INGEVITY+ Active Fixation Pace/Sense Lead Clinical Study

C1730

CLINICAL INVESTIGATION PLAN

Sponsored By

Boston Scientific Corporation

4100 Hamline Ave. N.

St. Paul, MN 55112

Contact Information

Role	Contact
Clinical Contact	Boston Scientific, Rhythm Management (RM) Gena Kantor 4100 Hamline Avenue North St. Paul, MN 55112 Phone: 1-800-CARDIAC
Coordinating Principal Investigator(s)	Devi G. Nair, MD Nair Associates, LLC 3878 Ridgewood Cove Jonesboro, AR 72404 Phone: (870) 935-6729

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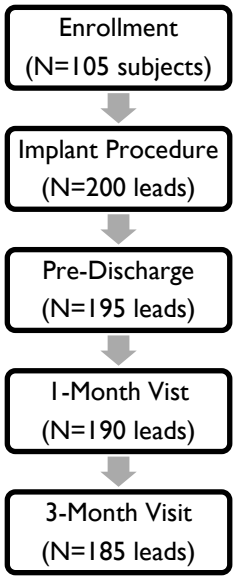
Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
A	10 September 2019	92120219 Rev/Ver C	N/A	Initial version	N/A
B	12 May 2020	92120219 Rev/Ver C	2.0, 7.1, 10.1, 10.6, 10.7, 10.8, 10.10, 10.12, 11.1.2, 11.4.2, 17.4, 19.2	Contact Information: Added Study PI name and contact information. 2.0: Synopsis updated to reflect Protocol changes. 7.1: Added clarification that the planned enrollment of 105 subjects only includes successfully implanted subjects, and does not include intent/attempt/partial attempt subjects. Enrollment and study duration updated to reflect current expectations. 10.1, 10.6, 10.7, 10.8, 10.10, 10.12: Language was added to the Protocol to allow for telephone/telehealth visits with LATITUDE transmission of lead measurements at the 1 and 3 month follow-up visits if it is not possible for a subject to complete an in-clinic follow-up visit. The requirement for three consecutive threshold measurements was also removed from the 3-month follow-up visit because it is not possible to obtain this from LATITUDE transmission of lead measurements. 11.1.2: Section focus was changed from subjects to leads.	Contact Information: Study PI selected since Rev. A of Protocol. 2.0: Synopsis updated to reflect Protocol changes. 7.1: To address the foreseen attrition rate and slower than previously anticipated enrollment due to uncertainty during the COVID-19 pandemic. 10.1, 10.6, 10.7, 10.8, 10.10, 10.12: The global COVID-19 pandemic has caused significant changes in the administration of healthcare and local restrictions at sites may exist for in-person clinic visits. 11.1.2: This is more consistent with the language elsewhere in Section 11. 11.4.2: Analyses to assess if LATITUDE measurements vs in-clinic measurements had any impact on lead data. 17.4: To provide direction to sites on how to report events under

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
				11.4.2: Added a sub-group analysis to compare pacing capture threshold test type (In-office vs. Auto-threshold). 17.4: Language was added to clarify how to report events. 19.2: CEC adjudication of lead related complications was removed.	usual circumstances, and when the EDC is not available. 19.2: The INGEVITY+ Study's Safety Endpoint was designed for comparability to other pace/sense lead studies, especially to the INGEVITY Study. The INGEVITY Study performed both BSC and CEC classifications of lead-related complications. BSC classifications were used for the Safety Endpoint evaluations and the CEC adjudications were used as a confirmation of BSC's classifications (as detailed in the PMA report). Though the CEC adjudications would provide a confirmation of the BSC classifications, the adjudications are not critical for the fulfillment of the study objectives. In an effort to achieve the 'least burdensome' means of assuring the safety and effectiveness of the INGEVITY+ Lead Family, especially during the COVID-19 pandemic this requirement was removed.

2. Protocol Synopsis

<table>
<tr><th colspan="2">INGEVITY+ Active Fixation Pace/Sense Lead Clinical Study</th></tr>
<tr><td>Study Objective(s)</td><td>The objective of this study is it to confirm the safety and effectiveness of the INGEVITY+ Active Fixation Pace/Sense Lead.</td></tr>
<tr><td>Indication(s) for Use</td><td>The INGEVITY+ lead is intended for chronic pacing and sensing in the right atrium and/or right ventricle when used with a compatible pulse generator.</td></tr>
<tr><td>Commercial Device/System applied as Standard of Care and sizes, if applicable</td><td>
<table>
<tr><td rowspan="4">INGEVITY+ Lead
Active fixation models</td><td>Model #</td><td>Lead length</td></tr>
<tr><td>7840</td><td>45 cm</td></tr>
<tr><td>7841</td><td>52 cm</td></tr>
<tr><td>7842</td><td>59 cm</td></tr>
</table>
</td></tr>
<tr><td>Study Design</td><td>The INGEVITY+ Clinical Study is a prospective, non-randomized, multi-center, post-market study.
 
