The Longitudinal Surveillance Study of the 4-SITE Lead/Header System

(The LSS of 4-SITE Study)

CLINICAL PROTOCOL

[90884085]
[Approved: 02-Nov-2012]

Sponsored By

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Revision History

Section	Major Document Changes	Reason for Change
↓ *Changes Below to Ver. 1.0 Resulting in Ver. 2.0 (Released: 14-JUL-2010)* ↓		
Entire Document	Several grammatical changes, syntactical improvements, and spelling corrections; major reorganization; multiple stylistic and formatting modifications; many document clarifications; and additional wording, all throughout the entire document.	Correct errors and for document clarity.
2.1	Specified required subject data if enrollment was post implant.	Enrollment clarity.
2.3.3	Enumeration of enrollment exclusion criteria.	Enrollment clarity.
3.4	Statement that BSC will seek FDA approval to close the study.	Closure clarification.
3.5.1	Enumeration of subject data needed to be collected (enroll/implant).	Data specification.
3.5.4	Statement requiring follow-up visits to be "in clinic".	Conduct clarification.
4.1.1	Adverse events < 30 days post implant to be included in endpoint.	Endpoint clarification.
4.2.2	Specify additional study analyses to further evaluate subject pre-implant versus post-implant (*e.g.,* adverse event rates, missing data).	Additional planned data analyses.
Appendix A	Enhanced definition of terms in Glossary.	General clarification.
↓ *Changes Below to Ver. 2.0 Resulting in Ver. 3.0 (Released: 06-OCT-2010)* ↓		
Entire Document	Several grammatical changes, syntactical improvements, and spelling corrections; major reorganization; multiple stylistic and formatting modifications; many document clarifications; and additional wording, all throughout the entire document.	Correct errors and for document clarity.
Doc. Title	Document title was changed from a "Registry" to a "Study".	General clarification.
2.3.1, 2.3.2, 2.4, 3.1, 3.5	Delete Latitude®-enabled PG as an enrollment criterion and needed for a site to participate in the study throughout document.	Not necessary for study data collection.
3.3	An individual center may not enroll more than 20% of ceiling.	Clarify enrollment.
3.5.1.2	Delete entire sub-section regarding active chart review.	Not necessary.
3.5.3	Delete entre sub-section on Latitude® initial submission(s).	Not necessary.
4.1	Specification of primary endpoint characteristics and adverse events.	Specific clarification.
5.2 (Table)	Fully revised Reportable Adverse Events table – changed from 3 to 4 columns to describe what AE is related to (*e.g.,* PG, lead, header).	Enhanced AE list with relation by cause.

Section	Major Document Changes	Reason for Change
6.0	Specifies that site staff must perform an active subject chart review in search for adverse events before/during/after follow-up visits.	Clarification to actively seek/report AEs.
6.1 - 6.8	Specify follow-up visit case report forms (CRFs) for study.	General clarification.
↓ Changes Below to Ver. 3.0 Resulting in Ver. 4.0 (Released: 26-OCT-2010) ↓		
Entire Document	A few grammatical changes, spelling corrections, minor stylistic and formatting modifications, and minor re-wording throughout the entire document.	Correct errors and for document clarity.
4.1.1.4	Including adverse events in the evaluation of the primary endpoint requires a re-calculation of the sample size (1,700 → 1,780).	Adverse events included in endpoint.
4.2.2	Under "Additional Analyses", AEs will contribute to the endpoint analysis (AE rate and confidence bounds will be provided).	Adverse events included in endpoint.
Changes Below to FDA-Approved Ver. 4.0 Resulting in ↓ 90884085, Ver.AC (Released: 12-APR-2012) ↓		
Entire Document	Relocation of every section and all sub-sections that were included in the FDA approved version 4.0 of the LSS of 4-SITE Study protocol document into a new Boston Scientific global protocol template resulting in version AC, Clinical Document Management 90884085. This was undertaken in order to achieve standardization concerning the presentation of BSC clinical study protocol documents as well as the conduct of BSC clinical studies. A Table of Changes is available that lists all of the relocations made to version 4.0.	New BSC corporate, global protocol template for standardization of clinical documents and study conduct.
Entire Document	Addition of a few new sections and many new sub-sections regarding standardized language included and required in the new, BSC global protocol template. A Table of Changes is available that lists all of the additions made to version 4.0.	New BSC corporate, global protocol template for standardization of clinical documents and study conduct.
Entire Document	Many grammatical changes, syntactical improvements, and spelling corrections; major document reorganization; multiple stylistic and formatting modifications; multiple document clarifications; and additional wording, all throughout the entire document.	To correct errors and for overall document clarity, and to have the document adhere to the new BSC global protocol template.

Section	Major Document Changes	Reason for Change
Changes Below to BSC 90884085, Approved Ver. AB, Resulting in ↓ BSC 90884085, Ver. AC(Released: 02-Nov-2012) ↓		
Entire Document	A few grammatical changes, syntactical improvements, and spelling corrections; minor document additions; several stylistic and formatting modifications; several document clarifications; and additional wording, all throughout the entire document.	Correct errors and for document clarity.
Entire Document	Change of Pre-Discharge visit window from 3-72hrs to 0-3days.	To be consistent with data collected in CRF
Section 8, Protocol Synopsis	Clarification of requirements for study subjects enrolled pre-implant and post-implant.	Clarify requirements
Section 10	Updated section 10.2	Provide clarity on study exit
Section 11	Clarification of requirements for study subjects enrolled pre-implant and post-implant; addition of new section 11.6	Clarify requirements
Section 13	Re-numbering of sub-sections, re-ordering	Improved flow of section
Section 18	Update table 18.2-1	Per FDA request

2. Protocol Synopsis

Longitudinal Surveillance Study of the 4-SITE Lead/Header System (The LSS of 4-SITE Study)	
Study Objective	The objective of the LSS of 4-SITE Study is to prospectively determine the chronic complication-free rate of the 4-SITE Lead/Header System in order to verify its long-term functional integrity and to meet the FDA's requirements for a post approval clinical study.
Marketing Performance Expectation	Boston Scientific CRM 4-SITE leads and devices are designed to be compatible with the International Standard ISO/DIS 27186 for quadripolar connectors, but they are currently labeled only for use with a compatible Boston Scientific 4-SITE device.
Lead Test Device Models	The 4-SITE ENDOTAK RELIANCE® G, SG and non-Gore coated leads are integrated bipolar endocardial cardioversion/defibrillation, pace/sense, steroid-eluting, active/passive fixation leads with a 4-SITE terminal connector. The following BSC lead model numbers are the only leads that will be investigated in the LSS of 4-SITE Study: 0265, 0266, 0275, 0276, 0282, 0283, 0285, 0286, 0292, 0293, 0295 and 0296. The abbreviation for these leads is "4-SITE leads".
PG Test Devices & Accessories	The 4-SITE Lead/Header System includes use of Boston Scientific 4-SITE pulse generators (PGs) that are compatible with the 4-SITE ENDOTAK® RELIANCE family of cardiac leads. The abbreviation for these devices is "4-SITE PGs" and the models vary in different geographies. The only PGs that will be utilized in this study are those commercially available from Boston Scientific that incorporate headers which are compatible with a 4-SITE lead. There are several 4-SITE Lead Accessories: (1) Model 7001 – EZ-4™ Terminal Connector Tool; (2) Model 7006 – Lead Pulling Tip; (3) Model 7007 – Lead Cap Kit; and (4) Model 6888 – Lead Tunneler Kit.
Study Design *(continued on next page)*	The LSS of 4-SITE Study is a prospective, non-randomized, multi-center, global clinical investigation of subjects implanted with the 4-SITE Lead/Header System. The LSS of 4-SITE Study is designed to collect product performance information, any reportable adverse events and withdrawal data. Study subjects who are enrolled prior to implantation of the device system will have an enrollment visit during which informed

Longitudinal Surveillance Study of the 4-SITE Lead/Header System (The LSS of 4-SITE Study)	
	consent is obtained, followed by device system implantation (*i.e.,* day 0) and a pre-discharge visit (0 to 3 days) after implantation, during which a full device system interrogation will be performed. Study subjects who are enrolled after device system implantation (up to 14 days post implant) will undergo an enrollment visit during which informed consent is obtained, followed by information gathered from their implant. Regarding the pre-discharge visit (0 to 3 days post implant) for subjects enrolled post implant, information from a full device system interrogation is optional and will be provided to Boston Scientific only if it is available. All study subjects will then have another full device system evaluation performed at the investigational site facility at 30 (+/- 7) days post implant. Thereafter, subjects are required to participate in a follow-up visit (to be performed at the investigational site facility) for a full device system (*i.e.,* pulse generator and lead) evaluation at least once every six (6) months (+/- 30 days). A deviation must be reported if the evaluation is not done within the required follow-up visit window timeframe. Study subjects will be followed for at least five (5) years from the time of implant or until death, withdrawal from the study, or termination/closure of the study.
Planned Number of Subjects	At least 1,780 subjects will be enrolled and successfully implanted with the 4-SITE Lead/Header System.
Planned Number of Centers / Countries	The study will be conducted at a maximum of 200 global centers. A maximum of 125 will be located in the US, with the remainder in Canada, Europe, Asia Pacific, Australia and New Zealand.
Primary Endpoint	The primary LSS of 4-SITE Study endpoint is the "chronic 4-SITE Lead/Header System-related complication-free rate" for the five (5) year follow-up period after the index implantation.
Safety Parameters	The 4-SITE Lead/Header System will be evaluated based on the "chronic 4-SITE Lead/Header System-related complication-free rate" for the five (5) year follow-up period after the index implantation. The primary endpoint analysis will include confirmed chronic 4-SITE Lead/Header System-related complications that result in study subject permanent loss of therapy, invasive intervention, injury or death.

Longitudinal Surveillance Study of the 4-SITE Lead/Header System (The LSS of 4-SITE Study)	
Method of Enrolling Subjects in the Study	Investigators are expected to approach all potentially eligible study subjects who have been, or will be, implanted with the 4-SITE Lead/Header System at the investigational center for enrollment into this study until the enrollment ceiling is reached. All study subjects must meet all the inclusion criteria and none of the exclusion criteria. Investigational centers are encouraged to enroll subjects in the LSS of 4-SITE Study prior to the implantation of the 4-SITE Lead/Header System. However, a maximum of fifty percent (50%) of the study subjects may be enrolled up to 14 days post device system implant as long as the required data are available from/since the implant.
Follow-up Visit Schedule	The 4-SITE Lead/Header System will be evaluated based on the "chronic 4-SITE Lead/Header System-related complication-free rate" for the five (5) year follow-up period after the device system implant. Thus, the LSS of 4-SITE Study is designed to collect product performance information, any reportable adverse events and withdrawal data. Study subjects who are enrolled prior to implantation of the device system will have an enrollment visit during which informed consent is obtained, followed by device system implantation (*i.e.,* day 0) and a pre-discharge visit (0 to 3 days) after implantation, during which a full device system interrogation will be performed. Study subjects will then have another full device system evaluation performed at 30 (+/- 7) days post implant. Thereafter, subjects are required to participate in a follow-up visit for a full device system (*i.e.,* pulse generator and lead) evaluation at least once every six (6) months (+/- 30 days). Study subjects will be followed for at least five (5) years from the time of implant or until death, withdrawal from the study, or termination/closure of the study. Study subjects who are enrolled after device system implantation (up to 14 days post implant) will undergo an enrollment visit during which informed consent is obtained, followed by information gathered from their implant. Regarding the pre-discharge visit (0 to 3 days post implant) for subjects enrolled post implant, information from a full device system interrogation is optional and will be provided to Boston Scientific only if it is available.
Study Duration	The entire study will be conducted for approximately eight (8) years; three (3) years for enrollment and five (5) years for follow-up visits.
Key	Study subjects will be indicated for implantation of a 4-SITE lead/PG

Longitudinal Surveillance Study of the 4-SITE Lead/Header System (The LSS of 4-SITE Study)	
Inclusion Criteria	and must meet <u>all</u> of the following inclusion criteria: • Subject is medically indicated for implantation of an ICD/CRT-D device system in their respective geography; and • Has been or will be implanted with the 4-SITE Lead; and • Has been or will be implanted with a BSC commercially available 4-SITE compatible pulse generator; and • Plans to remain in long-term care of his/her enrolling Investigator for the full five (5) year follow-up visit schedule; and • Is willing and capable (or appropriate legal representative is willing and capable) of authorizing access to and use of health information as required by an institution's Institutional Review Board (IRB), Research Ethics Board (REB) or Independent Ethics Committee (IEC); and • Is willing and capable (or appropriate legal representative is willing and capable) of providing authorization for participation in the study.
Key Exclusion Criteria *(continued on next page)*	Study subjects who meet <u>any one</u> of the following criteria will be <u>excluded</u> from participation in this clinical study: • More than 14 calendar days have passed since device system implant; or • For subjects enrolled within 14 calendar days post implant, they are excluded if any of the required implant data listed below is missing; or o Right ventricle (RV) lead and pulse generator (PG) date of implant; o RV lead and PG model and serial numbers; o RV lead implant attempts/repositioning (whether more than one lead or lead position was attempted to achieve a successful lead implant); o RV lead electrical measurements for final lead placement (*i.e.,* sensing, pacing threshold and impedance); or o Documented assessment of adverse event status since implant.

