/sense configurations are possible with the four distal 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. Available ACUITY X4 LV leads include: 4671, 4672, 4674, 4675, 4677, 4678.

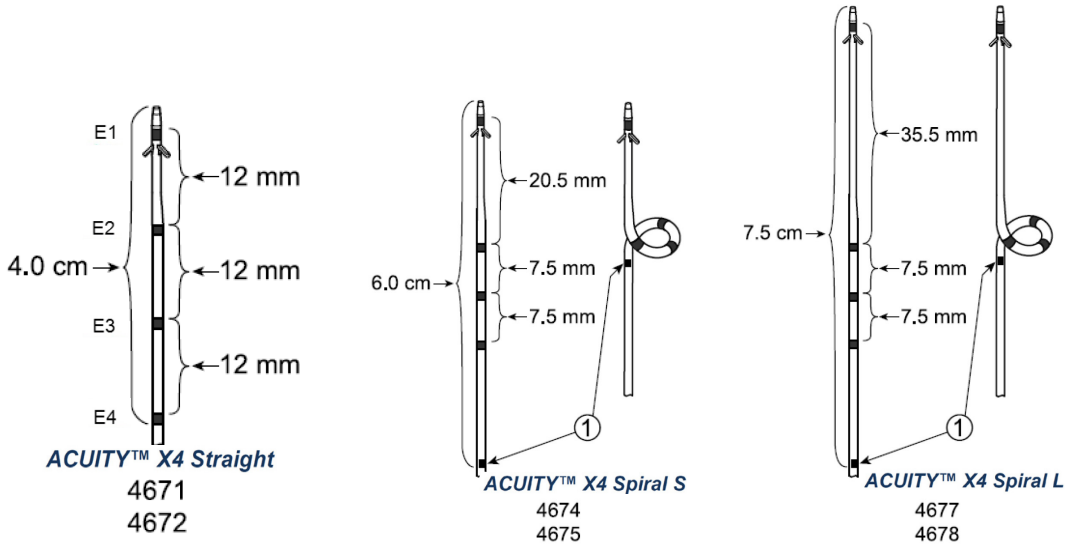

Figure 5-1: ACUITY X4 Leads and Electrode Placement

Note: Nomenclature of electrodes on the lead is E1, E2, E3, E4. The corresponding nomenclature on the BSC PRM is as follows:

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

5.1.2. SmartDelay

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

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

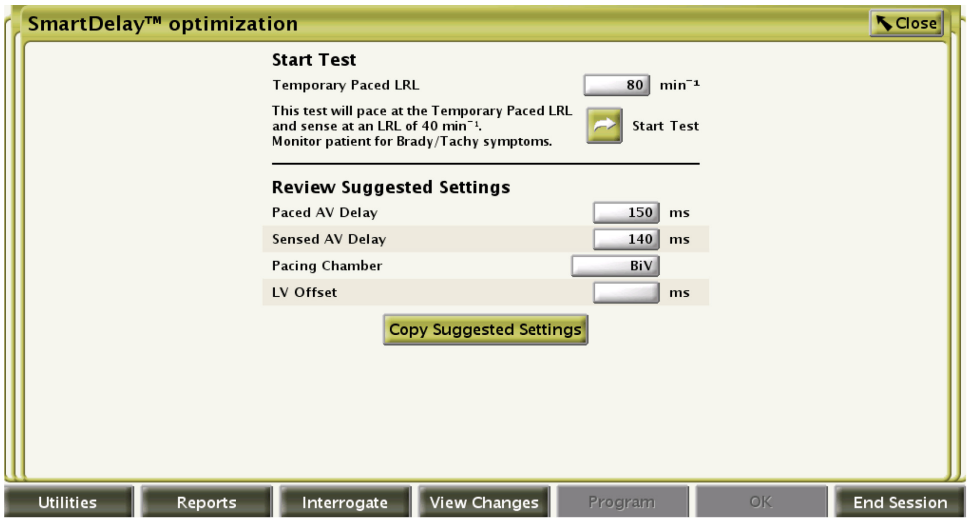

Figure 5-2: SmartDelay Example

5.1.3. LV VectorGuide

LV VectorGuide allows the clinician to evaluate multiple quadripolar LV pacing vectors quickly 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 (RV-LV Delay), the delay between detection of an intrinsic R-waves between the RV and LV EGMs
- LV lead impedance
- LV pace threshold
- Phrenic Nerve Stimulation (PNS)

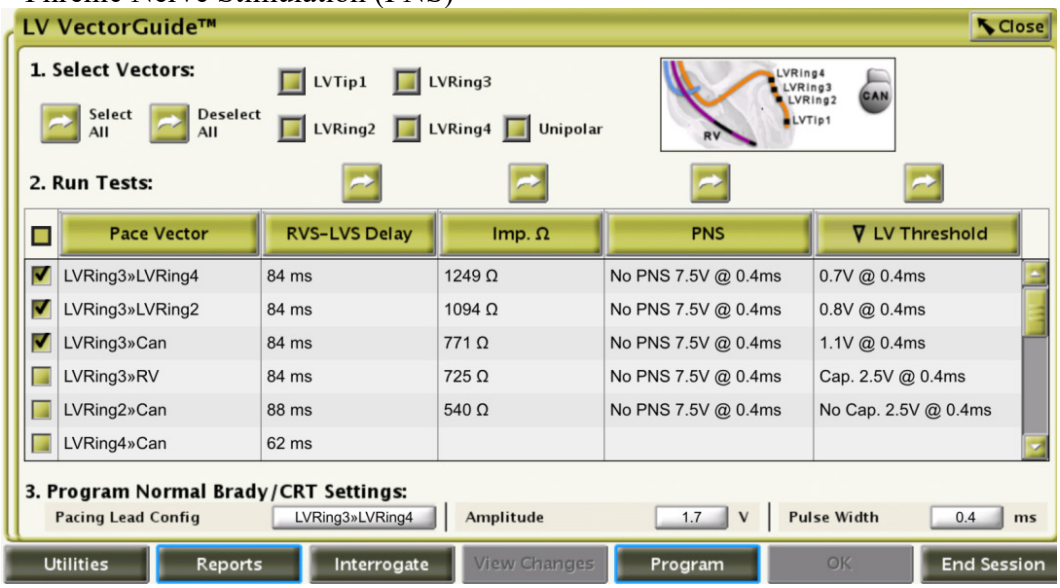

Figure 5-3: LV VectorGuide Example

6. Study Objectives

The primary objective is to show the benefit of SmartDelay in patients with a prolonged RV-LV interval.

7. Study Endpoints

The primary endpoint is comparing cardiac resynchronization therapy (CRT) response rates between AV Delay programming schemes defined by SmartDelay or a Fixed AV Delay of 120ms.CRT response is defined by a decrease in LVESV of ≥ 15% at 6 months compared to the pre-implant baseline.

8. Study Design

SMART CRT is a prospective, double-blind, multicenter, international, randomized controlled trial.

8.1. *Scale and Duration*

The study will be conducted at up to 100 sites globally. [redacted] The study progress will be monitored, and if necessary, the number of patients enrolled may be increased to ensure that an adequate number of patients complete the Six Month Follow-Up. The final sample size will be determined via an interim sample size re-assessment, as described in Section 12.1.2.