</td></tr>
<tr><td>Planned Number of Subjects</td><td>At least 105 subjects will be enrolled in the study to achieve 200 implanted or attempted leads.</td></tr>
</table>

INGEVITY+ Active Fixation Pace/Sense Lead Clinical Study	
Planned Number of Sites / Countries	This study will include approximately 20 sites in North America.
Primary Safety Endpoint	Lead-related Complication-Free Rate from Implant through 3-Months Post-Implant
Primary Effectiveness Endpoint	Pacing Capture Threshold at 3-Months Post-Implant
Secondary Effectiveness Endpoint	Sensed Amplitude and Pacing Impedance at 3-Months Post-Implant
Additional Analysis	Implant turn count, lead handling, lead maneuverability, lead-related device deficiencies, including extension/retraction and accessories used
Method of Assigning Patients to Treatment	This is a one-armed study where every subject is assigned to treatment, where treatment means implanted, or attempted implant of INGEVITY+ leads in the right atrium and ventricle.
Follow-up Schedule	Study procedures and clinic visits will occur at the following time periods. The study will be considered complete after all subjects have completed their 3-Month Clinic Visit and exited the study. – Enrollment Visit (less than or equal to 30 days before the implant procedure) – Implant Procedure (Day 0; all future follow-ups based on this date) – Pre-Discharge Clinic Visit (3 – 72 hours) – 1-Month Clinic Visit (30 ± 7 days) – 3-Month Clinic Visit (91 + 31 days)
Study Duration	Enrollment is expected to be completed in approximately 12 months; therefore, the total study duration is estimated to be approximately 16 months.
Participant Duration	The study duration for each subject is expected to be approximately 3 months. Subjects will be exited from the study after their 3 month visit.

INGEVITY+ Active Fixation Pace/Sense Lead Clinical Study	
Inclusion Criteria	1. Subject is willing and capable of providing informed consent 2. Subject is intended to undergo initial (de novo) pacing system implant using INGEVITY+ Leads in the Right Atrium (RA) and Right Ventricle (RV) and a Boston Scientific pulse generator 3. Subject meets an indication for a Boston Scientific Pacemaker or CRT-P device per product labeling (Physician's Technical Manual): o Pacemaker: ▪ Symptomatic paroxysmal or permanent second- or third-degree AV block ▪ Symptomatic bilateral bundle branch block ▪ Symptomatic paroxysmal or transient sinus node dysfunction with or without associated AV conduction disorders (i.e., sinus bradycardia, sinus arrest, sinoatrial [SA] block) ▪ Bradycardia-tachycardia syndrome, to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmias ▪ Neurovascular (vaso-vagal) syndromes or hypersensitive carotid sinus syndromes ▪ Adaptive-rate pacing for patients exhibiting chronotropic incompetence and who may benefit from increased pacing rates concurrent with increases in minute ventilation and/or level of physical activity ▪ Dual-chamber and atrial tracking modes for patients who may benefit from maintenance of AV synchrony ▪ Dual chamber modes are specifically indicated for treatment of the following: • Conduction disorders that require restoration of AV synchrony, including varying degrees of AV block • VVI intolerance (i.e., pacemaker syndrome) in the presence of persistent sinus rhythm • Low cardiac output or congestive heart failure secondary to bradycardia o CRT-P: ▪ Moderate to severe heart failure (NYHA Class III/IV) including left ventricular dysfunction (EF ≤ 35%) and QRS duration ≥ 120 ms and remain symptomatic despite stable optimal pharmacologic therapy for heart failure

INGEVITY+ Active Fixation Pace/Sense Lead Clinical Study	
	▪ Atrial tracking modes for patients who may benefit from maintenance of AV synchrony ▪ Adaptive-rate pacing for a patient exhibiting chronotropic incompetence and who would benefit from increased pacing rates concurrent with increases in minute ventilation and/or physical activity 4. Willing and capable of participating in all testing/visits associated with this clinical study at an approved clinical study center and at the intervals defined by this protocol 5. Age 18 or above, or of legal age to give informed consent specific to state and national law
Exclusion Criteria	1. Known or suspected sensitivity to dexamethasone acetate (DXA) 2. Has a mechanical tricuspid heart valve 3. Women of childbearing potential who are or might be pregnant at the time of study enrollment or INGEVITY+ Lead implant (method of assessment upon physician's discretion) 4. Currently requiring hemo- or peritoneal dialysis 5. Subject has or has had implanted any pacing or ICD system, including subcutaneous, transvenous or leadless systems 6. Intended to receive a single chamber device 7. Documented history of permanent or persistent AF 8. Currently on an active organ transplant list 9. Documented life expectancy of less than 12 months 10. Enrolled in any other concurrent study unless prior approval is received from the Sponsor
Statistical Methods	
Primary Safety Endpoint Statistical Hypothesis	H_0: Lead-Related Complication-Free rate at 3 months ≤ 93% H_A: Lead-Related Complication-Free rate at 3 months > 93% Performance goal = 93%, if the lower confidence limit exceeds 93%, the null hypothesis will be rejected Selected to ensure INGEVITY+ has similar rate to other market-approved pacing leads To account for variability in estimate of rate (i.e., confidence limit), 5% was subtracted from industry average rate of 98% to determine performance goal