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	• Subject is unable or unwilling to comply with the study protocol requirements; or • Subject is under the legal age for signing study consent in their country.
STATISTICAL METHODS	
Primary Statistical Hypothesis	**H_0**: The five (5) year chronic lead-related complication-free rate ≤ 92.5% **H_A**: The five (5) year chronic lead-related complication-free rate > 92.5% The null hypothesis (H_0) will be rejected if the lower one-sided 95% confidence bound for the chronic lead-related complication-free rate is greater than 92.5% (*i.e.,* H_A, the alternative hypothesis).
Statistical Test Method	A Kaplan-Meier analysis will be used to evaluate the "chronic 4-SITE Lead/Header System-related complication-free rate" for the five (5) year follow-up period after the index implantation. The primary endpoint analysis will include confirmed chronic 4-SITE Lead/Header System-related complications that result in study subject permanent loss of therapy, invasive intervention, injury or death.
Sample Size Parameters	

3. Table of Contents

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4. Introduction

Boston Scientific CRM intends to complete a Post-Approval/Condition of Approval study as required by the US 21 CFR 814.82(a)(2) and in accordance with the regulatory process in several other countries. Post-approval studies of implanted leads provide an opportunity to observe and assess patient outcomes and technology performance in a real-world setting. The goal of the study referred to in this document as the Longitudinal Surveillance Study of 4-SITE (i.e., LSS of 4-SITE) is to evaluate, document and report on the appropriate clinical performance, long term reliability and the functional integrity of the Boston Scientific ENDOTAK RELIANCE® 4-SITE™ Lead and the pulse generator 4-SITE Header (i.e., the 4-SITE Lead/Header System that incorporates four conductors into a quadpole DF-4 connection) that is found in market released ICD and CRT-D PGs. The study protocol takes into consideration existing guidance from the FDA on Post Approval Studies as well as applicable elements of Post Approval Studies currently being conducted.

4.1. *QUADRIPOLAR Technology*

The Boston Scientific 4-SITE Lead/Header System was designed and developed in parallel with, and with the intent of meeting, the approved quadripolar 'IS-4/DF-4' connector standard. The four-pole connector standard is designed to provide interchangeability between implantable leads and pulse generators from compliant manufacturers of these devices.

Given the intent of the connector standard to substantially supplant the IS-1/DF-1 versions of high voltage devices and leads, it is anticipated that this technology will be incorporated into other future medical device products. The 4-SITE technology will not affect current ICD and lead functionalities, such as sensing, pacing and defibrillation.

4.1.1. ISO Standard (ISO 27186) For Quadripolar Connectors and 4-SITE

The quadripolar connector standard was developed under the auspices of the Association for the Advancement of Medical Instrumentation (AAMI) CRM-Device Connector Task Force (Work Item PC 73). The International Standards Organization (ISO 27186) provides the dimensional and functional requirements for the new standard connector.

Boston Scientific CRM 4-SITE leads and devices are designed to be compatible with the International Standard ISO/DIS 27186 for quadripolar connectors, but they are currently labeled only for use with a compatible Boston Scientific 4-SITE device.

4.2. *Background*

Boston Scientific CRM (BSC) continuously strives to improve the performance of its products. To do so, a complete understanding of device performance is necessary through bench testing and real-world monitoring. While bench testing provides predictions as to

safety and performance, real-world monitoring aids in understanding *in vivo* failure mechanisms that require monitoring of large sample sizes over extended periods of time.

The LSS of 4-SITE Study will monitor the chronic performance of the 4-SITE Lead/Header System to assess time-dependent failure modes.

4.3. *Study Purpose*

The primary purpose of this study is to evaluate, document and report on the appropriate clinical performance, the long-term reliability and the functional integrity of the 4-SITE Lead/Header System. This 4-SITE Lead/Header System consists of a 4-SITE ENDOTAK® RELIANCE defibrillation lead connected to a 4-SITE Header (which is the only PG component under study) of a single or dual chamber (VR and DR) implantable cardioverter defibrillator (ICD) or a cardiac resynchronization therapy ICD (CRT-D) pulse generator. Additionally, system-related diagnostic information and implant data will be collected during the conduct of this study.

5. Description of Devices Under Surveillance

4-SITE leads and pulse generators with a 4-SITE Header as well as other components of the implanted system are included in this study. The initial products incorporating the 4-SITE quadripolar connector technology which are being evaluated are:

- Commercially available 4-SITE ENDOTAK® RELIANCE family of leads; and
- Commercially available 4-SITE Header (which in the only component under study of an implanted pulse generator).

5.1. *4-SITE ENDOTAK RELIANCE Leads*

The 4-SITE ENDOTAK RELIANCE® G, SG and non-Gore coated leads are integrated bipolar endocardial cardioversion/defibrillation, pace/sense, steroid-eluting, active/passive fixation leads with a 4-SITE terminal connector. The following BSC lead model numbers are the only leads that will be investigated in the LSS of 4-SITE Study: 0265, 0266, 0275, 0276, 0282, 0283, 0285, 0286, 0292, 0293, 0295 and 0296. The abbreviation for these leads is “4-SITE”.

5.2. *4-SITE Compatible Header*

Pulse generator (PG) models with headers compatible with the 4-SITE ENDOTAK® RELIANCE family of cardiac leads vary in different geographies. The only model PGs that will be utilized in this study are those commercially available from Boston Scientific that incorporate headers which are compatible with the 4-SITE lead. The general abbreviation for these devices is “4-SITE PGs”. The other functionalities of an implanted PG are not included within the scope of this study and will not be included in the endpoint analysis. Thus, adverse events, other than those directly related to the lead/header system, will be recorded separately, but excluded from the endpoint analysis.

5.3. *4-SITE Lead Accessories*

There are several 4-SITE Lead Accessories: (1) Model 7001 – EZ-4™ Terminal Connector Tool; (2) Model 7006 – Lead Pulling Tip; (3) Model 7007 – Lead Cap Kit; and (4) Model 6888 – Lead Tunneler Kit. The EZ-4 Terminal Connector Tool protects the lead terminal during the implant procedure, provides a safe and secure connection between pacing system analyzer (PSA) patient cables and the lead terminal, guides the stylet into the lead through the stylet funnel, and rotates the terminal pin to extend or retract the helix (for leads with a helix). The 4-SITE connector fits into one end of the Lead Pulling Tip which is a stainless steel bullet shaped slug that can be used subcutaneously to move the lead from the venous access site to the PG pocket if needed. The platinum cure silicon rubber Lead Cap is used to isolate and cover the quadripolar lead connector when it is not inserted in an ICD or CRT-D. The Lead Tunneler Kit includes a lead tunneling handle and two rods and tips for IS-1 and DF-1 connectors.

6. Study Objective

The objective of the LSS of 4-SITE Study is to prospectively determine the chronic complication-free rate of the 4-SITE Lead/Header System in order to verify its long-term functional integrity.

7. Study Endpoints

The 4-SITE Lead/Header System will be evaluated based on the "chronic 4-SITE Lead/Header System-related complication-free rate" for the five (5) year follow-up period after the index implantation. The primary endpoint analysis will include confirmed chronic 4-SITE Lead/Header System-related complications that result in study subject permanent loss of therapy, invasive intervention, injury or death. Investigator and study subject induced device dysfunctions (*e.g.,* Twiddler's Syndrome and inadvertent cutting of lead insulation during the implantation procedure) will be recorded, but will not be included in the study endpoint analysis.

8. Study Design

The LSS of 4-SITE Study is a prospective, non-randomized, multi-center, global clinical investigation of subjects implanted with the 4-SITE Lead/Header System. The LSS of 4-SITE Study is designed to collect product performance information, any reportable adverse events and withdrawal data. Study subjects who are enrolled prior to implantation of the device system will have an enrollment visit during which informed consent is obtained, followed by device system implantation (*i.e.,* day 0) and a pre-discharge visit (0 to 3 days) after implantation, during which a full device system interrogation will be performed. Study subjects who are enrolled after device system implantation (up to 14 days post implant) will undergo an enrollment visit during which informed consent is obtained, followed by information gathered from their implant. Regarding the pre-discharge visit (0 to 3 days post

implant) for subjects enrolled post implant, information from a full device system interrogation is optional and will be provided to Boston Scientific only if it is available.

All study subjects will then have another full device system evaluation performed at the investigational site facility at 30 (+/- 7) days post implant. Thereafter, subjects are required to participate in a follow-up visit (to be performed at the investigational site facility) for a full device system (*i.e.,* pulse generator and lead) evaluation at least once every six (6) months (+/- 30 days). A deviation must be reported if the evaluation is not done within the required follow-up visit window timeframe. Study subjects will be followed for at least five (5) years from the time of implant or until death, withdrawal from the study, or termination/closure of the study. The study design is presented below in Figure 8.1-1.

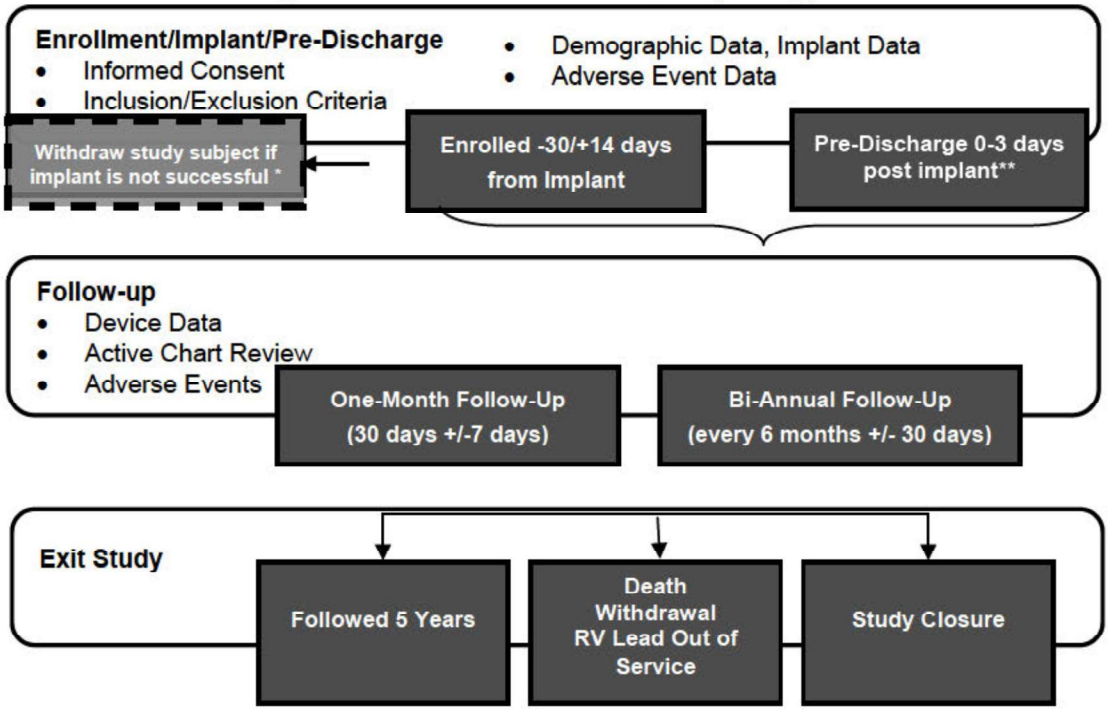
Subjects may be followed on the LATITUDE system (which may include weight scale and blood pressure sensors) from the time they are implanted. However, required LSS of 4-SITE Study follow-ups cannot be substituted with a LATITUDE remote follow-up.

8.1. *Scale and Duration*

The study will be conducted at a maximum of 200 global centers. A maximum of 125 will be located in the US, with the remainder in Canada, Europe, Asia Pacific, Australia and New Zealand. At least 1,780 subjects will be enrolled and successfully implanted with the 4-SITE Lead/Header System. However, any one individual center may not enroll more than twenty percent (20%) of this ceiling without prior approval from Boston Scientific CRM. Investigational centers may continue to enroll patients until the enrollment ceiling is reached or until notified by the Sponsor that study enrollment has been completed.

The entire study will be conducted for approximately eight (8) years; that is, three (3) years for enrollment and five (5) years for follow-up visits. All subjects enrolled in this study must be followed in strict accordance to the investigational plan unless BSC notifies the Investigator to the contrary or BSC has officially terminated/closed the study. Boston Scientific will seek FDA's concurrence to terminate/close the study if both parties determine the circumstances are appropriate for study termination/closure. Study subjects should expect data collection to last five (5) years from implantation. After a subject has completed five (5) years of follow-up, their participation in the study is complete.