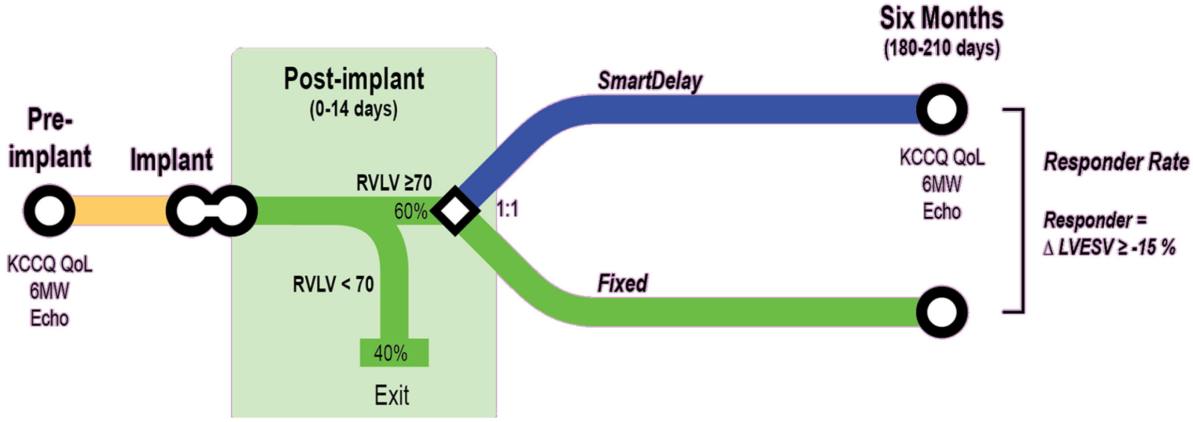

Figure 8-1: SMART CRT Study Design

8.2. *Treatment Assignment*

The RV-LV interval will be measured at the Post-Implant Assessment for all subjects enrolled and implanted with a BSC X4 CRT-D system. For those subjects identified with an

RV-LV ≥70ms, 1:1 randomization will occur via the electronic data capture (EDC) system. Subjects will be randomized to have either an AV Delay and pacing chamber determined by SmartDelay or a Fixed AV Delay of 120ms with BiV pacing. Randomization schemes can be obtained by logging onto the electronic data capture system (EDC) and registering the subject.

Study participation ends prior to randomization assignment for subjects with an RV-LV < 70ms (as shown in Figure 8-1: SMART CRT Study Design). Subjects with an RV-LV < 70ms will be exited from the study after 30 day contact to assess for any reportable safety events.

8.2.1. Treatment Arms

There will be two treatment arms of the trial:

Table 8-1: Treatment Arms

ARM 1= AV Delay and pacing chamber determined by SmartDelay	ARM 2 = Fixed AV Delay at 120ms with BiV pacing

8.3. *Justification for the Study Design*

NYHA Class I-II patients are now eligible for CRT following the MADIT CRT study[3], and there are no prior data for these patients using the SmartDelay feature. Furthermore, in the intervening seven years since the SMART AV trial results were first published, there have been changes in technology. Quadripolar leads are available and in use today rather than the unipolar/bipolar leads previously available. Potential changes in implant technique (optimizing lead position for position rather than electrical performance) as well as potential changes in the practice of medicine when treating heart failure patients. Accordingly, a randomized controlled trial was chosen. This study design helps assure that two comparable patient populations are obtained while mitigating bias such that any observed changes are due to the use of SmartDelay alone.

The parameters for the study design were taken from the predicate SMART AV study. The SMART AV study was designed to detect a decrease in LVESV of at least 15mL. The SMART CRT study is designed to detect a decrease in LVESV of at least 15%. The modification in the response definition for SMART CRT was made to represent a more appropriate clinical definition of CRT response. Increasing values of RV-LV were associated with an increased effect size. The cutoff value of 70 ms was chosen because it maximized the potential yield of screened patients while still preserving a clinically important effect size. New studies based on previous retrospective analyses may not precisely duplicate the magnitude of effect originally reported. Accordingly, this study was designed to detect at least 75% of the effect size to conserve a clinically meaningful proportion of the effect observed in SMART AV.

9. Subject Selection

9.1. *Study Population and Eligibility*

Subjects included in the SMART CRT Study should be selected from the investigator's general patient population of patients who are indicated for CRT-D implantation per BSC labeled indication provided in **Section 9.2**. Investigators are responsible for screening all potential subjects and selecting those who meet the eligibility criteria for the study as described in **Sections 9.2** and **Section 9.3** below.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 9-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Table 9-2) is met.

Table 9-1: Inclusion Criteria

Clinical Inclusion Criteria	• Subject must be indicated to receive a *de novo* quadripolar Boston Scientific Cardiac Resynchronization Therapy Defibrillator (CRT-D) in conjunction with an ACUITY X4 LV lead. This includes subjects who are indicated to receive an upgrade to a BSC X4 CRT-D device from a previously implanted device. • In order to achieve a homogenous population for the study, qualifying subjects are those with heart failure who meet BSC US indications for use defined as those subjects who receive stable optimal pharmacologic therapy (OPT) for heart failure and who meet any one of the following classifications: o Moderate to severe heart failure (NYHA Class III-IV) with EF ≤ 35% and QRS duration ≥ 120 ms o Left bundle branch block (LBBB) with QRS duration ≥ 130 ms, EF ≤ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure • Subject is age 18 years old or above, or of legal age to give informed consent specific to each country and national laws • Subject is willing and capable of providing informed consent • Subject is willing and capable of complying with visits and procedures as defined by this protocol

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 9-2) will be excluded from this clinical study.

Table 9-2: Exclusion Criteria

Clinical Exclusion Criteria	• Subjects with documented permanent complete AV block • Subjects with permanent or chronic atrial fibrillation (AF) or in AF at the time of enrollment • Subjects who have previously received cardiac resynchronization therapy with pacing in the left ventricle • Subjects on the active heart transplant list or who has or is to receive ventricular assist device (VAD) • Life expectancy shorter than 12 months due to any medical condition (e.g., cancer, uremia, liver failure, etc…) • Subject with a known or suspected sensitivity to dexamethasone acetate (DXA) • Subject is enrolled in any other concurrent clinical study, with the exception of local mandatory governmental registries and observational studies/registries, without the written approval from Boston Scientific • Women of childbearing potential who are or plan to become pregnant during the course of the trial • Subjects currently requiring dialysis

10. Subject Accountability

10.1. *Point of Enrollment*

Subjects who meet the eligibility criteria and are interested in participation will be provided with an informed consent approved by the center's Institutional Review Board (IRB) / Ethics Committee (EC).

All subjects who complete the informed consent process, sign and date the informed consent form are considered enrolled in the SMART CRT study. No study related procedures can take place until the ICF is signed. Screening tests that are part of Standard of Care (SOC) can be used to determine pre-eligibility. Subjects enrolled in this investigation must be followed per this investigational protocol.

10.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported.

Reasons for withdrawal include, but are not limited to:

- Subject found not to meet eligibility criteria
- Subject choice to withdraw consent
- BSC X4 CRT-D system was not able to be implanted
- Pre-implant echocardiography testing not completed prior to implant

- Device explanted and not replaced with a BSC X4 CRT-D system
- VAD insertion or heart transplant
- Investigator discretion
- Lost to follow-up, despite best efforts to locate the subject;
    - Three documented attempts to contact the subject, including one certified letter, are required to declare a subject lost to follow up.

If a subject withdraws from the clinical investigation, the reason(s) shall be reported on the End of Study electronic case report form (eCRF) in the EDC system. Data up to the point of withdrawal will be collected. All open adverse events should be closed or documented as chronic. Normal manufacturer vigilance monitoring of device performance will take place after a subject is withdrawn.

10.3. *Subject Status and Classification*

All subjects who complete the informed consent process, sign and date the ICF are considered enrolled. Subject status will be classified as below after enrollment:

Intent: A subject who has been enrolled, but does not have anesthesia administered in preparation for a BSC CRT-D system implant procedure. The original Informed Consent form and screening documentation for intent patients should be maintained in the Center's files and an End of Study form completed. Patients shall be withdrawn from the study and followed as per standard of care. No further follow-up is required.

Partial Attempt: A subject who has been enrolled and has had anaesthesia administered in preparation for a BSC CRT-D system implant procedure, but does not undergo an implant/main study procedure. The patient shall be contacted at least 30 days after the attempt to check for any reportable adverse event possibly related to the partial attempt and an *End of Study* form completed. No further follow-up is required after the 30 day contact.