INGEVITY+ Active Fixation Pace/Sense Lead Clinical Study	
Primary Safety Endpoint Statistical Test Method	The 97.5% one-sided lower confidence limit of the rate will be compared to performance goal. The complimentary log-log confidence limit of the 3-month Kaplan-Meier rate will be calculated. Data from RA and RV leads will be combined for the analysis.
Primary Effectiveness Endpoint Statistical Hypothesis	H_0: Pacing Capture Threshold Responders at 3 months ≤ 80% H_A: Pacing Capture Threshold Responders at 3 months > 80% Performance goal = 80%, if the lower confidence limit exceeds 80%, the null hypothesis will be rejected
Primary Effectiveness Endpoint Statistical Test Method	The 97.5% one-sided lower confidence limit of the responder rate will be compared to performance goal. A Clopper-Pearson (exact) confidence interval will be calculated. Data from RA and RV leads will be combined for the analysis.
Study Sample Size Parameters	A sample size of 185 leads with endpoint data is required to provide at least 90% power for all endpoints. Assuming ~7.5% attrition (due to attempted implant, death, withdrawal), at least 105 subjects will be enrolled to yield 185 leads with endpoint data. The sample size is driven by the primary safety endpoint.

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

4.1. *Background*

Pacemaker leads are an essential component of a pacemaker system. A pacemaker lead is the insulated electrical conductor between the implantable pulse generator (IPG) and the cardiac tissue. The lead is a complex mechanical structure that has to withstand biodegradation in the environment of the body, repetitive flexural cycles of the heart, and compressive and tensile forces in the extravascular space. Design requirements may include requirements related to ease of implant handling, fluoroscopic visualization, the diameter of the lead body, durability to last beyond the replacement of several IPGs, performance to stimulate the cardiac tissue with low energy, ability to reliably sense intrinsic cardiac activity, and design with consideration of future lead extraction.

The INGEVITY lead family, including models labeled as MR Conditional and corresponding models without MR Conditional labeling, has demonstrated outstanding clinical and commercial performance and safety. Although the implant performance experience is positive overall, physicians have provided feedback on the active fixation models regarding difficulty in extending and/or retracting the helix; this occurs during implantation when the lead is subjected to challenging bends due to tortuous vasculature based on patient anatomy and/or when combined with various physician techniques. To address physicians' feedback, Boston Scientific Corporation (BSC) initiated a project to improve the extension/retraction performance of the active fixation lead, and has developed, bench tested, and animal-tested three new models of the INGEVITY lead family called the INGEVITY+ lead.

Three design changes were implemented in the INGEVITY+ lead to achieve the goal of improving extension/retraction performance as part of the physician's handling experience without compromising the features and functionality of the original INGEVITY active fixation lead:

- Change 1: The inner coil was modified from a uni-filar coil with an Ethylene tetrafluoroethylene (ETFE) covering to a tri-filar coil with no ETFE covering to improve the consistency of helix extension/retraction performance.
- Change 2: To accommodate the inner coil change, the design of inner coil connections at the terminal pin (proximal end of coil) and the coupler (distal end of the coil) were revised to incorporate a counter-bore that allows the inner coil to be positioned within these two components.
- Change 3: The outer diameter of the distal seal is being increased by 0.001 inch to align with the design changes to the inner coil.

All other design specifications and other aspects of lead performance remain unchanged.

The INGEVITY+ Active Fixation Pace/Sense Lead Clinical Study will gather data to confirm the safety, performance, and effectiveness of the INGEVITY+ Lead.

4.2. *Study Rationale*

Boston Scientific Rhythm Management is conducting this study to fulfill post-approval regulatory requirements.

5. Commercial Device Description

5.1. *Commercial Device*

This lead family has the following characteristics:

- Endocardial pace/sense lead—intended for chronic bipolar pacing and sensing in the atrium and/or ventricle.
- IS-1 bipolar connector[i]—the industry standard connector to be used in conjunction with a compatible cardiac device that accepts the IS-1 connector.
- MR Conditional—leads can be used as part of the ImageReady MR Conditional Pacing System or the ImageReady MR Conditional Defibrillation System when connected to Boston Scientific MR Conditional pulse generators ("MR Conditional System Information" on page 2 of the Physicians Lead Manual (PLM)).
- Iridium Oxide (IROX)-coated electrodes—the electrodes are coated with IROX to increase the microscopic surface area.
- Steroid-eluting—upon exposure to body fluids, the steroid elutes from the lead to help reduce tissue inflammation response at the distal electrode. The steroid suppresses the inflammatory response believed to cause threshold rises typically associated with implanted pacing electrodes. Lower thresholds are desirable because they can increase pacing safety margins and reduce pacing energy requirements, potentially increasing pulse generator longevity. The nominal dose and structure of the steroid are listed in the specifications (Table 5 Specifications on page 30 of the PLM).
- Radiopaque suture sleeve—the radiopaque suture sleeve is visible under fluoroscopy and is used to secure, immobilize, and protect the lead at the venous entry site after lead placement. The window feature is designed to aid compression of the sleeve onto the lead during suturing.
- Extendable/Retractable fixation—the extendable/retractable helix design anchors the distal tip electrode to the endocardial surface without support of trabecular structures, offering various lead placement possibilities for the tip electrode in the right atrium and/or right ventricle. The helix serves as the cathode for endocardial pacing and sensing. The helix is extended and retracted using the fixation tool.
- Fluoroscopic markers—radiopaque markers near the distal tip can be seen under fluoroscopy. These markers show when the helix is fully retracted or fully extended.
- Lead body—the isodiametric lead body consists of a coaxial design that includes a tri-filar inner coil and a single-filar outer coil. Both the inner and outer coils are designed for MR Conditional use in the MRI environment and provide robust flexural fatigue performance. In addition, the tri-filar inner coil provides consistent helix deployment performance. The conductors are separated by both a silicone rubber and

[i] IS-1 refers to the international standard ISO 5841-3:2013.