Figure 8.1-1: LSS of 4-SITE Study Design



***NOTE**: Not applicable for subjects enrolled post implant.

****NOTE**: For subjects enrolled post implant, provide information if available.

8.2. *Anticipated Study Timeline*

The following is an anticipated schedule for conduct of the LSS of 4-SITE Study:

- **Study Initiation**: BSC intends to contact centers for participation in this study upon FDA approval of the protocol.
- **Center Participation Rate**: BSC anticipates that approximately five (5) centers per month will agree to participate in the study.
- **Center IRB Approval Rate**: BSC anticipates that approximately five (5) centers per month will obtain IRB approval within approximately 90 days of their agreement to participate.
- **Study Subject Enrollment Rate**: Participating centers are expected to enroll a minimum of one (1) subject per month.
- **Approximate Enrollment Completion**: Full study subject enrollment is anticipated to occur in approximately three (3) years after the first subject is enrolled.
- **Approximate Last Follow-up Visit**: The last study follow-up visit will be when the [redacted] subject has his/her five (5) year Post Implant Follow-up Visit or when five (5) years has passed since the final study implant, whichever occurs first.

- **Approximate Final Report Submission:** The final study report submission will occur within approximately six (6) months following the final study subject follow-up visit.

8.3. *Treatment Assignment*

The LSS of 4-SITE Study is a post-approval clinical study and as such study subjects will essentially include "all-comers" who meet enrollment criteria. Study Investigators are expected to approach all potentially eligible study subjects who have been (within 14 calendar days post-implant window), or will be, implanted with the 4-SITE Lead/Header System at the investigational center for enrollment into this study until the enrollment ceiling is reached.

8.4. *Justification for the Study Design*

The 4-SITE Lead/Header System will be evaluated based on the "chronic 4-SITE Lead/Header System-related complication-free rate" for the five (5) year follow-up period after the device system implant. Thus, the LSS of 4-SITE Study is designed to collect product performance information, any reportable adverse events and withdrawal data.

Study subjects who are enrolled prior to implantation of the device system will have an enrollment visit during which informed consent is obtained, followed by device system implantation (*i.e.,* day 0) and a pre-discharge visit (0 to 3 days) after implantation, during which a full device system interrogation will be performed. Study subjects will then have another full device system evaluation performed at 30 (+/- 7) days post implant. Thereafter, subjects are required to participate in a follow-up visit for a full device system (*i.e.,* pulse generator and lead) evaluation at least once every six (6) months (+/- 30 days). Study subjects will be followed for at least five (5) years from the time of implant or until death, withdrawal from the study, or termination/closure of the study.

Study subjects who are enrolled after device system implantation (up to 14 days post implant) will undergo an enrollment visit during which informed consent is obtained, followed by information gathered from their implant. Regarding the pre-discharge visit (0 to 3 days post implant) for subjects enrolled post implant, information from a full device system interrogation is optional and will be provided to Boston Scientific only if it is available. If such is not provided, the investigational site will not be considered to have deviated from this protocol.

9. Subject Selection

9.1. *Study Population and Eligibility*

Investigators are expected to approach all potentially eligible study subjects who have been (within 14 calendar days post implant window), or will be, implanted with the 4-SITE Lead/Header System at the investigational center for enrollment into this study until the

enrollment ceiling is reached. All study subjects must meet all the inclusion criteria and none of the exclusion criteria (listed hereinafter in Sub-sections 9.2 and 9.3, respectively). Investigational centers are encouraged to enroll subjects in the LSS of 4-SITE Study prior to the implantation of the 4-SITE Lead/Header System. However, a maximum of fifty percent (50%) of the study subjects may be enrolled up to 14 calendar days post device system implant as long as the required data are available from/since the implant. The required data for a post-implant enrollment must include the following implant information and data:

- Right ventricle (RV) lead and pulse generator (PG) date of implant;
- RV lead and PG model and serial numbers;
- RV lead implant attempts/repositioning (whether more than one lead or lead position was attempted to achieve a successful lead implant);
- RV lead electrical measurements for final lead configuration (*i.e.,* sensing, pacing threshold and impedance values from the implanted PG device);
- Assessment and documentation of the absence/presence of adverse events by reviewing available patient medical records including, but not limited to, the following:
    - Progress notes;
    - Laboratory reports;
    - Operations reports; and
    - Discharge summary.

For study subjects enrolled after device system implant (within 14 calendar days), the required One-Month Post-Implant Follow-up Visit is still required. Study subjects will then continue to have a complete device system interrogation at least once every six (6) months from the date of their device system implant for a five (5) year term. A deviation must be reported if a study subject is not seen within the follow-up visit window (*i.e.,* 6 months +/- 30 days).

Participation in another clinical study and/or registry is generally permitted for subjects enrolled in the LSS of 4-SITE Study unless its requirements conflict with the conduct of the LSS of 4-SITE Study. Enrollment in any concurrent clinical study and/or registry requires prior written approval from Boston Scientific CRM. However, governmental mandated clinical registries do not require prior approval.

9.2. *Inclusion Criteria*

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

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	CI-1. Subject is medically indicated for implantation of an ICD/CRT-D device system in their respective geography; and CI-2. Has been or will be implanted with the 4-SITE Lead; and CI-3. Has been or will be implanted with a BSC commercially available 4-SITE compatible pulse generator; and CI-4. Plans to remain in the long-term care of his/her enrolling Investigator for the full five (5) year follow-up visit schedule; and CI-5. Is willing and capable (or appropriate legal representative is willing and capable) of authorizing access to and use of health information as required by an institution's Institutional Review Board (IRB), Research ethics Board (REB) or Ethics Committee (EC); and CI-6. Is willing and capable (or appropriate legal representative is willing and capable) of providing authorization/consent for participation in the study.

9.3. *Exclusion Criteria*

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

Table 9.3-1: Exclusion Criteria

Clinical Exclusion Criteria	CE-1. More than 14 calendar days have passed since device system implant; or CE-2. For subjects enrolled within 14 calendar days post implant, they are excluded if any of the required implant data listed below is missing; or • Right ventricle (RV) lead and pulse generator (PG) date of implant; • RV lead and PG model and serial numbers; • RV lead implant attempts/repositioning (whether more than one lead or lead position was attempted to achieve a successful lead implant); • RV lead electrical measurements for final lead configuration (*i.e.,* sensing, pacing threshold and impedance); or • Documented assessment of adverse event status since implant. CE-3. Subject is unable or unwilling to comply with the study protocol requirements; or CE-4. Subject is under the legal age for signing study consent in accordance with state or national law.

10. Subject Accountability

10.1. *Point of Enrollment*

At enrollment, the Informed Consent form must be completed and signed/dated by the subject (or signed/dated by a legally authorized representative). Subjects who meet all of the inclusion criteria and none of the exclusion criteria, and who have signed an Informed Consent form, are considered enrolled in the study and will count toward the study enrollment ceiling. Patients may be consented only one time for this protocol and can only be enrolled with their initial implant of a 4-SITE lead. Even if an enrolled study subject is subsequently determined to be an ***attempt*** or ***intent*** with respect to the implantation of a device system (see Sub-section 11.5.2), he/she will be counted toward the study enrollment ceiling. ***Attempt*** subjects shall be withdrawn from participation in the study after collection of any potential 4-SITE Lead/Header System related adverse events. The original Informed Consent form and any screening documentation for ***intent*** subjects should be maintained in the center's administrative study files.

10.2. *Point of Study Exit*

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. Study subjects can exit the study for the following reasons: study completion (subject completed 5 years of follow-up), death, or withdrawal. If a subject withdraws from the clinical investigation, the reason(s) shall be reported.

Reasons for withdrawal include, but are not limited to: adverse event, Investigator discretion, Lost to follow-up, RV lead no longer in service, transplant or removal of target organ, or subject withdrew from participation in study. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. All applicable case report forms up to the point of subject withdrawal and an "End of Study" form must be completed. Subjects who are "lost-to-follow-up" should have documented attempts to contact them prior to completion of the "End of Study" form.

Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. All open adverse events should be closed or documented as chronic. Data collected up to the point of study subject withdrawal may be used.

10.3. *Subject Status and Classification*

Final study subject status is defined as being one of the following: an ***implant*** subject, an ***attempt*** subject or an ***intent*** subject. The detailed definitions of these classifications are presented within Sub-section 11.2.2.

10.4. *Enrollment Controls*

Investigational centers will be notified to cease enrolling patients for this study when the enrollment target is reached, or at the Sponsor's discretion in consultation with the FDA. This notification is expected to happen when at least 1,780 study subjects have been enrolled and successfully implanted with the 4-SITE Lead/Header System. In order to ensure geographical dispersion of investigational sites, individual study sites may not enroll more than twenty percent (20%) of the anticipated enrollment ceiling of 1,780 subjects (*i.e.,* not more than 356 subjects at any single site). For the study overall, no more than 50% of patients will be enrolled post-implant.

11. Study Methods/Procedures

11.1. *Enrollment in Study*

11.1.1. Subjects Consented Prior to Device System Implant

At the Enrollment Visit, the Informed Consent form must first be completed and signed/dated by the subject (or signed/dated by a legally authorized representative). Subjects who meet all of the inclusion criteria and none of the exclusion criteria as presented herein, and who have signed an Informed Consent form, are considered enrolled in the study and will count toward the enrollment ceiling even if their study eligibility is subsequently determined to be in error. Study subject demographics (such as age, race, gender, height and weight), where permitted by regulatory authorities, must be collected during this in office visit and should be recorded electronically using the appropriate case report forms provided by the study Sponsor. Source documentation of the visit and the consenting process must be maintained by the investigational site/center personnel in the study files. Where copies of original source documents are retained, these shall be signed and dated by a member of the investigational center team as confirmation that they are a true reproduction of the original source documents.

Table 11.1-1 below presents an overall summary of study procedures, timelines for follow-up visits and required data collection. A protocol deviation must be reported if the follow-up visit is not completed within the "allowed window" of the scheduled date.

Table 11.11-1: Study Procedures, Timelines and Data Collection

Study Procedure / Follow-Up Visit	Informed Consent	Demographics & Medical History	Device Implantation Information	Device System Interrogation	Adverse Events Reporting	Medical Chart & Records Review
ENROLLMENT	X	X	---	---	---	---
Device Implant (Day 0)	---	---	X	X	X	---
* Pre-Discharge (0 to 3 days)	---	---	---	X	X	---
30-Day Visit (30 days ± 7)	---	---	---	X	X	X
6-Mo. Visit (180 days ± 30)	---	---	---	X	X	X
12-Mo. Visit (365 days ± 30)	---	---	---	X	X	X
18-Mo. Visit (545 days ± 30)	---	---	---	X	X	X
24-Mo. Visit (730 days ± 30)	---	---	---	X	X	X
30-Mo. Visit (910 days ± 30)	---	---	---	X	X	X

Study Procedure / Follow-Up Visit	Informed Consent	Demographics & Medical History	Device Implantation Information	Device System Interrogation	Adverse Events Reporting	Medical Chart & Records Review
36-Mo. Visit (1,095 days ± 30)	---	---	---	X	X	X
42-Mo. Visit (1,275 days ± 30)	---	---	---	X	X	X
48-Mo. Visit (1,460 days ± 30)	---	---	---	X	X	X
54-Mo. Visit (1,640 days ± 30)	---	---	---	X	X	X
60-Mo. Visit (1,825 days ± 30)	---	---	---	X	X	X
UNSCHEDULED VISIT	---	---	---	X	X	X

* **NOTE**: For subjects enrolled post implant, provide information if available..

11.1.2. Subjects Consented Within 14 Calendar Days After Device Implant

Regarding subjects who are enrolled within 14 calendar days post implant, the Informed Consent form must first be completed and signed/dated by the subject (or signed/dated by a legally authorized representative). Subjects who meet all of the inclusion criteria and none of the exclusion criteria as presented herein, and who have signed an Informed Consent form, are considered enrolled in the study and will count toward the enrollment ceiling even if their study eligibility is subsequently determined to be in error. Study subject demographics (such as age, race, gender, height and weight), where permitted by regulatory authorities, must be collected during this in office visit and should be recorded electronically using the appropriate case report forms provided by the study Sponsor.

Information for the Enrollment Visit must be collected from the patient's medical records and visits during the period from implant until consent/enrollment in the study. Implant data is required for subjects enrolled post-implant, and must be collected from the study subject's medical records. Pre-discharge data (between 0-3 days after implant), if available, should be recorded using data collected from the study subject's medical records.

Source documentation regarding the Enrollment Visit and the consenting process must be maintained by the investigational site/center personnel in the study files. Where copies of original source documents are retained, these shall be signed and dated by a member of the investigational center team as confirmation that they are a true reproduction of the original source documents.