Attempt: A subject who has been enrolled, had anaesthesia administered in preparation for a BSC X4 CRT-D system implant procedure, undergoes a BSC CRT-D system implant procedure, but is not successfully implanted with the study system (RA lead, RV lead, ACUITY X4 LV lead, and BSC X4 CRT-D). The patient shall be contacted at least 30 days after the attempt to check for any reportable adverse event possibly related to the partial attempt and an *End of Study* form completed. No further follow-up is required after the 30 day contact.

Implant: A subject who has been enrolled, had anesthesia administered in preparation for a BSC CRT-D system implant procedure, undergoes a BSC X4 CRT-D system implant procedure and is successfully implanted with the study system (RA lead, RV lead, ACUITY X4 LV lead, and BSC X4 CRT-D).

10.4. *Enrollment Controls*

Each center may enroll up to a maximum of 72 subjects, no more than 10% of 726 expected subjects. If a center wishes to exceed this limit, the center must obtain prior written approval from the sponsor or sponsor's delegated representative.

Sites will be notified when the enrollment goal is close to being reached and once enrollment is complete.

11. Study Methods

11.1. *Data Collection*

Data will be collected from each subject at the following visits: Enrollment Visit, Pre-Implant Assessment, Post-Implant Assessment and Randomization, and Six Month Follow-Up. Additional follow-up visits must be collected if they are associated with a reportable adverse event, a suspected device deficiency, or a specified device programming change. Routinely scheduled office visits, for purposes other than the aforementioned events, do not require additional visit forms to be completed. Subjects classified as "partial attempt" and "attempt" will be contacted, either in person or by telephone, at least 30 days after the implant procedure in order to capture any reportable adverse events prior to withdrawal from the study.

Table 11-1: Data Collection Schedule

Procedure/Assessment	**Enrollment Visit** (< 30 days prior to implant)	**Pre-Implant Assessment** (< 30 days prior to implant)	**Post-Implant Assessment & Randomization** (0-14 days from implant)	**Six Month Follow-up** (Day 180 to 210 days after randomization)	**Additional Visits**
Informed consent process, including informed consent signature date	X				
Inclusion/Exclusion	X				
Demographics	X				
Physical assessment		X		X	
Medical history	X				
Echocardiography		X		X	
NYHA Class		X		X	
12 lead ECG		X			
Six-minute walk test		X		X	
Kansas City Cardiomyopathy Questionnaire (KCCQ)		X		X	
Patient & Physician Global Assessments				X	
Cardiac medications	X	X**	X**	X**	X**
RV and LV lead location			X		
Implanted device information			X		
Randomization – obtained via the EDC system			X*		
Device interrogation/ programming status			X	X	*
Reportable AE's, SAE's and HF events		*	*	*	*

X = required; *=Data required only if the event occurred; **= Only changes to cardiac medications are required to be documented

11.2. *Study Candidate Screening*

Any subject meeting all of the inclusion criteria and not meeting any of the exclusion criteria is enrollment eligible for the SMART CRT study. A formal screening log is not required to be maintained.

11.3. *Informed Consent and Enrollment*

Subjects who meet all of the inclusion criteria, none of the exclusion criteria, undergo the informed consent process, and sign and date the informed consent form less than 30 days prior to implant are considered enrolled in the study. No data collection, data entry, or study specific procedure shall be performed prior to having appropriately consented the subject. **Table 11-2** lists the data collection requirements at the enrollment visit.

Table 11-2: Source Documentation Requirements – Enrollment Visit

Data Collection Requirement	Retention of Original Source Documentation
• Informed Consent Form and process, including informed consent and signature date • Inclusion/Exclusion Criteria • Demographics • Medical History • Cardiac Medication(s)	Investigational Center

11.4. *Pre-Implant Assessment*

The following tests may only be performed after the Enrollment Visit and must be completed < 30 days prior to the implant procedure: physical assessment, echocardiogram (Appendix 27.1), six-minute walk test (Appendix 27.2), and Kansas City Cardiomyopathy Questionnaire (Appendix 27.3).

11.4.1. Physical Assessment

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

- Resting heart rate
- 12 lead ECG*
- Blood pressure
- NYHA Class assessment
- Presenting symptoms
- Height/weight

* Analysis of the 12 lead ECG by the investigator should include the following: ventricular rate, intrinsic PR interval, intrinsic QRS interval, and nature of interventricular conduction delay (left bundle branch block, right bundle branch block, or non-specific interventricular conduction delay).

- List of cardiac medications[**]

The subject's current NYHA Class must be determined based on Table 11-3.

Table 11-3: NYHA Classifications

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

11.4.2. Echocardiography

Echocardiography will be used to assess cardiac function and structure. Recordings of each echo session should be uploaded or mailed to the Echocardiographic Core Laboratory within 10 days of completion. A complete echocardiography protocol may be found in Appendix 27.1: Echocardiography Protocol.

11.4.3. Six-Minute Walk Test

To assess tolerance of every-day physical activity, subjects are required to complete a six-minute walk test. To perform this test, the subject is encouraged to walk *as far as possible* on a flat surface (e.g., clinic corridor) during a six-minute time period. The total distance traveled is measured (in feet or meters) and used for analysis. Detailed instructions may be found in Appendix 27.2: Six-Minute Walk Test.

Patients with orthopedic limitations (e.g., arthritis or wheelchair/cane/scooter use), known non-cardiac comorbidities that prevent normal walking (e.g., emphysema or need for supplemental oxygen), or for whom there are safety concerns (e.g., angina) are excused from six-minute walk testing. Inability to perform a six-minute walk due to medical reasons is not a deviation. Patients who complete a baseline six minute walk test but who cannot walk at least 150 m or more than 425 m or who begin the six minute walk test but terminate it for

[**] For study purposes, cardiac medications include: diuretics, ACE inhibitors/angiotensin receptor blockers, beta blockers, aldosterone antagonists, Class I/III antiarrhythmics, calcium channel blockers, anti-hypertensive drugs, and statins.

non-cardiovascular reasons or safety reasons will be excluded from testing of six-minute walk distance at the Six Month Follow-Up.

11.4.4. Kansas City Cardiomyopathy Questionnaire

The Kansas City Cardiomyopathy Questionnaire (KCCQ) will be administered at the Pre-Implant (baseline) Assessment and again at the Six Month Follow-Up visit. A detailed description of the questionnaire can be found in Appendix 27.3: Kansas City Cardiomyopathy Questionnaire.

Table 11-4: Source Documentation Requirements – Pre-Implant Assessment

Data Collection Requirement	Retention of Original Source Documentation
• Physical Assessment • NYHA Assessment • Cardiac Medication Changes • Six-minute walk test • KCCQ • Reportable Adverse Events, Device Deficiencies, and Protocol Deviations, if applicable	Investigational Center
• 12 lead ECG	Retain at Investigational Center and upload to the EDC system
• Echocardiogram	Retain at Investigational Center, copy uploaded or mailed to Echocardiography Core Lab

11.5. *Post-Implant Assessment and Randomization*

Recommended programming is DDD or DDDR with a lower rate limit (LRL) of 60bpm throughout participation in the study. If programming is different from this recommendation for clinical circumstances, the rational shall be provided. The Post-Implant Assessment must occur 0-14 days after the implant procedure. Tasks to be performed at this visit include:

- Documentation of device information, including manufacturer, model and serial number, and implant date(s) of the CRT-D device, RA lead, RV lead, and LV lead

- Pulse generator interrogation with routine lead evaluation of the implanted RA, RV and LV leads in final programming configuration which includes:
  - Intrinsic sensing (mV)
  - Pacing impedance (Ω)
  - Shock lead impedance (Ω)
  - Pacing capture threshold (V/ms; the pulse width is at investigator discretion)
  - Pacing capture threshold, impedance, and PNS for any LV vector which meets criteria in 11.5.1

Note: Patients must have functional RA, RV and LV leads. If one of the leads is not functional, patients cannot continue in the study and must be withdrawn at this point.