Polytetrafluoroethylene (PTFE) lining. The outer coil is covered in Ethylene tetrafluoroethylene (ETFE) for extra insulation protection. The entire lead body is encompassed in a polyurethane outer insulation.

- Stylet delivery method—the design consists of an open-lumen conductor coil to enable lead delivery using a stylet. Refer to the stylet information ("Stylets" on page 12 of the PLM).

The INGEVITY+ lead is indicated for chronic pacing and sensing in the right atrium and/or right ventricle when used with a compatible pulse generator.

Table 5-1 contains the model numbers, and lead lengths of the INGEVITY+ Leads used in this study.

Table 5-1: INGEVITY+ Lead Models & Lengths

Model Number	Lead Length
7840	45 cm
7841	52 cm
7842	59 cm

6. Study Objectives and Endpoints

See Table 6-1 below for a summary of the primary objectives and endpoints for the INGEVITY+ Study.

Table 6-1: Overview of objectives and endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Confirm the safety of the INGEVITY+ Lead	Lead-related Complication-Free Rate from Implant through 3-Months Post-Implant	Similar endpoints have been used to evaluate outcomes in other pace/sense lead studies
Confirm the effectiveness of the INGEVITY+ Lead	Pacing Capture Threshold at 3-Months Post-Implant	
Secondary		
Confirm the effectiveness of the INGEVITY+ Lead	Sensed Amplitude and Pacing Impedance at 3-Months Post-Implant	Similar endpoints have been used to evaluate outcomes in other pace/sense lead studies
Additional		
Confirm the device design changes of the INGEVITY+ Lead	Implant turn count, lead handling, lead maneuverability, lead-related device deficiencies, including extension/retraction, and accessories used	Confirm design changes had intended effects

7. Study Design

The INGEVITY+ Study is a prospective, non-randomized, multi-center, post-approval study utilizing performance goals to confirm the safety, performance, and effectiveness of the INGEVITY+ Lead.

7.1. *Scale and Duration*

The INGEVITY+ study will enroll at least 105 subjects at approximately 20 sites in the United States to achieve 200 implanted or attempted INGEVITY+ leads. The enrollment ceiling of 105 will not include attempt, partial attempt or intent subjects; see section 9.4 for subject status and classification definitions. A maximum of 21 subjects may be enrolled per site unless prior approval from the Sponsor is obtained. Enrollment is expected to be completed in approximately 12 months; therefore, the total study duration is estimated to be approximately 16 months. Follow up will be required at pre-discharge, 1-month, and 3-months post-implant.

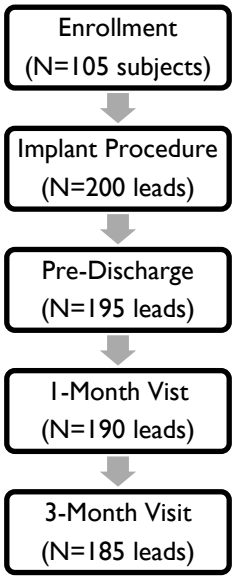


Figure 7-1: INGEVITY+ Study Design

7.2. *Treatment Assignment*

This is a one-armed study where every subject is assigned to treatment, where treatment means implanted, or attempted implant of INGEVITY+ leads in the right atrium and ventricle.

7.3. *Justification for the Study Design*

The potential clinical effect or impact of the design changes associated with the INGEVITY+ lead would be seen in the short-term use of the lead, which BSC will study in the post-approval study (PAS) plan outlined in this protocol. In addition, industry-average short-term evaluation period for establishing short-term safety and effectiveness of a pace/sense lead

equals three months and is slightly longer than the acute (i.e., short-term) period of ≤30 days established in the Industry Guidance for Uniform Reporting of Clinical Performance of Cardiac Rhythm Management Pulse Generators and Leads.[1]

8. Subject Selection

8.1. *Study Population and Eligibility*

Subjects included in the INGEVITY+ Study will be selected from the investigator's general patient population indicated for dual-chamber pacemaker or CRT-P implantation. Investigators are responsible for screening all potential subjects and selecting those who meet the eligibility criteria for the study as described in sections 8.2 and 8.3.

8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 8-1) may be considered for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.3) is met.

Table 8-1: Inclusion Criteria

Inclusion Criteria	1. Subject is willing and capable of providing informed consent 2. Subject is intended to undergo initial (de novo) pacing system implant using INGEVITY+ Leads in the Right Atrium (RA) and Right Ventricle (RV) and a Boston Scientific pulse generator 3. Subject meets an indication for a Boston Scientific Pacemaker or CRT-P device per product labeling (Physician's Technical Manual): o Pacemaker: ▪ Symptomatic paroxysmal or permanent second- or third-degree AV block ▪ Symptomatic bilateral bundle branch block ▪ Symptomatic paroxysmal or transient sinus node dysfunction with or without associated AV conduction disorders (i.e., sinus bradycardia, sinus arrest, sinoatrial [SA] block) ▪ Bradycardia-tachycardia syndrome, to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmias ▪ Neurovascular (vaso-vagal) syndromes or hypersensitive carotid sinus syndromes ▪ Adaptive-rate pacing for patients exhibiting chronotropic incompetence and who may benefit from

