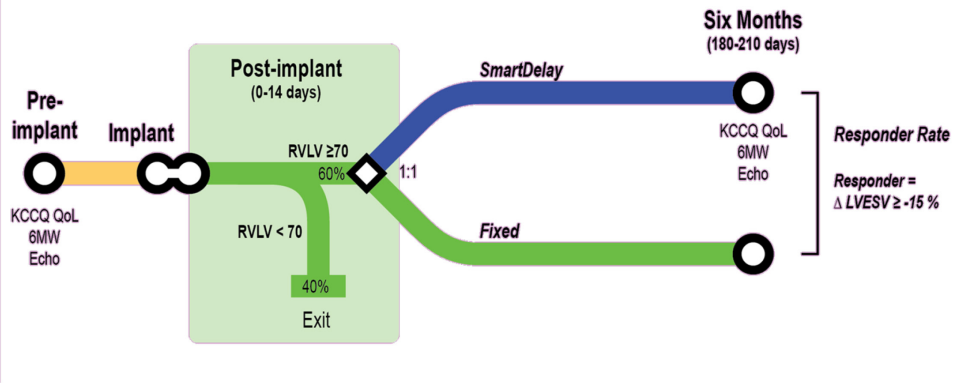
Strategic MAnagement to Optimize Response To Cardiac Resynchronization Therapy SMART CRT	

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.

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.

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:

- 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**);**

[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.

12.3.4. 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

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.

- 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

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.

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

- 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.

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

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

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.

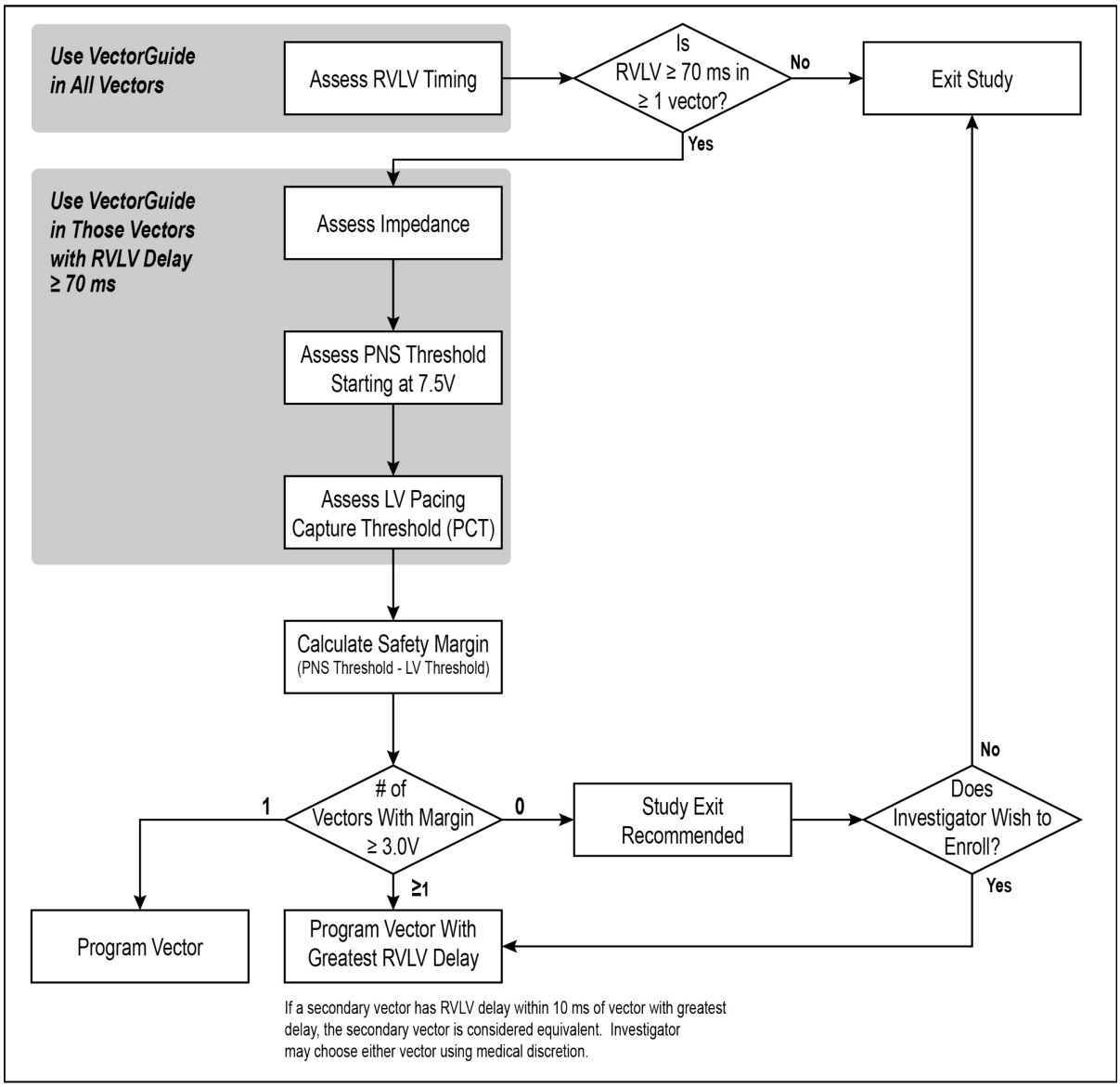


Figure 11-1: Post-Implant Assessment

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- **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]

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.

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

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:

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:

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

1. Higgins SL HJ, Niazi IK, et al. . Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol*. 2003;42:1454-1459.

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