- RV and LV lead location and, if known, rationale for LV lead placement. Such information is typically available by reviewing lead imaging documents including in-procedure fluoroscopy or post-implant chest X-rays, or obtained from the subject's medical record.
    - LV lead location should be defined as:
        - Anterior, anterolateral, lateral, posterolateral, or posterior
        - Basal, middle, or apical
    - RV lead location should be defined as: apex, free wall, septal wall, RV outflow tract, or other

- RV-LV timing assessment with VectorGuide as defined in section 11.5.1
- SmartDelay test results, if applicable
- Randomization programming, if applicable
- Save programmer interrogation session and specified reports to USB

11.5.1. RV-LV Timing Assessment and LV Pacing Vector Selection

VectorGuide must be utilized to assess LV pacing vectors with the following technique:

1. Identify RV-LV timing for each LV electrode using VectorGuide

2. Identify the impedance for each LV pacing vector with RV-LV delay ≥ 70ms using VectorGuide

3. Assess phrenic nerve stimulation (PNS) in any LV pacing vector with an RV-LV delay ≥ 70ms at an output of 7.5V using VectorGuide. PNS will be assessed as per standard of care, based on subject complaint (such as hiccups or twitching) and confirmed by palpation by a qualified HCP. The PNS threshold is defined as the first voltage step without PNS.
    a. Presence or absence of PNS and PNS threshold must be documented in the LV VectorGuide Report.

4. Assess the pacing capture threshold in each LV pacing vector with an RV-LV delay ≥ 70ms using VectorGuide. The pacing capture threshold for each LV pacing vector with an RV-LV delay ≥ 70ms must be documented on the VectorGuide Report.
    a. The recommended maximum acceptable pacing capture threshold for any LV vector is 4.5V@0.5ms.
    b. It is recommended that any vector with an RV-LV delay ≥ 70ms with PNS have a PNS threshold ≥3V above the pacing capture threshold.

5. If there are multiple LV pacing vectors with an RV-LV delay ≥ 70ms that meet the above criteria, the final programmed LV pacing vector can be programmed at the discretion of the investigator using the following criteria:

a. Preference should be given to the LV pacing vector with longest RV-LV delay.
b. The final programmed LV pacing vector must have an RV-LV delay within 10ms of the longest RV-LV delay of qualifying LV vectors.

If the subject does not have any LV pacing vectors that meet the above criteria, the subject should be programmed per physician discretion. The subject will be exited from the study after 30 day contact to assess for any reportable safety events.

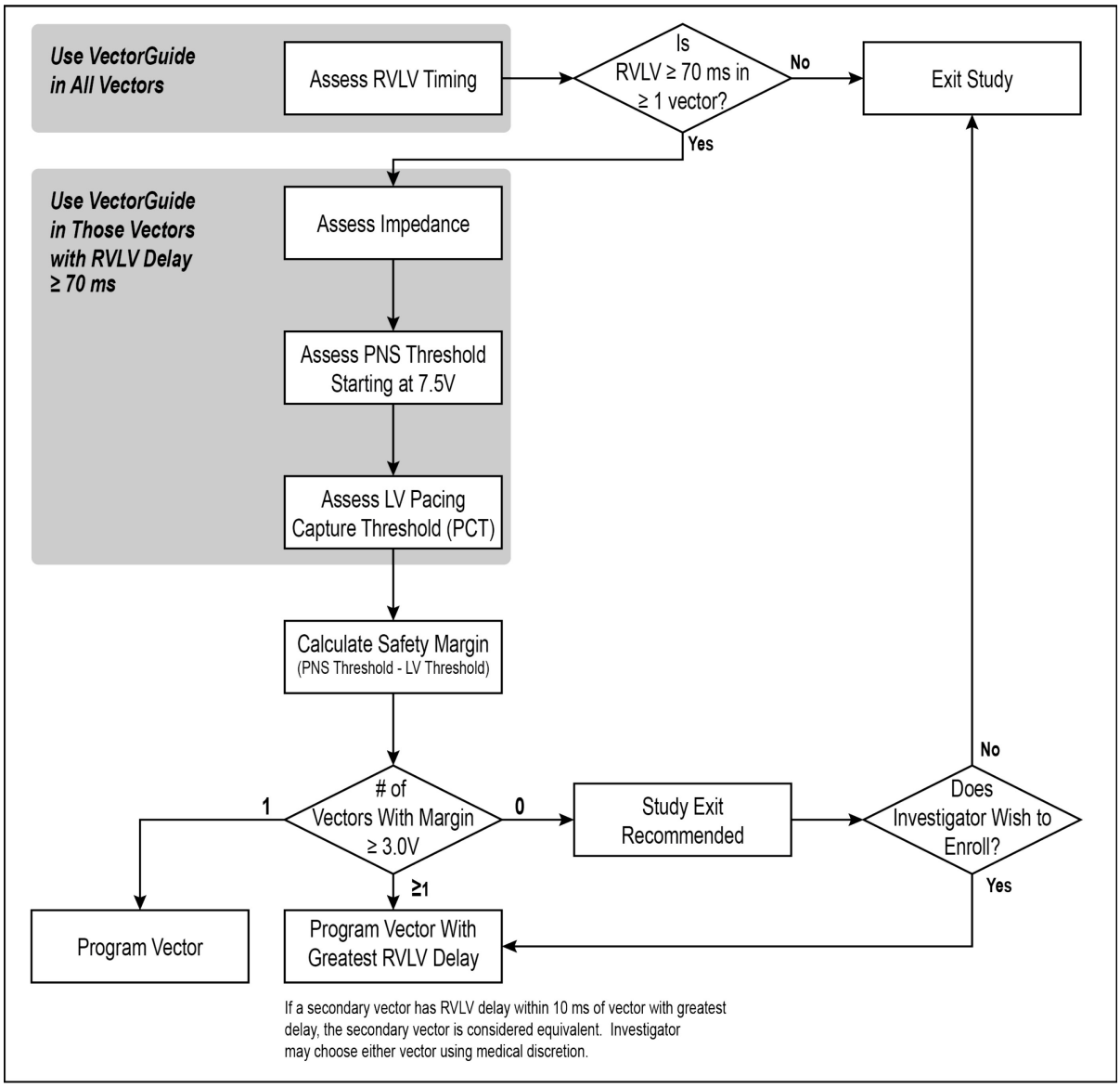

Figure 11-1: Post-Implant Assessment

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Source documents required for the Post-Implant Assessment are listed below in Table 11-5.

11.5.2. Randomization Assignment and Programming

All subjects who have a qualifying LV vector, as determined in Section 11.5.1, will be randomized. The randomization programming must occur when the patient's presenting rhythm is compatible with the SmartDelay algorithm.

Perform the randomization assignment via the EDC system. Randomization in the EDC cannot occur without entry of RV-LV timing in programmed LV pacing vector. Every reasonable attempt will be made to have subjects blinded to their randomized treatment arm assignment throughout the trial.

Tasks to be performed after randomization include:

- SmartDelay test to obtain programming recommendations for the AV Delay and pacing chamber
- Programming the device to the subject's randomized treatment arm
- Save interrogation session and specified reports to USB

Devices are required to be programmed according to this protocol.

11.5.2.1. SmartDelay Test

It is required to perform SmartDelay test for all subjects to obtain programming recommendations for the AV Delay and Pacing Chamber(s). LV offset should be set to 0ms throughout the duration of the study. For step-by-step guidance on how to perform the SmartDelay test, please refer to Appendix 27.4.

Record the following values from the SmartDelay test in the EDC system:

- Sensed AV Delay (SAV) and Paced AV Delay (PAV)
- Pacing Chamber (BiV or LV Only)

After running SmartDelay, copy settings without programming changes, print and save to USB the Settings Changes Report. This report will display recommended SAV, PAV, and Pacing Chamber.

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.

11.5.2.2. Programming Based on Randomization Assignment

Fixed AV Delay: If the subject is randomized to the Fixed AV Delay treatment arm, the SAV and PAV values must be set to 120ms with BiV pacing.

SmartDelay AV Delay: If the subject is randomized to the SmartDelay treatment arm, SAV, PAV, and pacing chamber settings must be programmed according to the results of the SmartDelay optimization throughout participation in the study. The final AV Delay programming must be captured on the printed Device Follow Up Report.