	increased pacing rates concurrent with increases in minute ventilation and/or level of physical activity ▪ Dual-chamber and atrial tracking modes for patients who may benefit from maintenance of AV synchrony ▪ Dual chamber modes are specifically indicated for treatment of the following: • Conduction disorders that require restoration of AV synchrony, including varying degrees of AV block • VVI intolerance (i.e., pacemaker syndrome) in the presence of persistent sinus rhythm • Low cardiac output or congestive heart failure secondary to bradycardia o CRT-P: ▪ Moderate to severe heart failure (NYHA Class III/IV) including left ventricular dysfunction (EF ≤ 35%) and QRS duration ≥ 120 ms and remain symptomatic despite stable optimal pharmacologic therapy for heart failure ▪ Atrial tracking modes for patients who may benefit from maintenance of AV synchrony ▪ Adaptive-rate pacing for a patient exhibiting chronotropic incompetence and who would benefit from increased pacing rates concurrent with increases in minute ventilation and/or physical activity 4. Willing and capable of participating in all testing/visits associated with this clinical study at an approved clinical study center and at the intervals defined by this protocol 5. Age 18 or above, or of legal age to give informed consent specific to state and national law

8.3. ***Exclusion Criteria***

Subjects who meet any one of the following criteria (Table 8-2) are not eligible for study participation.

Table 8-2: Exclusion Criteria

Exclusion Criteria	1. Known or suspected sensitivity to dexamethasone acetate (DXA) 2. Has a mechanical tricuspid heart valve 3. Women of childbearing potential who are or might be pregnant at the time of study enrollment or INGEVITY+ Lead implant (method of assessment upon physician's discretion) 4. Currently requiring hemo- or peritoneal dialysis 5. Subject has or has had implanted any pacing or ICD system, including subcutaneous, transvenous or leadless systems 6. Intended to receive a single chamber device 7. Documented history of permanent or persistent AF 8. Currently on an active organ transplant list 9. Documented life expectancy of less than 12 months 10. Enrolled in any other concurrent study unless prior approval is received from the Sponsor

9. Subject Accountability

9.1. *Point of Enrollment*

Subjects will be considered enrolled in the INGEVITY+ Study at the time of informed consent form (ICF) execution. All subject enrollments will be counted against the enrollment ceiling for the study.

9.2. *Withdrawal*

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

If the INGEVITY+ lead(s) of a study subject is explanted, the subject must be followed for 30 ± 7 days after the explant of the INGEVITY+ lead(s); any open adverse events must be closed or documented as chronic. Thirty days after the explant of the INGEVITY+ lead(s), a 30-day Follow-up eCRF must be completed, and the subject can be withdrawn from the study. An End of Study eCRF must be completed.

Reasons for withdrawal may include but are not limited to:

- Physician discretion
- Subject choice to withdraw consent
- Explant of all INGEVITY+ lead(s)
- Loss to follow-up
- Death

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 electronic case report form (eCRFs) up to the point of subject withdrawal and an End of Study eCRF must be completed. 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 subject withdrawal may be used.

9.3. *Lost to Follow-Up*

For subjects who are "lost-to-follow-up," the investigator/ center should have at least three documented attempts to contact the subject prior to completion of the End of Study eCRF. The end of study date for "lost-to-follow-up" subjects should be on or after the last documented contact attempt.

9.4. *Subject Status and Classification*

Intent - refers to a subject who has been enrolled, but then does not undergo an implant procedure. The original Informed Consent form and screening documentation for intent subjects must be maintained in the Center's files. There are no follow-up requirements for intent subjects. The subject can be withdrawn from the study, and an End of Study eCRF must be completed.

Partial Attempt – refers to a subject who has been enrolled and has had anesthesia administered in preparation for the surgical implant procedure but does not have the INGEVITY+ lead introduced into their vasculature. There are no follow-up requirements for partial attempt subjects. The subject can be withdrawn from the study, and an End of Study eCRF must be completed.

Attempt - refers to a subject who has been enrolled in the INGEVITY+ Study and has had anesthesia administered in preparation for the surgical implant procedure and has had the INGEVITY+ lead introduced into the subject's vasculature, but is not successfully implanted with an INGEVITY+ lead.

Attempt subjects must be followed 30 ± 7 days post-attempted INGEVITY+ lead implant to assure there are no associated adverse events, or to assure the resolution of any adverse events associated with the attempted INGEVITY+ lead implant. Thirty days after the attempt of the INGEVITY+ lead(s), a 30-day Follow-up eCRF must be completed, and the subject can be withdrawn from the study. An End of Study eCRF must be completed.

Implant - refers to a subject who is successfully implanted and/or tested with the INGEVITY+ Lead(s) per the study protocol. These subjects are followed in accordance with the follow-up schedule and included in all analyses of safety and performance.

9.5. *End-of-Study Definition*

A clinical trial is considered completed when participants are no longer being examined, and the last participant has exited the study, all data is reported, and the database is locked.