11.2. *Device System Implantation Visit*

The Device System Implantation Visit is considered as day zero (0) for all visits going forward. The following information must be collected at device system implant or during the post-implant enrollment visit:

- Right ventricle (RV) lead and pulse generator (PG) date of implant;
- RV lead and PG serial numbers;
- RV lead implant attempts/repositioning (*i.e.,* whether more than one lead or lead position was attempted to achieve a successful lead implant);
- RV lead electrical measurements for final lead placement and configuration (*i.e.,* sensing, pacing threshold and impedance values from the implanted PG device);
- Documented assessment of adverse event status since implant;
- Documented assessment of device deficiency; and
- Defibrillation test information (if available).

In addition, the following study subject data should be collected at implant:

- Medical history (*e.g.,* arrhythmia history, selected prescribed medications, non-cardiac disease history, etc.);
- PG implant pocket location (*i.e.,* right/left side as well as sub-pectoral or subcutaneous location);
- Lead implant technique (*e.g.,* subclavian stick, axillary stick or cut-down); and
- Handling experience using the Terminal Tool (per labeling) during pacing system analyzer (PSA) testing.

Study subject data collected during the Device System Implantation Visit must be promptly entered into the BSC electronic data capture system.

Additionally, at any point during the study, information regarding any newly implanted leads (RA or LV) or pulse generators should be recorded. Also, at device system revision, check for lead fixation in the header, check for set screw tightness, and check for incomplete lead insertion.

11.2.1. 4-SITE Lead/Header Connection Integrity

Lead and Pulse Generator Physician Technical Manuals describe lead impedance testing protocols that may be performed at the discretion of the Investigator. Upon device system implant, a low-energy impedance test may be performed to verify the 4-SITE Lead/Header connection integrity. A commanded low-energy impedance test is a more robust tool for identifying and verifying a potential open shocking lead condition. Also, Investigators, at their discretion, may perform a high- or maximum-energy ventricular tachyarrhythmia conversion test in accordance with RELIANCE 4-SITE Lead labeling. A high- or maximum-energy shock is a more robust test for identifying and verifying a potential shorted shocking lead condition and assessing sensing of ventricular fibrillation (VF). If defibrillation testing

is performed, then the data should be recorded as part of the general measurements regarding the just implanted device system.

11.2.2. Additional Implant Data Collection and Final Subject Status

The following information should be collected and recorded during enrollment, or during implant, as applicable:

- Accessories used for implanting each successfully implanted lead (*e.g.,* soft/firm stylets, 4-SITE Terminal Tool, Pacing System Analyzer and PSA cables, transvalvular insertion tool, etc.);
- Attempted devices (pulse generators or leads);
- Right ventricular lead location; and
- The Investigator's handling experience and ease of use of the 4-SITE System and its accessories compared to previous experience handling of DF-1 right ventricle leads.

Final study subject status is defined as being one of the following: an ***implant***, an ***attempt*** or an ***intent***. The ***implant*** subject status definition refers to a study subject who is successfully implanted with the 4-SITE Lead/Header System as specified in the protocol. The ***attempt*** subject status definition refers to a study subject who underwent anesthesia in preparation for an implant, but who was not implanted with the 4-SITE Lead/Header System. ***Attempt*** subjects are to be withdrawn from participation in the study after collection of any potential 4-SITE Lead/Header System related adverse events. The ***intent*** subject status definition refers to a study subject who has been enrolled in the study, but who is not prepped for surgery (*i.e.,* no anesthesia) and who does not undergo an implant procedure. The original Informed Consent form and any screening documentation for ***intent*** subjects should be maintained in the site's/center's administrative study files.

11.2.3. Source Documents

Source documentation (see Table 11.2.3-1 below) must be maintained by the center in the study files. Where copies of original source documents as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigational center team as confirmation that they are a true reproduction of the original source documents.

Table 11.2-1: Disposition of Required Source Documentation

SOURCE DOCUMENTATION REQUIREMENT	DISPOSITION of SOURCE DOCUMENTION
Documentation Regarding the Informed Consent Process	Retain at Investigational Site/Center

Documentation Regarding: • Study Subject Demographics • Cardiovascular Medication • Arrhythmia History • Cardiac Disease History • Device System Implant Procedure	Retain at Investigational Site/Center
Printout of Implanted Pulse Generator Measurements and Threshold Results	Retain at Investigational Site/Center
In the Event of Study Subject Death: • Death Narrative • Pertinent Medical Record Information • Copy of Death Certificate • Copy of Autopsy Report	Submit One (1) Copy of All Documents to Boston Scientific CRM – and – Retain a Copy of All Documents in the Study File at Investigational Site/Center

11.3. *Pre-Discharge Visit*

Study subject pre-discharge data is usually collected between 0 to 3 days post device system implant. A full device system evaluation must be performed during this visit as well as a check for adverse events since implant. The following study subject data must be collected during the Pre-Discharge Visit for all pre-implant enrolled subjects and, if available, for all post-implant enrolled subjects:

- Measurements regarding the 4-SITE Lead/Header System; and, for the RV lead, the following:
    - Amplitude (sensing);
    - Impedance (shock and pacing); and
    - Voltage pacing threshold (record pulse width used).
- 4-SITE Lead/Header System-related Adverse Events.
- The presence/absence of adverse events identified during active study subject medical record review.

    Upon device interrogation, if observed values show evidence of suspected lead/device malfunction, a chest radiograph(s) to determine lead position is strongly recommended, but at the discretion of the Investigator. If noise is detected in the intracardiac electrogram (EGM) storage, techniques such as pocket manipulation, arm maneuvers, valsalva maneuver, coughing and/or exploration of potential sources of external magnetic interference (EMI) may be used to detect system abnormalities, at the discretion of the Investigator.

Source documentation must be maintained by the center personnel in the study files. Where copies of original source documents as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site/center team as confirmation that they are a true reproduction of the original source documents. Any prolonged hospitalization should be considered as a serious adverse event and reported appropriately. Prolonged hospitalization for anticoagulation will be adjudicated by the Clinical Events Committee. Study subject data collected during the Pre-Discharge Visit must be promptly entered into the BSC electronic data capture system.

11.4. *One-Month Follow-up Visit*

At thirty (30) +/- 7 days following device system implant, study subjects must participate in an in office One-Month Follow-up Visit. A full device system evaluation must be performed during this visit as well as a check for adverse events since implant. The following study subject data must be collected during the One-Month Follow-up Visit:

- Measurements regarding the 4-SITE Lead/Header System; and, for the RV lead, the following:
    - Amplitude (sensing);
    - Impedance (shock and pacing); and
    - Voltage pacing threshold (record pulse width used).
- 4-SITE Lead/Header System-related Adverse Events; and
- The presence/absence of adverse events identified during active study subject medical record review.

    Upon device interrogation, if observed values show evidence of suspected lead/device malfunction, a chest radiograph(s) to determine lead position is strongly recommended, but at the discretion of the Investigator. If noise is detected in the intracardiac electrogram (EGM) storage, techniques such as pocket manipulation, arm maneuvers, valsalva maneuver, coughing and/or exploration of potential sources of external magnetic interference (EMI) may be used to detect system abnormalities, at the discretion of the Investigator.

Study subject data collected during the One-Month Follow-up Visit must be promptly entered into the BSC electronic data capture system. Source documentation must be maintained by the center in the study files. Where copies of original source documents as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site/center team with a statement that they are a true reproduction of the original source documents.

11.5. *Bi-Annual Study Subject Follow-up Visits*

The study subject's implanted device system must be evaluated on a regular basis at the investigational site's facility. An implanted device system interrogation must take place bi-annually (*i.e.,* every six months +/- 30 days) following the device system implant for a period

of five (5) years. All study follow-up visit dates are based on days from the device system implant. The dates for the follow-up visits are listed in Table 11-1 above.

A full device system evaluation must be performed during this visit at the investigational site's facility as well as a check for any adverse events occurring since implant. The following study subject data must be collected during all Bi-Annual Study Subject Follow-up Visits:

- Measurements regarding the 4-SITE Lead/Header System; and
  - Amplitude (sensing);
  - Impedance (shock and pacing);
  - Voltage pacing threshold (record pulse width used); and
  - 4-SITE Lead/Header System-related adverse events.
- The presence/absence of adverse events identified during active study subject medical record review.

Follow-up visit data must be promptly entered into the BSC electronic data capture system. Source documentation must be maintained by the investigational site/center personnel in the study files. Where copies of original source documents as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site/center team as confirmation that they are a true reproduction of the original source documents.

11.5.1. Missed Bi-Annual Study Subject Follow-Up Visits

In the event that a Bi-Annual Study Subject Follow-Up Visit is missed, investigational site/center personnel are expected to make every effort to contact the study subject (*e.g.,* via certified mail, telephone calls, Email messages, etc.) in order to determine the subject's status. Study subjects are considered "lost-to-follow-up" after three (3) documented contact attempts and should be immediately withdrawn from the study if investigational site/center personnel have not had any contact with a study subject after three attempts. The date of the study subject's last in-clinic follow-up visit (scheduled or unscheduled) will be used as the date that he/she was "lost-to-follow-up" and therefore ended their participation in the study. Study subjects will be withdrawn at any time if they express their desire to cease their participation in the study.

11.6. *Unscheduled Follow-Up Visits*

Unscheduled Follow-up Visits occurring between regularly scheduled study visits are intended to collect information on adverse events, or in response to a sponsor-requested visit.

NOTE: For visits where device reprogramming is completed, or other regular interim visits not required by the study (i.e. optimization of programmed settings); this information is not required to be reported on an Unscheduled Follow-Up Form.

11.7. *Study Completion*

Study subjects should expect data collection to last five (5) years from the index device system implant or if BSC has officially terminated/closed the study. After a subject has completed his/her last scheduled bi-annual visit (at five years post implant) or the study has been terminated, their participation in the study is complete. Subsequent to the completion of this last visit and the recording of any adverse events, the subject will no longer be considered enrolled in the study and all parameters regarding the implanted device system may be managed at the discretion of a qualified investigator. An "End of Study Form" is required to be completed, whenever a study subject exits the study (regardless of timing).

12. Statistical Considerations

12.1. *Primary Study Endpoint*

The primary LSS of 4-SITE Study endpoint is the "chronic 4-SITE Lead/Header System-related complication-free rate".

12.1.1. Description and Rationale for Endpoint Selection

The 4-SITE Lead/Header System will be evaluated based on the "chronic 4-SITE Lead/Header System-related complication-free rate" for the five (5) year follow-up period after the index implantation. The primary endpoint analysis will include confirmed 4-SITE Lead/Header System-related complications that result in permanent loss of therapy, invasive intervention, injury or death.

12.1.2. Endpoint-related Adverse Events

Inclusion of adverse events in the endpoint is based on the adjudication of the adverse event by the independent Clinical Events Committee (CEC), and on the time of occurrence of the adverse event.

The following adverse events will all be reported, and those adverse events that result in permanent loss of therapy, invasive intervention, injury or death will be included in the endpoint analysis regardless of cause or time of occurrence:

- Pneumothorax;
- Perforation; and
- Cardiac tamponade.

The following adverse events, occurring at 30 days or less from lead-related surgery, will all be reported, and those adverse events that result in permanent loss of therapy, invasive intervention, injury or death and that are also determined to be attributable to a structural lead/header failure by the Clinical Events Committee (CEC) will included in the endpoint analysis:

- Right ventricular lead dislodgment;

- Extra-cardiac (diaphragmatic/pectoral) stimulation caused by the RV lead;
- Inability to place or position the right ventricle (RV) lead;
- Implant procedure-related complications such as arrhythmias and hematoma formations;
- Infection;
- In-patient damage to RV lead (*e.g.,* accidental cut to lead body during pocket revision, device replacement, etc.);
- Other procedure-related adverse events identified at implantation;
- Lead under-insertion identified at implant; and
- Loose header set screws identified at implant.

The following adverse events, occurring more than 30 days after lead-related surgery, will all be reported, and those adverse events that result in permanent loss of therapy, invasive intervention, injury or death will be included in the endpoint analysis for the 4-SITE Lead/Header System:

- Right ventricular lead dislodgment;
- Extra-cardiac (diaphragmatic/pectoral) stimulation caused by the RV lead;
- Low/High impedance values; and
- High right ventricle (RV) pacing threshold with sudden change (>2 volts), intermittent RV capture and non-capture of the RV lead.