If the LV MultiSite Pacing feature is available in the implanted device, this feature must be turned OFF throughout the duration of the study.

Table 11-5: Source Document Requirements – Post-Implant Assessment and Randomization

Data Collection Requirement	Retention of Original Source Documentation
• Cardiac Medications Changes • RV and LV lead location • Reportable Adverse Events, Device Deficiencies, and Protocol Deviations, if applicable	Investigational Center
• Device Follow Up Report • Settings Change Report (to capture SmartDelay suggested settings) • Arrhythmia Logbook • LV VectorGuide Report • Patient Data Report	Printed reports and electronic reports on USB retained at Investigational Center

11.6. *Six Month Follow-Up Visit*

Tasks to be performed at this visit include:

- Pulse generator interrogation with routine lead evaluation on implanted RA, RV and LV leads which includes:
  - Intrinsic sensing (mV)
  - Pacing impedance (Ω)
  - Shock lead impedance (Ω)
  - Pacing threshold (V) (pulse width at physician discretion)
- Counter information (%RA, %RV, %LV, %AT/AF)
- RV-LV timing assessment with VectorGuide for each LV electrode
- SmartDelay test results
- Save interrogation session to USB

A Device Settings Report should be printed prior to completing any device testing at the Six Month Follow-Up. The HCP completing these assessments must be blinded to the subject's treatment arm and should not have access to the patient's randomization status or the EDC:

- Physical Assessment (refer to 11.4.1), including NYHA Class assessment
- Echocardiogram completed with programmed pacing therapy active (Appendix 27.1)

- Six-minute walk test (Appendix 27.2)
- KCCQ (Appendix 27.3)
- Patient Global Assessment (11.6.2)
- Physician Global Assessment (11.6.2)

The subject's device may be programmed at the investigator's discretion once all study testing has been completed.

11.6.1. SmartDelay Test

It is required to perform the SmartDelay test for all subjects to obtain programming recommendations for the AV Delay and Pacing Chamber(s). For step-by-step guidance on how to perform the SmartDelay test, please refer to Appendix 27.4.

Record the following values from the SmartDelay in the EDC system:

- Sensed AV Delay (SAV) and Paced AV Delay (PAV)
- Pacing Chamber (BiV or LV Only)

After running SmartDelay, copy settings without programming changes, print and save to USB the Settings Changes Report. This report will display recommended SAV, PAV, and Pacing Chamber.

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.

11.6.2. Quality of Life Global Assessment

In addition to the KCCQ, quality of life will be assessed at six months using the Patient Global Assessment and Physician Global Assessment. This consists of two questions, one of which is directed to the physician who is examining the patient and the other question is directed to the patient to address how well the patient is doing since enrolling in the study.

Figure 11-2: Quality of Life Global Assessment

Physician Global Assessment

How is the patient's clinical status today compared to his or her status at the time of pre-implant assessment?

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

Patient Global Assessment

How do you feel today compared to how you felt when you started the study?

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

- Moderately worse
- Markedly worse
- Much worse
- Very much worse

Table 11-6: Source Document Requirements – Six Month Visit

Data Collection Requirement	Retention of Original Source Documentation
• Physical Assessment • NHYA Class Assessment • Cardiac Medication Changes • Six-minute walk test • KCCQ • Patient Global Assessment • Physician Global Assessment • Reportable Adverse Events, Device Deficiencies, and Protocol Deviations, if applicable	Investigational Center
• Echocardiogram	Retain at Investigational Center, copy uploaded or mailed to Echocardiography Core Lab
• Device Settings Report (printed prior to device testing) • Device Follow Up Report (including counter information) • Settings Change Report • Arrhythmia Logbook • LV VectorGuide Report	Printed reports and electronic reports on USB retained at Investigational Center

11.7. *Additional Follow-Up Visits*

Physician office visits, emergency room visits, out-patient hospital visits, and hospitalizations shall be recorded as an additional follow-up visit only if they are associated with system revision, device deficiency, reportable adverse event, protocol deviation or device programming change as listed below. Other scheduled and unscheduled visits throughout the year (e.g., standard of care device checks) that do not meet these criteria are not required by the protocol.

Changes in the following programming settings require an Additional Visit to be completed:

- AV Delay
- Pacing chamber (BiV pacing or LV only pacing)
- LV pacing vector configuration selected at the Post-Implant Assessment
- LV Offset
- Pacing mode (e.g. DDD, VVI)
- LRL
- Any time the device counter is reset

- Date the counter is reset
- Percent of RV and LV pacing prior to resetting the counter in subjects

A rationale of the setting changes is required.

The following documentation is required:

- Settings Changes Report
- Combined Follow Up Report

A summary of the source documentation required at the Additional Visit is described Table 11-7.

Table 11-7: Additional Follow-Up Visit Data Collection

Data Collection	Retention of Original Source Documentation
• Reportable Adverse Events, Device Deficiencies, and Protocol Deviations, if applicable • Cardiac Medication Changes	Investigational Center
• Combined Follow Up Report • Settings Change Report	Printed reports and electronic reports on USB retained at Investigational Center

11.8. *Device Programming Outside of the Investigational Plan*

Once a subject is programmed to a randomized treatment arm, every effort must be made to keep the subject's device programmed per the required programming in this protocol. Any device reprogramming of AV Delay change, including the reason for change, must be recorded as a protocol deviation and the clinical circumstances must be documented. After reprogramming to device settings outside of the required programming per protocol, subjects will remain in the assigned treatment arm until the end of the study to follow the methodology of intention-to-treat (ITT). Deviated programming doesn't qualify as reason for study withdrawal, and subjects will continue to be followed per the investigational plan.

11.9. *Study Completion*

Subject participation in the study is considered complete for the following reasons:

- **Study completion per protocol**
  - A Six Month Follow-Up visit has been recorded at least 180 days from the date of the randomization OR
  - Subject does not have an RV-LV delay ≥ 70ms on any electrode (E1, E2, E3, E4) with a qualifying pacing vector at the Post-Implant Assessment
- **Death (**see 19.7 for reporting requirements**);**

- **Withdrawal** for reasons that include, but are not limited to:
    - Subject found not to meet eligibility criteria
    - Subject did not get randomized
    - Subject choice to withdraw consent
    - Device explanted and not replaced with a CRT-D system
    - VAD insertion or heart transplant
    - Investigator discretion
    - Lost to follow-up, despite best efforts to locate the subject;
    - Three documented attempts to contact the subject, including one certified letter, are required to declare a subject lost to follow up.

11.10. *Source Documents*

Original source documents are required to be retained at the center. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

NOTE: If thermal paper from the device programmer was used for source documentation, photocopies or printed pdfs should be prepared and kept for source documentation.

12. Statistical Considerations

12.1. *Primary Endpoint*

The primary endpoint will compare the CRT response rates of randomized subjects. CRT response is defined by >15% decrease in LVESV from pre-implant baseline through 6 months.

12.1.1. Hypotheses

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

$$H_o: p_{\text{(SmartDelay)}} \leq p_{\text{(Fixed)}}$$
$$H_1: p_{\text{(SmartDelay)}} > p_{\text{(Fixed)}}$$

Where p represents the proportion of CRT responders. Response is defined as a >15% decrease LVESV ($[LVESV_{6M} – LVESV_{BL}]/ LVESV_{BL} < - 15\%$).

12.1.2. Sample Size

[redacted]

[redacted]

12.1.3. Statistical Methods

Randomized subjects with paired LVESV data – baseline and 6 months – will be included in the analysis. Subjects will be analyzed according to their randomization group. To avoid making erroneous assumptions about incomplete/missing endpoint data, data from subjects with incomplete/missing data will not be imputed; therefore the statistical analysis of the Primary Endpoint will be a modified intention-to-treat analysis. [redacted]

A pure intention-to-treat analysis, in which the incomplete/missing endpoint data is imputed and included in the analysis, may be performed as a sensitivity analysis.