10. Study Methods

10.1. *Data Collection*

Data will be collected from each subject at enrollment, implant, pre-discharge, 1-month and 3-months post-implant and results recorded on the appropriate eCRF. Additional follow-up visits must be collected as defined in Section 10.9. All study-related visit windows are calculated from the date of initial INGEVITY+ lead implant.

The data collection schedule is shown in Table 10-1.

Table 10-1: Data Collection Schedule

Procedure/Assessment*	Enrollment ≤ 30 days prior to Implant	Index Procedure Day 0[1]	Post-procedure/ Prehospital Discharge 3-72 hours[1]	Follow-up Visits		
				1 Month (30 ± 7 Days)[1] Clinic Visit	3 Month (91+31 Days)[1] Clinic Visit	Additional Visit
Informed consent process, including informed consent signature date	X	-	-	-	-	-
Demographics	X	-	-	-	-	-
Physical assessment, including weight and height	X	-	-	-	-	-
Medical history	X	-	-	-	-	-
Implant Questionnaire	-	X	-	-	-	-
PSA measurements for all leads	-	X	-	-	-	-
PA and lateral chest X-ray and/or fluoroscopic image of lead distal tip fixation	-	X		-	-	-
Cardiovascular Medications	X	-	-	-	X	-
IPG lead measurements for all leads	-	X	X	X	X	O / X**
Adverse events assessment/reporting	X	X	X	X	X	X
Device deficiency assessment/reporting		X	X	X	X	X
Protocol deviation	X	X	X	X	X	X

X = Required; - = Not required/Not Applicable; O = Optional

[1] Clock starts after end of implant procedure, day of implant is day 0, and pocket closure is hour 0

* See Table 10-3 in Section 10.12 for full source requirements

**Required if there is a lead-related AE or device deficiency, otherwise optional

10.2. *Study Candidate Screening*

For the INGEVITY+ Study, physician investigators are responsible for screening all potential patients and selecting those who are appropriate for study inclusion. The patients selected for participation should be from the investigator's general patient population with an indication for implantation of a Boston Scientific dual-chamber pacemaker or CRT-P system according to the product labeling (Physician's Technical Manual).

10.3. *Informed Consent*

Patients who appear to meet all of the inclusion criteria and none of the exclusion criteria and agree to participate in the INGEVITY+ Study must give written informed consent in a form approved by the investigational center's IRB prior to study participation and data collection. The Investigator is responsible for ensuring that Informed Consent is obtained prior to any study-required procedure and/or testing, or data collection. Patients who complete the informed consent process and sign and date the informed consent for the INGEVITY+ Study will be considered enrolled in the study at the point of executing an ICF.

10.4. *Enrollment Visit [≤ 30 days prior to Implant]*

The data to be collected during enrollment into the INGEVITY+ Study includes subject demographic data, a physical assessment of the subject, including height and weight, arrhythmia history, cardiac disease history, and current cardiovascular medications.

Implant or attempted implant of the INGEVITY+ Leads must occur ≤ 30 days of the subject signing informed consent.

10.5. *Implant Visit [Day 0]*

The IPG and INGEVITY+ leads should be implanted and tested in accordance with the Physician's Manuals. The implant procedure, peri-implant management, and post-operative care of the INGEVITY+ leads are standard of care for cardiac pacemaker and CRT-P implants. There are no special tools or procedures required to implant INGEVITY+ leads.

Subjects in this clinical study will be required to be attempted with INGEVITY+ Leads in their RA and RV. The data to be collected from the implant procedure includes:

- IPG:
  - Type
  - Manufacture
  - Model
  - Serial number
  - Pocket location
  - Device location in pocket
  - Time of pocket closure
- Leads (all attempted and successfully implanted):
  - Lead location
  - Model

  - Serial number
  - Anatomical space
  - Number of turns to fully extend the helix
  - Number of turns to fully retract the helix, for repositioning if applicable
  - Voltage threshold, sensed amplitude(s), and pacing impedance of the leads measured with a pacing system analyzer (PSA)
  - Voltage threshold, sensed amplitude(s), and pacing impedance of the leads measured with the implanted IPG
- Implant accessories used:
  - Vein pick
  - Stylet
  - Stylet guide
  - Fixation tool
  - Slit Suture Sleeve

10.5.1. Baseline Lead Measurements with PSA

The voltage threshold, sensed amplitude(s), and pacing impedance of the leads measured with a pacing system analyzer (PSA) will be obtained to verify adequate signals. Electrical performance of the leads will be verified before attaching the leads to the pulse generator. Baseline measurements will be performed after allowing sufficient time for the effect of local tissue trauma to subside (approximately 10 minutes).

If the baseline measurements do not meet clinically acceptable values, it is recommended the Investigator reposition the lead system. Table 10-2 includes the recommended baseline measurements from the INGEVITY+ Physician's Lead Manual.

Table 10-2: Recommended Threshold and Sensing Measurements at Implant with PSA

Measurements	Atrial Data	Ventricular Data
Voltage Threshold (pulse width setting at 0.5ms)	≤ 1.5 V	≤ 1.0 V
P-wave/ R-wave	≥ 2.0 mV	≥ 5.0 mV
Impedance	200-2000 Ω	200-2000 Ω

10.5.2. Fluoroscopic Image/Chest x-ray

Either a fluoroscopic image or PA and lateral chest X-ray of the lead distal tip fixation must be obtained at implant or pre-discharge.