The following adverse events, occurring more than 30 days after lead-related surgery, will all be reported, and those adverse events that result in permanent loss of therapy, invasive intervention, injury or death and that are determined to be attributable to a structural 4-SITE Lead/Header System failure by the Clinical Events Committee will be included in the endpoint analysis. Examples of events which will be sent to the Clinical Events Committee are listed below. Many of these may be adjudicated by the Clinical Events Committee to be unrelated to malfunction of the 4-SITE Lead/Header System,

- Lead/Header connection-related adverse events in systems not tested using a high- or maximum-energy ventricular tachyarrhythmia conversion test;
- RV lead-related thrombosis;
- Twiddler's syndrome (*i.e.,* permanent malfunction of a pacemaker due to the patient's manipulation of the pulse generator in the implant pocket) leading to RV lead dislodgment;
- Infection;
- Atrial lead, CRT lead or generator adverse events requiring additional interventions;
- RV lead-related hospitalizations;
- Death;
- Lead revisions to optimize therapy;

- Exit block or failure to capture (*i.e.,* delay or failure of an impulse to be conducted from a specific region to surrounding tissues);
- Physiologic over-sensing or under-sensing;
- Non-physiologic over-sensing from an unidentifiable cause;
- Lead under-insertion identified at implant; and
- Loose header set screws identified at implant.

Regardless of endpoint inclusion, all reportable adverse events will be collected and reported during the conduct of the LSS of 4-SITE Study. For further explanation, see the definition of common adverse events presented in the Potential Risk and Benefits Section 18.

12.1.3. Hypotheses

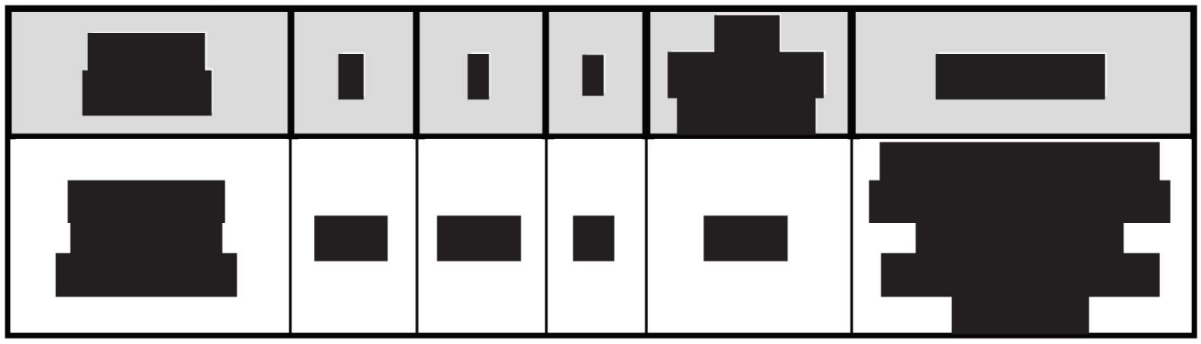
H_0: The five (5) year chronic lead-related complication-free rate $\leq$ 92.5%

H_A: The five (5) year chronic lead-related complication-free rate > 92.5%

The null hypothesis (H_0) will be rejected if the lower one-sided 95% confidence bound for the chronic lead-related complication-free rate is greater than 92.5% (*i.e.,* H_A, the alternative hypothesis).

12.1.4. Study Subject Sample Size

[redacted]



[redacted]

12.2. *Number of Subjects per Investigative Site*

In order to ensure geographical dispersion of investigational sites, individual study sites may not enroll more than twenty percent (20%) of the anticipated enrollment ceiling of 1,780 subjects (*i.e.,* not more than 356 subjects at any single site). It is anticipated that the majority of investigational centers conducting the LSS of 4-SITE Study will enroll about one (1) subject per month.

12.3. *Data Analyses*

12.3.1. Primary Study Endpoint Analysis

Regarding the 4-SITE Lead and the compatible header in a PG, the primary study endpoint is the evaluation of the proportion of subjects without a chronic 4-SITE Lead/Header-related complication within five (5) years post-implant period. When the final study subject reaches five (5) years of follow-up, the primary analysis will be performed based on the Kaplan-Meier method for the estimation of the five (5) year chronic lead-related complication-free rate, including the lower one-sided 95% confidence interval. The censoring mechanism of the Kaplan-Meier analysis incorporates all available data on study subjects, including those that withdrew or were lost-to-follow-up.

The Kaplan-Meier analysis will begin at the time of implant for each study subject. All subjects who are successfully implanted with the 4-SITE Lead/Header System will be included in the analysis. The endpoint adverse events are defined as complications meeting the criteria described in Sub-section 12.1.2 above. The determination for inclusion of adverse events in the endpoint analysis will be made by an independent Clinical Events Committee (see Sub-section 22.1 hereinafter). Additionally, since this study is focused on chronic 4-SITE Lead/Header System performance, except as noted in Sub-section 12.1.2

above, acute adverse events associated with attempted lead implants will not be included in this analysis. These events fall within the 30 days of an invasive cardiac surgery and do not meet the criteria outlined in Sub-section 12.1.2 above.

12.3.2. Additional Analyses/Changes to Planned Analyses

In addition to the primary endpoint analysis, the adverse events contributing to the endpoint will be analyzed. The individual adverse event rates and 95% upper confidence bounds will be provided.

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

12.3.3. Subgroup Analyses

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

- Sex (Female vs. Male);
- Geography (International vs. United States);
- Age (< 65 years vs. ≥ 65 years); and
- Enrollment Timing (Pre-Implant versus Post-implant).

The baseline covariate will be added to a univariate logistic regression model and a test for significance at the 5% level will be performed. For each baseline covariate in which a significant difference exists between subgroups, the results for each subgroup will be presented separately.

12.3.4. Center Pooling Analysis

Center-to-center heterogeneity will be assessed for the primary endpoint by performing a random effects logistic regression analysis. Centers will be deemed to be heterogeneous if the variance of the random center effect is found to significantly differ from zero. A significance level of 10% will be used for this test.

12.3.5. Trend Analysis

BSC trend management procedures provide criteria for initiating trend analysis and will be utilized in conjunction with data collected in this study. Device performance information is received from many sources through various channels including clinical studies and device registries. BSC also monitors product performance information from many sources including suppliers, testing, manufacturing, clinicians, physicians, patients and field-based personnel to identify opportunities for product improvement. When a device is returned to BSC,

laboratory technicians and engineers assess overall device function and perform analyses using specific tests related to the clinical observation(s). Test results are compared to the original manufacturing records and design intent. Clinical observations are added to laboratory findings to help determine the root cause of the clinical observation(s). Each discrete event is then compared to other similar-appearing events. If a pattern is detected, actions are taken to identify a common root cause, and device enhancements that are focused on improving product reliability may be implemented. Improvements, when implemented, may include design changes to the existing products or to subsequent generations, manufacturing and supplier process modifications, software updates, educational communications and/or labeling changes, for example.

12.3.6. Progress Reporting Analysis

Progress reports to the FDA will be provided by the Sponsor every six (6) months. These reports will generally include:

- A summary of enrollment and lead status;
- A Kaplan-Meier plot of time to first endpoint-defined chronic 4-SITE Lead/Header System-related complication;
- A summary of trend analysis; and
- A summary of RV lead and header-related adverse events.

12.3.7. Product Performance Reporting

In order to share information learned from this study with practitioners on an on-going basis, data will be published in a BSC Product Performance Report. However, this will occur no sooner than one (1) year post study initiation when at least 200 subjects are participating in the study and who have implanted with the 4-SITE Lead/Header System and when at least 50 subjects having reached a reporting interval in the United States.

13. Data Management

13.1. *Data Collection, Processing and Review*

Study subject data will be recorded in a limited access secure electronic data capture (EDC) system provided by the Sponsor.

The clinical database will reside on a production server hosted by Medidata Solutions (New York, NY). All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) or its representative. The associated RAVE software application 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 on a regular basis.

For the LSS of 4-SITE Study, all data will be entered into electronic case report forms (eCRFs) that are located on BSC's study electronic data capture system (EDC). Study subjects' medical records/charts serve as source documentation for electronically entered data.

Center personnel are required to conduct an active study subject review of medical records/charts (*e.g.,* involving implantation, subject discharge and any subsequent in office follow-up visits) to ensure the capture of all possible adverse events during and between study subject follow-up visits. Following thorough review of each study subject's medical records/charts, site/center research personnel are asked whether adverse events were identified by answering a designated questionnaire on the corresponding case report form. Site/center research personnel verify whether any of the reportable adverse events as described in Sub-section 12.1.2 and Section 18 have occurred.

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. Investigational site staff will be responsible for resolving all queries in the database.

13.2. *Data Retention*

The Investigator will maintain, at the investigative site, in original format 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 two (2) years after the last approval of a marketing application or until at least two (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 local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

13.3. *Case Report Forms*

13.3.1. Enrollment Case Report Form

An Enrollment Case Report Form is completed when a study subject has completed their enrollment visit and all required data collection is complete**.**

13.3.2. Implant Case Report Form

An Implant Case Report Form is completed at the device system implant of a study subject or at post-implant enrollment, as applicable. All required data collection must be completed.

13.3.3. Pre-Discharge Case Report Form

A Pre-Discharge Case Report Form will be completed to record all lead measurements collected at the time of hospital/center discharge. For study subjects enrolled post-implant, this data is requested, but not required. An active medical records/charts review will be conducted to identify all adverse events, as defined in Sub-section 12.1.2 and Section 18.

13.3.4. One-Month Follow-up Case Report Form

A One-Month Follow-up Case Report Form will be completed to record all lead measurements collected during this study subject follow-up visit. An active medical records/charts review will be conducted to identify all adverse events, as defined in Sub-section 12.1.2 and Section 18.

13.3.5. Bi-Annual Follow-up Case Report Form

The Bi-Annual Follow-up Case Report Form will be completed every six (6) months (+/- 30 days) to record all lead measurements collected during this study subject follow-up visit. These forms are labeled by visit within the EDC system (*e.g.,* 6-Month Follow-up, 12-Month Follow-up, etc.). An active medical records/charts review will be conducted to identify all adverse events, as defined in Sub-section 12.1.2 and Section 18.

13.3.6. Unscheduled Visit Case Report Form

In the event of an unscheduled study subject visit, an Unscheduled Visit Case Report Form will be completed to provide the reason for the visit and record any adverse events, as defined in Sub-section 12.1.2 and Section 18.

13.3.7. Adverse Event Case Report Form

Upon discovery of an adverse event with a study subject, an Adverse Event Case Report Form must be completed to record any adverse events, as defined in Sub-section 12.1.2 and Section 18.

13.3.7.1. Additional Information Collected at Device System Revision/Replacement or Upgrade

Should study subjects undergo surgical intervention for lead or pocket revision/reposition, this information is captured on the Adverse Event Case Report form. In the event of a 4-SITE RV lead revision, a detailed assessment of the proximal end of the lead and the header at lead revision/reposition should be completed. The investigator should also document any lead damage.

13.3.8. Device Deficiency Case Report Form

In the event a device deficiency (as defined in the protocol (Table 20.1-1)) is identified, a Device Deficiency Case Report Form will be completed.

13.3.9. End of Study Case Report Form

An End of Study Case Report Form will be completed when a study subject is no longer active in the LSS of 4-SITE Study. Reasons for a change in study subject status include study completion, death and withdrawal.

The status of the 4-SITE lead must be reported at the time of subject withdrawal from the study.

13.3.10. Explanted and Out-of-Service Device Case Report Form

For any implanted devices which are explanted and/or taken out of service (whether capped or removed), the Explanted and Out-of-Service Case Report Form must be completed.

NOTE : If the 4-SITE RV lead is explanted and/or taken out of service, the study subject must be withdrawn from the study.

13.3.11. Deviations Case Report Form – Definition & Major Reasons

Protocol deviations are defined as any divergence from the study protocol. Reasons for a deviation include, but are not limited to, the following: study subject consent not obtained, testing incomplete/not performed, and/or follow-up outside the scheduled protocol required follow-up visit window. Study protocol deviations are further clarified in Section 15

13.4. *Additional Information Collected at Suspected Lead Failure*

If the reason for study subject withdrawal is lead failure, supporting objective evidence is required. Objective evidence includes, but is not necessarily limited to, the following: Pacing System Analyzer (PSA) measurements demonstrating lead performance (thresholds, impedance, and/or sensing), stored EGMs, cine recordings and/or radiographic evidence. Techniques such as pocket manipulation, arm maneuvers, valsalva maneuver, coughing and/or exploration of potential sources of external magnetic interference (EMI) may be used to detect system abnormalities, at the discretion of the Investigator. Please refer to Sub-section 26.2 hereinafter for suggested suitable confirmation information depending on the lead failure mode.

A detailed assessment and report by the explanting Investigator/ Physician of the proximal end of the lead and the header at device change-outs is required. Data collected during explant of a lead will also be required, including extraction method and tools/instruments

used.