12.2. *General Statistical Methods*

12.2.1. Analysis Sets

All subjects with paired data at baseline and 6 months will be included the analysis of the outcome of interest (i.e., LVESV, subject global assessment, etc.).

12.2.2. Control of Systematic Error/Bias

Subjects will be randomized to minimize subject selection bias. To eliminate the potential for a placebo effect to affect the Primary Endpoint results, the objective measure of LVESV was chosen. Every attempt will be made to blind subjects to their randomized treatment assignment in order to minimize a placebo effect on qualitative analyses, such as quality of life. To reduce the inter-observer variability that can occur with echocardiographic measurements, a core lab blinded to treatment assignment will be used.

12.2.3. Number of Subjects per Investigative Site

A maximum of 72 enrolled subjects will be allowed from an investigational site[redacted]

12.3. *Additional Data Analyses*

12.3.1. Other Endpoints/Measurements

The following outcomes will be evaluated in addition to the Primary Endpoint analysis, each comparing subjects according to their randomized groups:

- LVESV as a continuous variable
- Clinical Composite Endpoint
  - All-cause mortality
  - Heart failure events (as defined in Section 19.1)
  - NYHA Class
  - Quality of Life (Patient Global assessment instrument)
- Components of the Clinical Composite Endpoint
- KCCQ
- Left-ventricular ejection fraction (LVEF)

12.3.2. Tertiary/Exploratory Analyses

The following tertiary analyses will be performed and considered exploratory in nature:

- Six minute walk, compared between randomized groups.
- Optimal cutoff analysis. An RV-LV cutoff of 70 ms was used to identify which subjects will be randomized. Analyses will be performed to find the optimal cutoff – greater than or equal to 70 ms – as determined by the data.

12.3.3. Primary Endpoint Sensitivity Analyses

The Primary Endpoint, in addition to the additional analyses listed above, will be evaluated using modified intention-to-treat methodology, in which subjects with complete datasets are evaluated according to their randomized treatment groups. Sensitivity analyses include the following:

- Pure intention-to-treat – Subjects are analyzed according to their randomized group and missing data is imputed via multiple imputation
- On treatment – Subjects are analyzed according to the actual treatment received
- Per protocol – Subjects are analyzed according to their randomized group, but limited to subjects that received the randomized assignment.

12.3.4. Interim Analyses

When at least half of the required 6 month datasets [redacted] have been completed and reviewed by the core lab, an interim sample size re-assessment will be performed. The pooled and blinded response rate across both groups will be assessed in this interim sample size re-assessment cohort. The observed rate will be weighted by the number of patients in each group and compared to the assumed weighted rate. If the observed rate is less than the assumed rate, the number of patients required for randomization will be increased accordingly[redacted]. The treatment effect will not be calculated, thereby maintaining the blind.

There are no formal interim analyses planned to terminate the study for effectiveness of futility.

12.3.5. Subgroup Analyses

The subgroups that will be evaluated include, but are not limited to, the following:

- Age < 65 years vs. ≥ 65 years
- Females vs. Males
- Ischemic vs. Non-ischemic etiology
- LBBB vs Non-LBBB
- QRS < 150 ms vs. ≥ 150 ms
- Apical vs. Non-apical lead placement (for each RV lead and LV lead placement)
- NYHA Class I/II vs. III/IV
- SmartDelay recommended programming
    - LV only vs. biventricular (BiV) pacing
    - AV Delay (equal to 120±20 ms vs. all others)

The interaction between the subgroup and randomized groups will be evaluated (e.g., gender by randomization group). Additionally, each subgroup will have the SmartDelay vs. Fixed comparison calculated separately (e.g., SmartDelay vs. Fixed evaluated in Females).

12.3.6. Multivariable Analyses

Multivariate analyses will be performed using characteristics listed in Section 12.3.5**Error! Reference source not found.**. Additional covariates may also be considered. The primary approach to multivariate modeling will be as follows:

- Univariate to Multivariate: Univariate modeling is first performed. Significant covariates are considered for inclusion in the final multivariate model. Non-significant covariates are dropped from consideration. A model selection technique (e.g., best subsets, stepwise regression) is then employed to determine the final multivariate model.

Additionally, the following multivariate modeling approaches may be used:

- Recursive Partitioning: The overall population is classified into mutually exclusive subgroups in the form of a decision tree. Each characteristic is dichotomized, though

the cutpoint used for dichotomization is determined by the data during the analysis. To avoid potential problems with model overfitting, methods related to recursive partitioning – such as random forests or stochastic gradient boosting – may be employed.

- Risk Score: Characteristics considered to be associated with CRT Response – determined by analyses of SMART Registry data or by clinical/medical experts – will be combined and converted into a score that can be used to predict CRT Response.

12.3.7. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in the 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 change.

13. Data Management

13.1. *Data Collection, Processing, and Review*

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

The clinical database will reside on a production server hosted by EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

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

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

13.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of

the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other country/regional/local regulations.

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

13.3. *Core Laboratories*

All echocardiography measurements will be performed by an independent Echocardiography Core Laboratory. The Echocardiography Core Laboratory determined values will be used for the Primary Endpoint analysis as well as all echo related additional analyses.

14. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC) 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 when applicable the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

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

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

16. Compliance

16.1. *Statement of Compliance*

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

16.2. *Investigator Responsibilities*

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

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

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.

- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

16.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing

appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study. An investigator must not participate in study related tasks prior to completion of required study training.

16.3. *Institutional Review Board/ Ethics Committee*

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

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

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

16.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

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

16.4.1. Role of Boston Scientific Representatives

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

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during implant or follow-up, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities. Typical tasks may include the following.

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Performing lead diagnostic testing using a Pacing System Analyzer or programmer to obtain pacing and sensing thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from Pacing System Analyzers, programmers, and other equipment
- Entering technical data on technical source form as long as the responsible investigator verifies and signs the completed worksheet
- Print out programming reports directly from the clinician programmer and provide original to clinical site as source documentation
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

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

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

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

16.5. *Insurance*

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

17. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

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

18. Potential Risks and Benefits

18.1. *Anticipated Adverse Events*

The following anticipated adverse events (AE) have been identified for anyone receiving a CRT-D system.

Table 18-1-1: Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System Implants

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System*	
Air embolism	Lead dislodgment
Allergic reaction	Lead fracture
Bleeding	Lead insulation breakage or abrasion
Bradycardia	Lead perforation
Cardiac tamponade	Lead tip deformation and / or breakage
Chronic nerve damage	Local tissue reaction
Component failure	Loss of capture
Conductor coil fracture	Myocardial Infarction (MI)
Death	Myocardial necrosis
Elevated thresholds	Myocardial trauma (e.g., tissue damage, valve damage)
Erosion	Myopotential sensing
Excessive fibrotic tissue growth	Oversensing / undersensing
Extracardiac stimulation (muscle/ nerve stimulation)	Pacemaker-mediated tachycardia (PMT) (Applies to dual-chamber devices only.)
Failure to convert an induced arrhythmia	Pericardial rub, effusion
Fluid accumulation	Pneumothorax
Foreign body rejection phenomena	Pulse generator migration

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System*	
Formation of hematomas or seromas	Shunting current during defibrillation with internal or external paddles
Heart block	Syncope
Heart failure following chronic RV apical pacing	Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
Inability to defibrillate or pace	Thrombus, thromboemboli
Inappropriate therapy (e.g., shocks, and antitachycardia pacing [ATP] where applicable, pacing)	Valve damage
Incisional pain	Vasovagal response
Incomplete lead connection with pulse generator	Venous occlusion
Infection including endocarditis	Venous trauma (e.g. perforation, dissection, erosion)
Insulating myocardium during defibrillation with internal or external paddles	Worsening heart failure

From the DYNAGEN, INOGEN, ORIGEN, INCEPTA, ENERGEN, PUNCTUA, TELIGEN Physician's Technical Manual Oct 01, 2015; Part Number: 359403-002

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

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

18.2. *Anticipated Adverse Device Effects*

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

18.3. *Risks Associated with Participation in the Clinical Study*

In addition to the risks common to all patients who receive CRT implantation, subjects participating in the SMART CRT study may be exposed to additional risks. Specifically, some subjects may be at risk for arrhythmias during the six-minute walk testing. However, the intensity of the exercise is at the discretion of the individual subject, and the test (without electrocardiogram monitoring) has been performed in thousands of subjects with HF or cardiomyopathy[17,18,19] without serious adverse events. Moreover, risks can be minimized by addressing the following safety issues: performing the test in a location where a rapid, appropriate response to an emergency is possible with a crash cart in a near known location; a technician certified in cardiopulmonary resuscitation with a minimum of Basic Life Support[20]; it is up to the physician ordering the test to decide whether physician attendance at a specific test is required as physicians are not required to be present at all tests.