10.5.3. Lead Measurements with IPG

Lead measurements, including pacing thresholds, sensed amplitudes, and pacing impedances are required post-implant for all implanted leads. After the implant procedure is complete, pacing and sensing evaluation of the leads using the IPG (either pacemaker or CRT-P) must be performed. Lead baseline measurements are required unless the testing is inhibited by a subject condition (subject has no intrinsic rhythm or subject is in atrial fibrillation).

During the INGEVITY+ Study, pacing threshold measurements will be collected in a standard manual fashion in bipolar electrode configuration. At least two (2) cardiac cycles at a given voltage level shall be obtained before stepping down to the next voltage level. A count of two (2) non-capture beats is required at a given voltage level to declare a loss of capture (LOC) for any of these tests. The threshold is defined as one voltage level above the level where two (2) non-captured beats are observed.

The following baseline measurements must be taken utilizing the IPG to ensure adequate sensing and pacing function of all leads:

- Intrinsic amplitude (mV)
- Voltage pacing capture threshold in the bipolar mode lead configuration (V, at 0.4 ms pulse width)
- Lead impedance (Ω)

10.5.4. Implant Questionnaire

An implant questionnaire is included as a part of the implant procedure. It includes questions regarding the implanting physicians' experience with this new lead, including overall handling of the lead, as well as other related questions.

10.5.5. AEs/ /Device Deficiencies/ Deviations

Document any applicable adverse events, device deficiencies, and deviations that have occurred.

10.5.6. Source Documentation Requirements

See Table 10-3 in Section 10.12 for required source documentation for the implant procedure.

10.6. *Pre-Discharge [3-72 hrs]*

Subjects will have a lead evaluation prior to leaving the hospital.

The pre-discharge follow-up must be performed between 3 hours and 72 hours after implant. If the subject needs to stay more than 72 hours in the hospital after implant for any reason, the pre-discharge procedure should be performed prior to the end of 72 hours even if the subject is still in the hospital. Any reasons for prolonged or ongoing hospitalization need to be appropriately documented (i.e., Adverse Event eCRF, if applicable). If the subject will be followed on the LATITUDE system, the automatic threshold or automatic capture (TREND or Auto) feature must be turned on prior to discharge for all chambers in which INGEVITY + leads are implanted.

10.6.1. Lead Measurements with IPG

Lead measurements, including pacing thresholds, sensed amplitudes, and pacing impedances are required at the pre-discharge visit for all implanted leads. Pacing and sensing evaluation using the IPG (either pacemaker or CRT-P) must be performed. Lead measurements are

required unless the testing is inhibited by a subject condition (subject has no intrinsic rhythm or subject is in atrial fibrillation).

During the INGEVITY+ Study, pacing threshold measurements will be collected in a standard manual fashion in bipolar electrode configuration. At least two (2) cardiac cycles at a given voltage level shall be obtained before stepping down to the next voltage level. A count of two (2) non-capture beats is required at a given voltage level to declare a loss of capture (LOC) for any of these tests. The threshold is defined as one voltage level above the level where two (2) non-captured beats are observed.

The following measurements are to be taken utilizing the IPG to ensure adequate sensing and pacing function of all leads:

- Intrinsic amplitude (mV)
- Voltage pacing capture threshold in the bipolar mode lead configuration (V, at 0.4 ms pulse width)
- Lead impedance (Ω)

10.6.2. Fluoroscopic Image/Chest x-ray

Either a fluoroscopic image or PA and lateral chest X-ray of the lead distal tip fixation must be obtained at implant or pre-discharge.

10.6.1. AEs/ Device Deficiencies/ Deviations

Document any applicable adverse events, device deficiencies, and deviations that have occurred.

10.6.2. Source Documentation Requirements

See Table 10-3 in Section 10.12 for required source documentation for the pre-discharge visit.

10.7. *1-Month follow-up visit [30 ±7 days]*

Study follow-up visits shall be completed in-clinic; however, if it is not possible to complete an in-clinic follow-up visit (e.g., local restrictions due to global health crisis) a telephone or telehealth visit with LATITUDE remote transmission of lead measurement can be substituted.

10.7.1. Lead Measurements with IPG

Lead measurements, including pacing thresholds, sensed amplitudes, and pacing impedances are required at the one-month visit for all implanted leads. Pacing and sensing evaluation using the IPG (either pacemaker or CRT-P) must be performed. Lead measurements are required unless the testing is inhibited by a subject condition (subject has no intrinsic rhythm or subject is in atrial fibrillation).

If the visit is performed in-clinic during the INGEVITY+ Study, pacing threshold measurements will be collected in a standard manual fashion in bipolar electrode configuration. At least two (2) cardiac cycles at a given voltage level shall be obtained before stepping down to the next voltage level. A count of two (2) non-capture beats is required at a given voltage level to declare a loss of capture (LOC) for any of these tests. The threshold is defined as one voltage level above the level where two (2) non-captured beats are observed.

The following measurements are to be taken utilizing the IPG to ensure adequate sensing and pacing function of all leads:

- Intrinsic amplitude (mV)
- Voltage pacing capture threshold in the bipolar mode lead configuration (V, at 0.4 ms pulse width)
- Lead impedance (Ω)

If a remote visit with LATITUDE lead measurements is performed see section 10.10

10.7.1. AEs /Device Deficiencies/Deviations

Document any applicable adverse events, device deficiencies, and deviations that have occurred.