> **NOTE: For *US and Canadian site* personnel, please make every attempt to return explanted product to the manufacturer. Boston Scientific provides a *Returned Products Kit* (Model #6499) that can be requested through BSC's Customer Service Department at 1-800-CARDIAC (1-800-227-3422), by phoning 1-651-582-2698 or by submitting an online request at: www.bostonscientific.com/ppr. Site representatives from *Other Countries* should please contact the local Boston Scientific office and/or affiliate for assistance (contact information may be found at the BSC website: www.bostonscientific.com/home.bsci).**

13.5. *Additional Information Collected at Study Subject's Death*

Additional data must be collected and recorded upon a study subject's death as follows:

- Was the pulse generator explanted (Yes, No, or Unknown)? Please attempt to return pulse generator to BSC upon the death of a study subject.
- Was an autopsy performed (Yes, No, or Unknown)?
- Was the pulse generator interrogated "in situ" after death (Yes, No, or Unknown)?
- Pulse generator interrogated data and status at time of death: monitor + therapy, monitor only, off, not functioning, or unknown?
- Primary organ cause of death: cardiac: arrhythmic, pump function, ischemic, other cardiac, or unknown; non-cardiac; or unknown?
- If cardiac ischemia, was it: acute, myocardial infarction (MI), non-acute MI or unknown?
- Temporal course of death: sudden, non-sudden or unknown / presumed sudden, or unknown?
- Antecedent worsening heart failure (Yes, No or Unknown)?
- Operative relationship: pre-operative, peri-operative or post-operative?
- Death witnessed (Yes, No or Unknown)?
- Death monitored (Yes, No or Unknown)?
- If death was monitored, were any of these observed: VT, brady-arrhythmia, pulseless electrical activity, unknown or other?
- If brady-arrhythmia was observed, was it: sinus brady-arrhythmia, high-degree AV Block with slow ventricular response or asystole?
- What was the cause of death: procedure-related, pulse generator-related, lead/catheter-related, unknown or other?
- If a death is considered 4-SITE Lead/Header System-related, it will be adjudicated by medical review.*

* Post mortem assessment is strongly encouraged. Whenever possible, the device should be interrogated and deactivated with the device information saved prior to being disconnected from the lead(s). Lead extraction and return are also strongly encouraged.

13.6. *Study Subject Data Confidentiality*

All information sent to Boston Scientific (BSC) or entered in the electronic data capture website concerning subjects or their participation in the study will be considered and treated as confidential information. Authorized BSC and the FDA personnel, as well as representatives of other regulatory agencies, have the right to inspect and/or copy all records pertinent to the LSS of 4-SITE Study. Data from the study that are used in reporting will be without identifiable reference to an individual study subject.

For questions regarding any matter, BSC may be contacted as follows:

Boston Scientific Corporation
CRM Clinical Department
4100 Hamline Avenue North, [redacted]
Saint Paul, Minnesota 55112-5798

Telephone: 1-800-CARDIAC (1-800-227-3422)
Fax: 651-582-4982

13.7. *US Health Insurance Portability and Accountability Act (HIPAA)*

The HIPAA requirements affect clinical trials[1] in three key areas as described below:

Accounting of Disclosures: Data collected during the conduction of prescreening activities for this study are subject to the HIPAA accounting of disclosures' regulations. It is the responsibility of the investigative center personnel to tell all study subjects whose records were screened for eligibility in the study that their records were used in this manner if he or she requests an accounting of when his or her data were disclosed.

Consent: All subjects participating in the study will be made aware that their participation in the study will involve disclosure of certain protected health information to BSC and for what purpose. The Subject Informed Consent Form will contain a listing of the type of information that will be disclosed during the course of the clinical study.

Withdrawal of Consent: HIPAA specifically allows companies such as BSC that are subject to the jurisdiction of the FDA access to protected health information for activities related to the quality, safety or effectiveness of devices. This means that BSC can use data from this study even if the individual withdraws his or her authorization.

14. Study Protocol Amendments

If a LSS of 4-SITE Study protocol revision is necessary which affects the rights, safety or welfare of the subjects or scientific integrity of the data, an amendment is required. Appropriate approvals (*e.g.,* IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation of amendments.

15. Study Protocol Deviations

An Investigator must not make any changes or deviate from this study protocol, except to protect the life and physical well-being of a subject in an emergency. An Investigator shall notify the Sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a study 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 five (5) regular work days after the emergency occurred, or in accordance with prevailing local requirements, if such requires notification sooner than five (5) regular work 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 via Email, CRF and/or EDC. Sites may also be required to report deviations to the IRB/EC, in accordance with local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis during the conduct of the LSS of 4-SITE Study and, as necessary, appropriate corrective and preventive actions (including notification, center re-training and/or participation discontinuation) will be instituted by the Sponsor.

16. Compliance

16.1. *Statement of Compliance*

This study will be conducted in accordance with FDA regulations, 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 center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, 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 study subject.

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

- Prior to beginning the study, sign the Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol;
- Provide his/her qualifications and professional experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date *curriculum vitae* or other relevant documentation, and disclose potential conflicts of interest, including financial conflicts of interest, that may interfere with the conduct of the clinical study or interpretation of its results;
- Make no changes in or deviate from this study 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 conduct of the clinical study and ensure their availability with direct access during monitoring visits or audits – ensure that all clinical-investigation-related records are retained in accordance with requirements;
- Ensure the accuracy, completeness, legibility and timeliness of the data reported to the Sponsor in the case reports forms (CRFs) and in all required reports;
- Record, report and assess (seriousness and relationship to the device system/procedure) every adverse event and observed device system deficiency;
- Report to BSC, per the protocol requirements, all serious adverse events (SAEs) and device system deficiencies that could have led to a serious adverse device event (SADE);
- Report to the IRB/EC and regulatory authorities any SAEs and device system deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event;
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use;
- Allow the Sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during and regarding monitoring visits;

- Allow and support regulatory authorities and the IRB/EC when performing auditing activities;
- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC requirements;
- Provide adequate medical care to a study 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 study subject of the nature and possible cause of any adverse events experienced;
- As applicable, provide the study subject with necessary instructions on proper use, handling, storage and return of the investigational device when it is used/operated by the subject;
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required;
- Provide the study 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 study 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 study subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights;
- Ensure that an adequate investigational site team and facilities exist, and are maintained and documented during the conduct of the clinical investigation; and
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

16.3. *Delegation of Responsibility*

When specific tasks are delegated by an Investigator, including but not limited to conducting the informed consent process, the Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The Investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.4. *Institutional Review Board / Ethics Committee*

Prior to achieving approval-to-enroll subject status, the investigational center 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 study protocol (or permission to conduct the study) and Informed Consent Form, must be received by the Sponsor before recruitment of subjects into the study. Investigators must provide IRB approval of revisions to the study subject Informed Consent Form or amendments to the protocol. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to study subjects.

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 in a timely manner.

16.5. *Sponsor Responsibilities*

Boston Scientific (BSC) will serve as the Sponsor of this clinical investigation. A Sponsor is defined as a person or organization that initiates, but does not actually conduct, the clinical investigation. It is the responsibility of BSC as the Sponsor to ensure proper monitoring of the investigation and to see that all clinical requirements are met. In addition, BSC representatives may participate in the conduct of the trial to the extent described in the following section that describes the role of BSC representatives. BSC personnel may or may not be blinded to the study results. Participation in the study's conduct will be limited to BSC personnel who are appropriately qualified and trained such as those personnel with an engineering, technical or nursing degree or equivalent training, or who have significant experience in cardiology, electrophysiology or the implantable cardiovascular device industry. All personnel will be aware of general clinical study regulations and guidelines for medical device trials.

All information and data sent to BSC concerning study subjects or their participation in this clinical study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this clinical study. Study data collected during this study may be used by BSC for the purposes of this study, for

publication purposes, 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' 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 clinical 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.

16.6. *Role of Boston Scientific Representatives*

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

At the request of the Investigator and while under his/her supervision, BSC personnel may operate equipment during implantation or subject follow-up visits, assist with the conduct of testing specified in the protocol, and interact with the study subject to accomplish requested activities. Typical tasks may include the following:

- Interrogating the device system or programming device parameters to the Investigator's requested settings;
- Performing lead diagnostic testing using a Pacing System Analyzer (PSA) or programmer to obtain pacing and sensing thresholds and impedance measurements;
- Clarifying device system behavior, operation or diagnostic output as requested by the Investigator or other health care personnel; and
- Assisting with the collection of study data from Pacing System Analyzers, programmers and/or other equipment.

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 study protocol compliance; and
- Reviewing collected data and study documentation for completeness and accuracy.

Boston Scientific personnel will not perform 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 HCP;
- Independently collect critical study data (defined as primary or secondary endpoint data); or
- Enter data in electronic data capture systems or on paper case report forms.

16.7. *Insurance Coverage*

When required by local and/or country regulation, the type and proof of insurance coverage secured by Boston Scientific for subjects in the study will be provided.

17. Study Monitoring

A monitor and/or BSC representative may visit an Investigator during the clinical study to assess the following criteria:

- Adherence to the study protocol and applicable regulations regarding the obligations of the Investigator; and/or
- Maintenance of adequate records; and/or
- Accurate clinical study data entry.

In the event of noncompliance (*e.g.,* repeated failure to transfer data, multiple study protocol deviations), as determined by BSC study management, a monitor and/or BSC representative may attempt to secure compliance by one or more actions such as the following:

- Corresponding with the Investigator; and/or
- Telephoning the Investigator to have discussion(s); and/or
- Visiting the Investigator at the investigational site/center; and/or
- Implementing a Corrective Action Plan for the site/center.

If an Investigator is found to be repeatedly noncompliant with the terms and conditions in the signed agreement, with the requirements specified in the protocol or with any other conditions of the study, then BSC will either secure compliance or, at its sole discretion, terminate the Investigator's participation in the study.

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the 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 Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The 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 Investigator and relevant clinical study personnel are available during on-site monitoring visits and/or audits and that sufficient time is devoted to the process.

18. Potential Risks and Benefits

18.1. *Adverse Event Reporting*

The Investigator must report all adverse events occurring **at or after device system implant** to BSC in a timely manner following the occurrence or discovery of such an event. Specific event reporting requirements and timeframes are presented in Sub-section 20.3 and Table 20.3-1. Adverse events must be reviewed and classified by the Investigator for the study using the definitions outlined below.

18.2. *Adverse Event Definitions*

An adverse event is defined as any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. Adverse events may be a result of inappropriate performance of the 4-SITE Lead/Header System (*i.e.,* a 4-SITE Lead and/or just the 4-SITE Header component of a PG) which results in an undesirable or unanticipated procedure or clinical occurrence. Investigators are responsible for providing a description of the event, classifying each reported adverse event as being either related or unrelated to a 4-SITE Lead/Header System malfunction, describing the corrective action taken, explaining the method used to confirm the adverse event, reporting the clinical outcome, and determining the root cause of the adverse event based on available information. All adverse events must be reported on the Adverse Event Form and reported in accordance with Medical Device Regulations.

The list of possible causes for reportable adverse events is presented in Table 18.2-1 below and the supporting adverse event information is presented in Table 18.2-2 below. This tabular information is intended to be complete, but additional adverse events may be identified as more is learned about the device system's performance.

18.3. *Potential Lead Implantation Adverse Events*

Potential adverse events from implantation of a lead system include, but are not limited to, the following: allergic/physical/physiologic reaction; death; erosion or migration; fibrillation or other arrhythmias; lead or accessory breakage (fracture/insulation/lead tip); hematoma or seroma; inappropriate or inability to provide therapy (shocks/pacing/sensing); infection; procedure related; and component failure. In rare cases severe complications or device failures can occur.

Table 18.2-1: Some Examples of Possible Causes for Reportable Adverse Events

PG-Related	RA Lead-, RV Lead-, or LV Lead and Accessories-Related	Header-Related	Physician & Subject–Related (Non-Device System-Related)
• Accelerated arrhythmia episode (ventricular) • Inability to deliver shock or pace therapy • Inappropriate shock/ therapy (*e.g.,* shocks, ATP, pacing) • Migration of pulse generator • Pectoral muscle stimulation • Possible malfunction (*e.g.,* premature battery depletion) • PG-related adverse event requiring additional interventions • Post-shock rhythm disturbances • Pulse generator fault code detected • Skin erosion • Oversensing, undersensing, noise • Other PG-related, please specify	• Cardiac perforation /tamponade • Lead dislodgement • Elevated thresholds • Extra-cardiac stimulation (*e.g.,* phrenic, diaphragm) • High or low pacing impedance • High or low shock impedance • High or low shock impedance when attempting to deliver a shock • Inability to place lead • In-subject damage to RV lead • Inappropriate shock due to over-sensing • Intermittent sensing • Lead revisions to optimize therapy • Loss of capture • Pacing impedance changes • RA or LV lead-related adverse event requiring additional intervention(s) • RV lead-related thrombosis • Shock impedance changes • Oversensing, undersensing, noise • Suspected lead fracture • Suspected lead abrasion • Lead insulation breach • Header/connector problem • Subclavian lead crush damage • Other lead or accessories-related, please specify	• Difficulty with placing existing lead • Difficulty with placing new lead in header • Difficulty with removing lead from header • Difficulty with tightening set screw • Elevated thresholds • High pacing impedance • High shock impedance • High shock impedance when attempting to deliver a shock • Inability to deliver shock or pace therapy • Inappropriate shock • Loose set screws identified at implant • Loss-of-capture • Low pacing impedance • Low shock impedance • Pacing impedance changes • Shock impedance changes • Significant r-wave amplitude decrease during two (2) weeks or less • Oversensing, undersensing, noise • Other header-related, please specify	• Hematoma • Pain • Pneumothorax • Twiddler's Syndrome • Infection • Allergic reactions • Drug reactions • Implant procedure related complications (i.e arrhythmias and hematoma) • Lead under-insertion identified at implant • Non-RV lead-related death • Non-RV lead-related hospitalization(s) • Other procedure-related adverse events identified at implant, please specify **NOTE:** Physician and study subject induced injury will be recorded, but will not be included as adverse events in the endpoint analysis of the study (*e.g.,* auto accident causing lead/header dysfunction, or inadvertent cutting of lead insulation by physician during the implantation procedure).