Some additional risks may apply to those subjects for which the SmartDelay test is run. Tachycardia therapy is disabled during SmartDelay optimization. The SmartDelay test also temporarily switches to a DDD mode of pacing with a lower rate limit of 40ppm and an AV Delay of 400ms. Any subject with symptomatic bradycardia may be affected.

18.4. *Risk Minimization Actions*

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

18.5. *Anticipated Benefits*

There may be no additional benefit to the subject due to the study specific programming. However, medical science and future patients may benefit from their participation in this clinical study. If there is a superior or inferior arm, the subjects can be programmed at the conclusion of the study to the best programming suitable to their needs.

18.6. *Risk to Benefit Rationale*

The implantable device systems and accessories used for this clinical study will be commercially available and are considered to be standard of care for patients indicated for such implants. The risks involved with subject participation in this study are essentially the same as those for patients not participating in the study.

19. Safety Reporting

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

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

- All Serious Adverse Events
- All Device Related Adverse Events
    - Events listed in the arrhythmia logbook should be reported only if determined to be clinical significant by the investigator and/or delegated site staff (i.e. ATR, PMT, etc.)
    - All arrhythmias which received inappropriate shock therapy as identified by a study investigator must be reported
- All Serious Adverse Device Events
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- All Heart Failure (HF) Related Events:

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

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

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

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

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

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation. Death should not be reported as an SAE, but should be reported as an outcome of an SAE and only one SAE should have the outcome documented as fatal (see Table 19-1 for AE definitions).

Refer to Section 18 for the known risks associated with the study device(s).

19.2. *Definitions and Classification*

Adverse event definitions are provided in Table 19-1. Administrative edits were made on the definition of serious adverse event from ISO 14155and MEDDEV 2.7/3 for clarification purposes. Reportable events are defined in Section 19.1.

Table 19-1: Safety Term Definitions

Term	Definition

Table 19-1: Safety Term Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: • Led to death, • 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 • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare

Table 19-1: Safety Term Definitions

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

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

19.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in Table 19-2:

Table 19-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

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

Table 19-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
	- the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

19.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 19-3.

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

SMARTCRT.Safety@bsci.com

Table 19-3: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline post-market studies** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 business days after becoming aware of the event or as per local/regional regulations. • Reporting required through the end of study
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	• When documentation is available
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source	• When documentation is available

Table 19-3: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline post-market studies** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
	documentation (unidentified) for reported event	
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency eCRF with all available new and updated information.	• 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.	• In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information • Reporting required through the end of study

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

19.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Device failures and malfunctions should also be documented in the subject's medical record.

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

Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

19.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

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

19.7. *Subject Death Reporting*

A subject death during the study must be reported to Boston Scientific as soon as possible and, in any event, within ten (10) days or per local regulations of site notification. The center's IRB/EC must be notified of any deaths in accordance with that center's IRB/EC policies and procedures. Whenever possible, the device should be interrogated and BSC system components (e.g., the device) should be removed intact and returned promptly to BSC RM for analysis.

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

• Date and time of death;

• Place death occurred;

• Immediate cause of death;

• Rhythm at the time of death, if known (include any available documentation);

• Whether or not the death was witnessed;

• Whether the subject had worsening heart failure;

• Any other circumstances surrounding the death;

• Approximate time interval from the initiating event to death (temporal course) – items to consider include, but are not limited to: information regarding last time subject was seen by investigator, last office visit, etc.

• Investigator or co-Investigator signature and date.

Other Source documents maybe requested at BSC. The Clinical Events Committee (CEC) must review information regarding subject deaths if heart failure could not be ruled out as the cause of death.

20. Informed Consent

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

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

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

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

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

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning

of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

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

21. Committees

21.1. *Safety Monitoring Process*

To promote early detection of safety issues, the BSC Medical Safety group will provide evaluations of safety events. A CEC will provide evaluations of all HF events and deaths in which HF could not be eliminated as the cause. 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 the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

21.2. *Steering Committee*

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

21.3. *Clinical Events Committee*

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that reviews and adjudicates predefined events as reported by study investigators. For this study, 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 HF events and subject deaths. CEC responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

22. Suspension or Termination

22.1 Premature Termination of the Study

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

22.1.1 Criteria for Premature Termination of the Study

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

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

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

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

22.3 Requirements for Documentation and Subject Follow-up

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

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

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

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

22.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 6 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed All subjects enrolled in the study at the site will continue to be followed according to the standard of care. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

23. Publication Policy

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

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

24. Reimbursement and Compensation for Subjects

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

25. Bibliography

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26. Abbreviations

Table 26-1: Study Abbreviation

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AV	AtrioVentricular
BiV	Biventricular
BSC	Boston Scientific Corporation
CCE	Clinical Composite Endpoint
CEC	Clinical Events Committee
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
DD	Device Deficiency
DDD/DDDR	International Code for pacing mode: pacing site(s), sensing site(s), pacing mode, rate responsiveness
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FCS	Field Clinical Specialist
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare Provider
HF	Heart Failure
ICF	Informed Consent Form
ICD	Implantable Cardioverter Defibrillator
IQRMP	Integrated Quality Risk Management Plan
IRB	Institutional Review Board
IV	Intravenous

Abbreviation	Term
LBBB	Left Bundle Branch Block
LRL	Lower Rate Limit
LV	Left Ventricle
LVED	Left Ventricular End Diastolic
LVEF	Left Ventricular Ejection Fraction
LVEDV	Left Ventricular End Diastolic Volume
LVESV	Left Ventricular End Systolic Volume
ms	Millisecond
mV	millivolts
NYHA	New York Heart Association
Ω	Ohms
OPT	Optimal Pharmacologic Therapy
PA	Paced Atrium
PAV	Paced AtrioVentricular
PCT	Pacing Capture Threshold
PG	Pulse Generator
PI	Principal Investigator
PNS	Phrenic Nerve Stimulation
QLV	Q-Left Ventricular
RA	Right Atrium/ Atrial
RM	Rhythm Management
RV	Right Ventricle/ Ventricular
RV-LV	Right Ventricle-Left Ventricle
RVs-LVs	Right Ventricle sense-Left Ventricle sense
SA	Sensed Atrium
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAV	Sensed AV
US	United States of America
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
UADE	Unanticipated Adverse Device Effect
V	Volts

Abbreviation	Term
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

27. Appendices

27.1. *Echocardiography Protocol*

The following parameters must be measured as part of the echocardiography exam at the pre-implant and 6 month visits:

- LVESV / LVEDV (by Simpson's Method of Discs)
- LVEF
- Valve function: tricuspid, mitral & aortic regurgitation
- LA volume

The measurements should be taken at the Six Month Follow-Up visit with pacing therapy active.

Digitally store data in a DICOM format then copy to a CD-R. Maintain a copy of the study CD-R at the site and either send or upload a copy to the Echocardiography Core Lab within 10 days of completion. Each site will be responsible for identifying experienced sonographers (echocardiographic technicians) who will perform study echocardiograms, which will be a limited version of the standard echocardiographic examination. Sites will be supplied with training materials that will describe in detail the methodology for obtaining study echocardiograms. Training sessions will be conducted and documented for all participating sites.