Table 18.2-2: Supporting Adverse Event Information

Corrective Action	Method Used to Confirm Event	Root Cause of Event (Investigator Assessment)
Any of the following corrective actions will be collected to aid in determination of a device malfunction. ~ ~ ~ ~	Appropriate methods for confirmation of specific event types are included in the specific event definition in Sub-section 26.2. ~ ~ ~ ~	4-SITE Lead/Header System-related complications must be reported as possibly lead/header-related unless confirmed. ~ ~ ~ ~
• Lead surgically repositioned • Lead surgically abandoned/capped • Lead electrically abandoned (*e.g.,* changed PG pacing mode) • Lead/pulse generator explanted • Lead/pulse generator replaced • Lead polarity changed (*e.g.,* unipolar to bipolar, bipolar to unipolar) • Lead pace/sense configuration changed • Device output programming adjusted (*e.g.,* changed pulse width) • Pulse generator pacing mode changed • No action taken based on medical judgment • Shock lead vector changed • Other, please specify	• Device-based (programmer) • Direct visual observation • EGM-based • Imaging (*e.g.,* x-ray, cine, fluoroscopy, etc.) • Isometric testing (*e.g.,* Valsalva maneuver, subject position, etc.) • Pocket manipulation • Pacing System Analyzer (PSA) test(s) • Other, please specify	• Pulse generator-related • Lead-related * (assign lead: RA, RV, LV) o Confirmed lead-related o Possibly lead-related • Patient condition • Conductor fracture • Lead migration dislodgement • Lead insulation break or abrasion • Non-physiologic over-sensing from an identifiable cause • Over-sensing/multiple counting • Twiddler's Syndrome leading to RV lead dislodgement • Cross Threading set screw • Screw down in bore (new devices) • Exit block • Infection

* Additional information will be required if the adverse event is suspected to be 4-SITE Lead/Header System-related in order to determine if the adverse event is a chronic lead/header system-related complication.

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

This clinical study does not involve additional risks to study subjects since it is simply collecting additional data that is consistent with approved device labeling and with investigator standard of care. The risks associated with participation in this study are the same as those associated with all standard device system procedures. Please see the BSC Physician's Manual for reference.

18.5. *Risk Minimization Actions*

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

18.6. *Anticipated Study Subject Benefits*

Subjects enrolled in this clinical study may not receive any direct medical benefit from their participation. However, the field of medical science and future study subjects who require implantation with a 4-SITE Header/Lead System may derive a benefit from the results of this clinical investigation.

18.7. *Risk to Benefit Rationale*

The implantable device systems and accessories used for this clinical study are all commercially available and are considered to be "the standard of care" for study subjects indicated for such implants. The risks involved with subject participation in this study are essentially the same as those for study subjects not participating in the study. There are no additional risks from the implantation of the device system for a study subject compared to study subjects not participating in this study.

Thus, even though there may be no direct clinical benefit for an individual study subject, study participants will not be exposed to any additional risks than they would encounter in the normal course of treatment for their malady. Further, the study protocol required follow-up visitation schedule and procedures may exceed the standard of care and thereby offer enhanced clinical observation for the five (5) years following the implant procedure.

19. Study Subject Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all study subjects or their 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 national regulations and local Ethics Committee (EC) and/or regulatory authority body, as applicable. The Informed Consent Form (ICF) must be approved by the center's IRB/EC, or central Institutional Review Board (IRB), if applicable.

Boston Scientific (BSC) 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 center's IRB/EC. However, any modification requires approval from BSC prior to use of the form. The ICF must be in a language understandable to the study subject

and if needed, BSC will assist the center in obtaining a written informed 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 consist of the following:

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

The ICF must always be signed and personally dated by the study subject or by his/her legal representative, and by the Investigator or an authorized designee responsible for conducting the informed consent process. If a legal representative signs the ICF, then the study 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 investigational center 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 study subject consent will be reported by BSC to the applicable regulatory body according to their requirements (*e.g.,* FDA's requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as study protocol deviations to the Sponsor and to local regulatory authorities (*e.g.,* IRB/EC), as appropriate.

If new information becomes available that can significantly affect a study 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 study 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 protocol, a change in Principal Investigator, administrative changes and/or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the study subject population to be re-consented.

NOTE: Outside the US, the transmission of confidential subject data, such as copies of source documents, is only permissible if the study subject has given prior consent, so the ICF must include a statement to this effect.

NOTE: Informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written ICF and any other information shall be read aloud and explained to the prospective study subject or his/her legally authorized representative and, whenever possible, either one shall sign and personally date the ICF. The witness also signs and personally dates the ICF attesting that the information was accurately explained and that informed consent was freely given.

20. Safety Reporting

20.1. *Definitions and Classification*

Adverse event (AE) definitions are provided in Table 20.1-1. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3-12/2010.

Table 20.1-1: Adverse Event Definitions

AE Term	Adverse Event Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3-12/2010*	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: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan).

Serious Adverse Event (SAE)
 	
Ref: ISO 14155-2011
 	
Ref: MEDDEV 2.7/3-12/2010
	Adverse event that led to one of the following:
	• Led to death;
	• Led to serious deterioration in the health of the subject, that resulted in one of the following; or
	  o a life-threatening illness or injury; or
	  o a permanent impairment of a body structure or a body function; or
	  o in-patient or prolonged hospitalization of existing hospitalization; or
	  o 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: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.

Table 20.1-1: Adverse Event Definitions

AE Term	Adverse Event Definition
Adverse Device Effect (ADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event related to the use of an investigational medical device **NOTE 1**: This definition includes any adverse event resulting from insufficient or inadequate 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 from intentional misuse of the investigational medical device.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	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: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

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

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the clinical investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Table 20.1-1 for adverse events definitions). Any AE experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

Refer to Section 18 for the known risks associated with the study devices.

20.2. *Relationship to Study Device*

The Investigator must assess the relationship of an adverse event (AE) to the study device as being either related or unrelated. See criteria in Table 20.2:

Table 20.2: Criteria for Assessing Relationship of Device to Adverse Event

AE Relationship	Description to Determine AE Relationship
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the adverse event.

20.3. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 20.3-1.

Table 20.3: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
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 including 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 documentation (unidentified) for reported event.	• When documentation is available.
Adverse Event	Complete AE eCRF page, which contains such information as date of AE, treatment or AE resolution, assessment of seriousness and relationship to the device.	• No later than 10 working days after becoming aware of the information. • Reporting required through the five (5) year follow-up period or when study is completed, whichever occurs first.
Device Deficiencies (including but not limited to failures, malfunctions, and	Complete eCRF with all available new and updated information.	• Within 1 business day of first becoming aware of the event and

Table 20.3: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
product nonconformities)		as per local/regional regulations. • Reporting required through the end of the study.

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

20.4. *Boston Scientific Device Deficiencies*

All device deficiencies (including, but not limited to, failures, malfunctions, use errors, product nonconformities and labeling errors) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. If it is not possible to return the device, the Investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the study subject's medical record.

NOTE: For *US and Canadian site* personnel, please make every attempt to return explanted product to the manufacturer. Boston Scientific provides a *Returned Products Kit* (Model #6499) that can be requested through BSC's Customer Service Department at 1-800-CARDIAC (1-800-227-3422), by phoning 1-651-582-2698 or by submitting an online request at: www.bostonscientific.com/ppr. Site representatives from *Other Countries* should please contact the local Boston Scientific office and/or affiliate for assistance (contact information may be found at the BSC website: www.bostonscientific.com/home.bsci).

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

Further, 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.

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

BSC is responsible for reporting adverse event information to all participating Investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC and regulatory authorities of USADE and SAE as required by local/regional regulations.

21. Committees

21.1. *BSC Global Safety Office – Safety Monitoring Program*

In order to promote early detection of safety issues, the Boston Scientific Safety Trial Operations staff will provide evaluations of study safety events. Success of this program requires dynamic collection of unmonitored data as soon as an event is reported. This process is expedited through BSC's Global Safety Office which is responsible for coordinating the collection of information for the subject dossier from the investigational centers and core laboratories. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

21.2. *Clinical Events Committee*

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that reviews and adjudicates study endpoints and relevant adverse events reported by study Investigators. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, for all reported cases of serious adverse events, serious adverse device events and the death of a study subject.

Committee membership will include practitioners with professional expertise in cardiology or electrophysiology who are engaged in device system implantation as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories mentioned above. CEC responsibilities, qualifications, membership and committee procedures are outlined in the CEC charter. The CEC ensures consistency of adverse event classification thereby providing enhanced compliance with accepted classification and accuracy.

22. Study Termination and Center/Site Suspension

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 study subjects. Investigators, associated IRBs/ECs and regulatory authorities, as applicable, will be notified in writing in the event of the termination of the LSS of 4-SITE Study.

22.2. *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; or
- A decision on the part of Boston Scientific as study Sponsor to suspend or discontinue development of the device.

22.3. *Termination of Study Participation by the Investigator or Withdrawal of IRB/EC Approval*

Any Investigator or an IRB/EC engaged with the LSS of 4-SITE Study may discontinue participation in the study or withdraw 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 such an occurrence.

22.4. *Requirements for Documentation and Study 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 centers by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will also 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 an Investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Investigator must return all documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the study subjects.

22.5. *Criteria for Suspending/Terminating a Study Center*

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

In the event of termination of Investigator 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 study subjects. The IRB/EC and regulatory authorities, as applicable, should be notified. All subjects enrolled in the study at the center will continue to be followed for the full five (5) year post implant follow-up, if possible. The Principal Investigator at the center/site must make provision for these follow-up visits unless BSC notifies the investigational center/site otherwise.

23. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, 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. In accordance with the Corporate Policy for the Conduct of Human Subject Research, 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 Contributor-ship 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 regarding publication preparation provided the following guidelines are adhered to:

- All authorship and contributor-ship 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 Study Steering Committee (if one is convened) at the onset of the project; and
- The First and Senior authors are the primary drivers of decisions regarding manuscript content, review, approval and submission.

24. Bibliography

1. Muhlbaier, L.H. "HIPAA - A Training Handbook for Researchers." Marblehead, MA: Opus Communications, Inc; 2002.

25. Protocol Abbreviations/Acronyms and Study Definitions

25.1. *Protocol Abbreviations/Acronyms*

Abbreviations are shown in Table 25.1-1. This table is in alphabetical order based on the letters of the abbreviation/acronym.

Table 25.1-1: Study Abbreviations/Acronyms

ABBREVIATION/ ACRONYM	USED TO REPRESENT THIS WORD(s) or PHRASE
AAMI	Advancement of Medical Instrumentation
ACC	American College of Cardiology
AdvaMed	The Advanced Medical Technology Association (AdvaMed) advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology.
AE	Adverse Event(s)
AF	Atrial Fibrillation/Atrial Flutter
AHA	American Heart Association
ASADE	Anticipated Serious Adverse Device Effect(s)
BSC	Boston Scientific Corporation
CA	Competent Authority
CDM	Clinical Data Management database at BSC for controlling and archiving clinical documents (incorporated within the PDM database).
CEC	Clinical Events Committee (members are study independent)
CFR	Code of Federal Regulations
Co-I	Co-Investigator of clinical study conduct
CRF(s)	Case Report Form(s)
CRM	Cardiac Rhythm Management Group of BSC
CRT	Cardiac Resynchronization Therapy

ABBREVIATION/ ACRONYM	USED TO REPRESENT THIS WORD(s) or PHRASE
CRT-D	Cardiac Resynchronization Therapy - Defibrillator
CRV	Cardiac, Rhythm and Vascular group operating as part of Boston Scientific Corporation.
DR	A dual-chamber ICD combining ventricular tachyarrhythmia therapy with both ventricular and atrial pacing and sensing.
EC	Ethics Committee
EC	European Commission
eCRF	Electronic Case Report Form(s)
EDC	Electronic Data Capture (system)
EGM	(Intracardiac) Electrogram/Electrocardiograms
EGMs/egms	Electrograms
EMI	External Magnetic Interference
ERC	Ethics Review Committee
ESSC	Executive Study Steering Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice(s)
H_A	The “alternative” hypothesis (statistics)
H_0	The “null” hypothesis (statistics)
HCP	Health Care Professional
HE	High Energy ICD device
HF	Heart Failure
HIPAA	Health Insurance Portability & Accountability Act

ABBREVIATION/ ACRONYM	USED TO REPRESENT THIS WORD(s) or PHRASE
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IDE	Investigational Device Exception
IEC	International Electrotechnical Commission
IRB	Institutional Review Board
IS-1/DF-1	Standard, single terminal lead connector
IS-4/DF-4	Standard quadripolar (4-pole) terminal lead connector
ISO	International Organization for Standardization
K-M Plot (Kaplan-Meier plot)	An estimator for estimating the survival function from life-time data – in medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment.
LESS	Low Energy Safety Study conducted by Guidant during the late 1990's (IDE # G960259)
LSS	Longitudinal Surveillance Study
LSS of 4-SITE	Acronym for the clinical study title: "Longitudinal Surveillance Study of 4-SITE Lead/Header System"
MEDDEVs	Guidelines aimed at promoting a common approach by medical device manufacturers and Notified Bodies involved in the conformity assessment procedures according to the relevant annexes of the Directives, and by the Competent Authorities charged with safeguarding Public Health.

ABBREVIATION/ ACRONYM	USED TO REPRESENT THIS WORD(s) or PHRASE
Medidata	A leading global company that provides clinical development solutions typically involving computerized database approaches.
MI	Myocardial Infarction
NASPE	No. American Soc. for Pacing and Electrophysiology
NYHA	New York Heart Association
Ohms	A unit of electrical resistance measurement – the ohm is defined as a resistance between two points of a conductor when a constant potential difference of 1 volt, applied to these points, produces in the conductor a current of 1 ampere.
OOS	Out-of-Service (device)
PDM	Product Data Management master database at BSC for controlling/arching information, data and documents.
PG	Pulse Generator
PI	Principal Investigator of clinical study conduct
PSA	Pacing System Analyzer
RAVE (Rave)	Rave® is an industry-leading system for capturing, managing and reporting clinical research data – it is designed to help companies optimize their research by efficiently streamlining the clinical trial process.
RC	Research Coordinator (clinical study conduct)
RV	Right Ventricle (right ventricular)

ABBREVIATION/ ACRONYM	USED TO REPRESENT THIS WORD(s) or PHRASE
R (r) wave	Regarding ECGs, the R wave is the first upward deflection after the P wave (even when Q waves are absent). The R wave is normally the easiest waveform to identify on the ECG and represents early ventricular depolarization.
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
4-SITE	The Lead/Header System designed and developed in parallel with, and with the intent of meeting, the approved quadripolar 'IS-4/DF-4' connector standard.
Sponsor	Boston Scientific is the Sponsor of the LSS of 4-SITE Clinical Study.
T (t) wave	Regarding ECGs, the T wave represents ventricular repolarization and is longer in duration than depolarization.
USADE	Unanticipated Serious Adverse Device Effect(s)
ULN	Upper Limit of Normal
VR	A single-chamber ICD combining ventricular tachyarrhythmia therapy with ventricular pacing and sensing.

25.2. *Study Protocol Definitions*

Certain key study protocol terms are defined in Table 25.2-1 below.

Table 25.2-1: Study Protocol Definitions

STUDY TERM	DEFINITION of THIS TERM
Source Data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation necessary for the reconstruction and evaluation of the clinical investigation. Source data are contained in the source documents (original records or ceritifed copies).
Source Documentation	Printed, optical or electronic original documents containing source data. Examples include the following: hospital records, laboratory notes, device accountability records, photograhic negatives, radiographs, and records/charts kept at the investigation site, at the laboratories and at the medico-technical departments involved in the conduct of the clinical investigation.
Twiddler's Syndrome	A well-known complication of pacemaker treatment, it involves a patient manipulating and rotating the pulse generator in the pocket so many turns that it results in lead dislodgment, diaphragmatic stimulation and/or loss of capture.
Pocket Revision	Assuming that the subject continues to participate in the study, a pocket revision is an invasive procedure that involves modification in some manner to the extra-thoracic device pocket and/or lead(s) therein. There is no repositioning of the lead(s) tip in the heart.
Lead Revision / Reposition	Assuming that the subject continues to participate in the study, a lead revision/reposition is an invasive procedure that involves manipulation of the lead(s) to modify the anatomical location of all, or just a

STUDY TERM	DEFINITION of THIS TERM
	segment, of the intra-thoracic portion of the lead.

26. Appendices

26.1. *Investigator/Center Selection Criteria*

BSC will consider many factors to ensure selection of investigational centers that are suitable to conduct the study, and investigators who are qualified through their training and experience to properly conduct the study. Diverse investigational centers will be selected with respect to geography and clinical setting (*e.g.,* university medical centers, private practices, etc.).

The current BSC process for evaluating and selecting investigational centers will be utilized. The evaluation and selection criteria include, but are not limited to, the following:

- Centers that have the personnel with knowledge to conduct a clinical study and enroll study subjects in full accordance with FDA regulations and good clinical practice guidelines. It is recommended that centers have a dedicated Research Coordinator; however, exceptions will be evaluated on a case-by-case basis;

- Centers that have a Principal Investigator (PI; physician or equivalent HCP) who has a commitment to conducting clinical research and is in good standing with the FDA;

- Centers that have the necessary professional and clinical staff with the knowledge and experience to implant Boston Scientific CRM products and that also have the study subject volume to meet study enrollment expectations;

- Centers with personnel who have a commitment to study protocol compliance as well as who are obligated to data gathering and submission in a timely and accurate manner using an electronic data entry system; and

- Centers that will support on-site clinical data monitoring during the conduct of the study.

26.2. *Glossary of Definitions*

Cardiac Perforation – Penetration of the lead tip through the myocardium to the pericardium or beyond (including micro-perforation) or associated venous anatomy, either clinically suspected or confirmed by chest x-ray, fluoroscopy, echocardiogram, intra-cardiac electrogram and/or visually. ◊

Cardiac Tamponade - also known as pericardial tamponade, is an acute type of pericardial effusion in which fluid accumulates in the pericardium. Cardiac tamponade will be considered as a serious adverse event if invasive intervention is required for treatment.

Conductor Fracture/Lead Fracture – A mechanical break within the lead conductor (includes connectors, coils and/or electrodes) observed visually, electrically or radiographically. . ◊

Elevated Pacing Thresholds – At implant, pacing thresholds for the permanently programmed electrode that are greater than 3.0 volts and at follow-up pacing thresholds for the permanently programmed electrode that are either: (1) An observed increase of 2-fold over the first chronic threshold; or (2) An observed threshold greater than 3.5 volts. Please note that these elevations in pacing threshold values may be physiologic, pathologic or device-related.

Extracardiac Stimulation (*e.g.*, phrenic, diaphragm) – Clinical observation of inadvertent muscle/nerve stimulation other than cardiac muscle. ◊

Hematoma – if a hematoma requires invasive intervention to evacuate the hematoma, it will be considered a serious adverse event.

High Pacing Impedance – Pacing impedance is considered abnormal based on lead model and measurement range of the device.. ◊

High Shock Impedance – Shock impedance is considered abnormal based on lead model and measurement range of the device. . ◊

High Shock Impedance when attempting to deliver a shock – High shock impedance is considered abnormal based on lead model and measurement range of the device when attempting to deliver a shock. ◊

Inappropriate shock due to over-sensing – Shock delivered due to over-sensing resulting from either physiologic or non-physiologic causes. ◊

Inappropriate shock – shock delivered by the device which is not appropriate therapy/treatment per the device programming.

Infection – If oral/topical antibiotics are prescribed for treatment of an infection, it will be considered as an adverse event. If Intravenous (IV) antibiotics are required for treatment of the infection (with associated increase in white blood cells), then it will be considered a serious adverse event.

Intermittent Sensing – Intermittent loss of sensing or failure to detect intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity settings. ◊

Lead Abrasion – Upon returned product analysis, leads are analyzed for abrasion. Known examples of lead abrasion occur 1) proximal abrasions associated with lead-on-lead or lead-on-PG contact in the pocket; 2) mid-lead insulation damage caused by clavicle flex-fatigue or crush, suture or suture sleeve, insulation wear in the area of vein insertion and 3) distal region wear due to lead-on-lead (intracardiac), lead-on-heart valve or lead-on-another anatomy contact ◊

Lead Insulation Breach – A disruption or break in lead insulation observed visually, electrically or radiographically. ◊

Lead Migration/Dislodgment – Radiographic and electrical evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing and/or lead performance. ◊ Micro-dislodgement is not included.

Loss-of-Capture – Intermittent or complete failure to stimulate cardiac stimulation (atrial or ventricular) at programmed output delivered outside of the cardiac refractory period. .◊

Low Pacing Impedance – Pacing impedance is considered abnormal based on lead model and measurement range of the device. ◊

Low Shock Impedance – Shock impedance is considered abnormal based on lead model and measurement range of the device. ◊

Low shock impedance when attempting to deliver a shock – Low shock impedance is considered abnormal based on lead model and measurement range of the device) when attempting to deliver a shock. ◊

Normal Battery Depletion - For pulse generators, the condition when a) a device is returned with no associated complaint and the device has reached its elective replacement indicator (s) with implant time that meets or exceeds the nominal (50 percentile) predicted longevity at default (labeled) settings, or b) the device is returned and the device has reached it elective replacement indicator(s) with implant time exceeding 75% of the expected longevity using the longevity calculation tool available at the time of product introduction, calculated using the device's actual use conditions and settings.

Other, Lead related – Specific proprietary attributes of a lead, such as sensors which affect a leads ability to perform as designed and remain in service. ◊

Other, Pulse Generator/Header related – Specific proprietary attributes of a pulse generator/header, which affect a device's ability to perform as designed and remain in service.

Oversensing– The occurrence of cardiac or non-cardiac events being misinterpreted as cardiac depolarization, (*e.g.,* T waves, multiple counting, skeletal muscle potentials and extra-cardiac electromagnetic interference (EMI)). ◊

Pacing Impedance Changes – Pacing impedance changes are considered clinically significant if the value changes by more than a 2:1 ratio from the previous value.

Pain - Pain requiring oral medications is not considered serious. Pain requiring Intravenous analgesics or results in prolonged hospitalization will be considered a complication.

Pneumothorax - Is a collection of air or gas in the pleural space of the lung, causing the lung to collapse. It will be considered a serious adverse event if invasive intervention is needed for treatment.

Possible Malfunction - May be considered if neither of the two listed below occurred.

a) Malfunction with compromised therapy, PG – The condition when a device is found to have "malfunctioned" in a manner that compromised pacing or defibrillation therapy (including complete loss or partial degradation) while implanted and in service. Therapy is considered to have been compromised if no therapy is available or critical patient protective pacing or defibrillation therapy is not available

b) **Malfunction without compromised therapy, PG -** The condition when a device is found to have "malfunctioned" in a manner that did not compromise pacing or defibrillation therapy while implanted and in service. Therapy is not compromised as long as critical patient protective pacing or defibrillation therapies are available. Changes in device setting that occur as intended by design (i.e. Power-on-reset (POR)) that do not result in loss of critical patient protective therapies but are reported as reasons for explant, shall be classified as malfunctions without compromised therapy. ◊

Shock Impedance Changes – Shock impedance changes are considered clinically significant if the value changes by more than a 2:1 ratio from the previous value.

Significant r-wave amplitude decrease over 2 weeks or less – A decrease in r-wave value is considered clinically significant if the value changes by more than a 2:1 ratio over the course of two (2) weeks or less.

Suspected Lead Fracture – May be manifested by abnormal device measurements (i.e. RV lead impedance, thresholds, inappropriate shocks) which may be caused as a result of conductor/lead fracture. Investigator are requested to complete a through lead assessment (as defined in section 13.4); confirm through visual, radiographic and electrical analysis, and are strongly recommended to return the lead to for analysis.

Suspected Lead Abrasion – May be manifested by abnormal device measurements (i.e. RV lead impedance, thresholds) which may be as a result of unknown lead abrasion type (which are not already defined above). Investigators are requested to complete a through lead assessment (as defined in section 13.4); and strongly recommended to return the lead to for analysis.

Twiddler's Syndrome - A well-known complication of pacemaker treatment, it involves a patient manipulating and rotating the pulse generator in the pocket so many turns that it results in lead dislodgment, diaphragmatic stimulation and/or loss of capture.

Undersensing – Complete or intermittent loss of sensing or failure to detect the intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity. ◊

◊ **Definition based on AdvaMed's May 2009** ***Industry Guidance for Uniform Reporting of Clinical Performance of Cardiac Rhythm Management Pulse Generators and Leads*****.**