A subset of a standard echocardiographic examination will be performed. All subjects will undergo 2-D echocardiography with the following views:

Parasternal Long Axis View (PLAX):

- 2D imaging of Left Ventricle to determine septal and posterior wall thickness and LV diameters at *end diastole* and *end systole*. Make measurements in the mid-LV adjacent to postero-lateral papillary muscle. LV outflow diameter is measured in the frame following aortic valve opening.
- Color Doppler imaging performed for presence of mitral regurgitation. Color Doppler imaging should be performed with a nyquist limit (scale) .5-.6m/sec. Demonstrate MR jet at the coaptation of the mitral leaflets for measurement of jet width.

Parasternal Short Axis View (PSAX)/right ventricular outflow view:

- Pulsed Wave Doppler of the right ventricular outflow tract velocities should be obtained just proximal to the pulmonary valve leaflets to measure pre-ejection period

(PEP) – PEP is the time from onset of the QRS complex to the onset of RV outflow systolic velocity envelope. Velocities must be recorded at a 100mm/s sweep speed.

Apical 4-chamber view:

- 2D imaging to demonstrate the RA, RV, LV and LA chambers within the sector image at the proper depth in at least 3-5 cardiac cycles.
- Color Doppler imaging If present, continuous-wave Doppler of the tricuspid valve regurgitant jet velocity for estimation of RV systolic pressures.
- Color Doppler imaging performed for detection of mitral regurgitation. Demonstrate origin of the jet at the coaptation of the mitral leaflets for measurement of jet width and the maximal jet area.
- Continuous wave Doppler of the mitral valve regurgitant jet velocity. Zero velocity baseline and scale should be adjusted to clearly display systolic jet envelope profile at a 100mm/s sweep speed.
- Pulsed-wave Doppler of mitral inflow velocities should be obtained at the mitral leaflet tips, recorded at 100mm/s sweep speed. Measurements will include E-wave and A-wave velocities, E-wave deceleration time and diastolic filling time.
- Pulsed-wave tissue Doppler imaging (TDI) is performed at the lateral and septal LV base (i.e., mitral annulus) to obtain systolic (S') and diastolic myocardial velocities (E'). The sample volume size should be set at a 3-5mm axial length; Doppler signal gain and velocity scale should be adjusted to display peak S' and Em velocities, recorded at 100mm/s sweep speed. Measurements include time from onset of QRS to peak (or onset) of S' velocity at each site.

Apical 2-chamber view:

- 2D imaging of LV and LA endocardial borders demonstrated in the sector image at the proper depth setting in at least 3-5 cardiac cycles.
- Color Doppler imaging performed for the presence of mitral regurgitation.

Apical 5-chamber view:

- Pulsed-wave Doppler sample volume of the LV outflow tract. Display closing "click" of the aortic valve with well-defined systolic velocity envelope recorded at 100mm/s sweep speed. Measurements include pre-ejection period (PEP) and velocity-time integral (VTI).

- Continuous-wave Doppler used to obtain peak aortic flow velocity, with well-defined spectral envelope that includes aortic valve opening and closing clicks, recorded at 100mm/s sweep speed.

27.2. *Six-Minute Walk Test*

The six-minute walk test is a self-paced sub-maximal exercise test that has proven useful as an outcome measure for patients with congestive HF. Previous studies[18,19] have shown that

this test is well tolerated by individuals and is more closely related to the patient's daily activities than maximal exercise testing.

The walking test should be conducted in an enclosed corridor on a course approximately 100 feet (30.5 meters) long. The length should be marked in either feet or meters to allow easy measurement of the distance walked. The corridor should not be heavily transited and should be free of obstacles and distractions. Chairs should be placed at either end of the course so that subjects may rest when needed. If for any reason an individual physician does not recommend a subject to perform the six-minute walk then record the reason on the case report form.

Instructions
The subject is to take nothing by mouth except for clear liquids for at least two hours prior to the test. Prescribed medications should be taken as usual. Subjects should be advised not to smoke for at least two hours prior to exercise and to wear suitable footwear. Subjects are instructed to walk the marked course from end to end at their own pace, covering as much distance as possible in six-minutes. Subjects may slow down or stop to rest if necessary, but should be instructed to resume walking when they feel they are able to do so. The aim is that at the end of the test, the subject believes that they could not have walked any further in the six-minutes.

The following instructions are to be read to the subject verbatim:

"The purpose of this test is to determine how far you can walk in six-minutes. You will start here and go to the end of the hall, turn around, and walk back. After arriving back at the starting point, you will go back and forth again. Go back and forth as many times as you can in the six-minute period. If necessary, stop and rest and stay here until you can start again. However, the most important thing about the test is that you cover as much distance as possible during the six-minute period."

"I will let you know when each minute has passed. When I say 'STOP' after six-minutes, please stand right where you are.'

"Do you have any questions about the test?"

"Please explain to me what you are going to do."

"Are you ready?"

"Start when I say 'GO'."

Protocol

The walk test should be performed after completing the physical assessment of the subject. Subject safety is the highest priority, and the walk test should not be initiated if the physician, coordinator or subject has concerns regarding the subject's ability to perform the test. If the

subject begins the walking test, and concerns arise regarding their ability to continue, stop the test.

1. Stand the subject at the beginning of the course.
2. Simultaneously say 'GO" and start the watch. Observe the subject for the six-minute period while recording the successful completion of each length of the course. In order to standardize the test, **encouragement is not offered during the walk**. Do not otherwise speak to the subject except to answer questions he or she poses. Stop the test if the subject reports severe shortness of breath, muscular pain, dizziness, or angina symptoms.
3. At the end of the six-minute interval, tell the subject to "STOP".
4. Record the distance traveled to the nearest foot or meter. If the subject ceases participation prior to the end of the six-minute interval, record the distance covered (to the nearest foot or meter) and the subject's heart rate at the time he or she stops walking.

27.3. *Kansas City Cardiomyopathy Questionnaire (KCCQ)*

The KCCQ is a disease-specific instrument for monitoring the health status and quality of life of subjects with congestive heart failure. It includes a total of 23 items that assess quality of life in the following domains: physical function, symptom frequency and severity, symptom stability, self-efficacy and knowledge, social function, and overall quality of life. These domains can be combined into a functional status summary score (derived from the physical function and symptom scales) and an overall summary score which combines the physical function, symptom, social function and quality of life domains. The KCCQ has been validated in subjects with CHF using a variety of standard techniques (1), is highly reproducible among stable subjects. In cross-sectional analyses, the KCCQ has been shown to be highly correlated with event-free survival. Finally, the responsiveness of the KCCQ as assessed by the "responsiveness statistic" (ratio of mean change among subjects with improved CHF to the standard deviation among stable subjects) is superior to other measures including the SF-36, the Minnesota Living with Heart Failure Questionnaire, and NYHA classification (Spertus JA, personal communication).

<u>References</u>

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27.4. *SmartDelay Step-by-Step Guidance*

Follow these steps to perform SmartDelay test.

Step 1. Navigate to the SmartDelay Optimization screen

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

- From the *Settings – Normal Brady/CRT* screen, choose *SmartDelay Optimization*
- The nominal *Temporary Paced LRL* is set at 80 bpm. Set the *LRL* at 10 to 15 beats above the subject's intrinsic heart rate.
- Program LV Offset to 0ms.

Step 2. Run the SmartDelay test

- From the SmartDelay Optimization screen, choose *Start Test.* The test typically last up to 2.5 minutes.
- SmartDelay will recommend *AV delay* and *Pacing Chamber* (*BiV* or *LV Only*).
- If the SmartDelay test fails, the nominal value will be displayed.

Step 3. Program AV Delays and Pacing Chambers

- If following the recommended *AV Delay* and *Pacing Chamber* value determined by the SmartDelay, choose *Copy Suggested Settings* and push the program button to program the device.

Step 4. Record the required value

- Record in the follow-up eCRF both the SmartDelay recommendation and final programmed value for *AV Delay* and *Pacing Chamber*. Also record the final programmed *LV offset*.
- Once the *Pacing Chamber* is selected for a subject at Randomization Visit, the same *Pacing Chamber* must be used throughout the trial for that subject.