10.7.2. Source Documentation Requirements

See Table 10-3 in Section 10.12 for required source documentation for the 1-month follow-up.

10.8. *3-Month follow-up visit [91 + 31 days]*

Study follow-up visits shall be completed in-clinic; however, if it is not possible to complete an in-clinic follow-up visit (e.g., local restrictions due to global health crisis) a telephone or telehealth visit with LATITUDE remote transmission of lead measurement can be substituted.

10.8.1. Lead Measurements with IPG

Lead measurements, including pacing thresholds, sensed amplitudes, and pacing impedances are required at the 3-month visit for all implanted leads. Pacing and sensing evaluation using the IPG (either pacemaker or CRT-P) must be performed. Lead measurements are required unless the testing is inhibited by a subject condition (subject has no intrinsic rhythm or subject is in atrial fibrillation).

If the visit is performed in-clinic during the INGEVITY+ Study, pacing threshold measurements will be collected in a standard manual fashion in bipolar electrode configuration. At least two (2) cardiac cycles at a given voltage level shall be obtained before stepping down to the next voltage level. A count of two (2) non-capture beats is required at a given voltage level to declare a loss of capture (LOC) for any of these tests. The threshold is defined as one voltage level above the level where two (2) non-captured beats are observed.

The following measurements are to be taken utilizing the IPG to ensure adequate sensing and pacing function of all leads:

- Intrinsic amplitude (mV)
- Voltage pacing capture threshold in the bipolar mode lead configuration (V, at 0.4 ms pulse width).
- Lead impedance (Ω)

If a remote visit with LATITUDE lead measurements is performed see section 10.10

10.8.2. Cardiovascular Meds/AEs /Device Deficiencies/Deviations

The subject's cardiovascular medications must be assessed for any updates or changes. Any changes to the subject's cardiovascular medication must be documented.

Document any applicable adverse events, device deficiencies, and deviations that have occurred.

10.8.3. Source Documentation Requirements

See Table 10-3 in Section 10.12 for required source documentation for the 3-month follow-up.

10.9. *Additional follow-up visits*

All follow-ups outside of the designated follow-up windows or multiple visits inside any follow-up window need to be reported on an Additional Follow-up eCRF if associated with a reportable adverse event or device deficiency. Routinely scheduled office visits for purposes other than these events do not require an Additional Follow-up eCRFs to be completed.

Document any applicable adverse events, device deficiencies, and deviations that have occurred.

Device evaluation is optional at these visits unless an adverse event is related to the INGEVITY+ lead(s) or there is a device deficiency, then an evaluation of the device is required.

10.9.1. Source Documentation Requirements

See Table 10-3 in Section 10.12 for required source documentation for additional follow-ups.

10.10. *Remote Follow-up*

Study follow-up visits shall be completed in-clinic; however, if it is not possible to complete an in-clinic follow-up visit (e.g., local restrictions due to global health crisis) a telephone or telehealth visit with LATITUDE remote transmission of lead measurements can be substituted. The reason for the remote follow-up visit must be documented. Subjects may be followed on the LATITUDE system from the time they are implanted. If a patient is followed on the LATITUDE system, the automatic threshold or automatic capture (TREND

or Auto) feature must be turned on for all chambers in which INGEVITY+ leads are implanted.

The subject will be contacted for a telephone or telehealth visit, within the applicable follow-up window. Any applicable adverse events, device deficiencies, and deviations that have occurred will be documented. If it is the subject's 3-month follow-up, cardiovascular medications must be assessed for any updates or changes. Any changes to the subject's cardiovascular medication must be documented.

When a LATITUDE remote transmission is performed to obtain lead measurement data for the 1-Month and/or 3-Month Follow-up visits, the following measurements of all leads are to be entered in the case report forms:

- Intrinsic amplitude (mV)
- Voltage pacing capture threshold from automatic threshold or automatic capture test (V, at 0.4 ms pulse width). Automatic threshold or automatic capture tests in the right atrium are performed in the unipolar mode lead configuration. Automatic threshold or automatic capture tests in the right ventricle and left ventricle are performed in the programmed configuration.
- Lead impedance (Ω)

The available lead measurements closest to the target visit date should be entered into the case report forms. For the 1-Month Follow-up Visit, if complete data from the 30th day post-implant are available, these data should be used. If complete data from the 30th day post-implant are not available, then complete data from the first of the following days post-implant are to be used: 29th, 31st, 28th, 32nd, 27th, 33rd, 26th, 34th, 25th, 35th, 24th, 36th, 23rd, 37th day post-implant. The alternating pattern is outlined for consistency in which data is entered in the case report form and to obtain data from the closest available date in the +/- visit window. If complete data is not available from any day within the follow-up visit window, data from the target visit date will be entered.

For the 3-Month Follow-up Visit, if complete data from the 91st day post-implant are available, these data should be used. If complete data from the 91st day are not available, then complete data from the first available date in the follow-up window are to be used (e.g., 92nd, 93rd, 94^{th,} 95th, etc.). If complete data is not available from any day within the follow-up visit window, data from the target visit date will be entered.

See Table 10-3 in Section 10.12 for required source documentation for remote follow-ups.

10.11. *Study Completion*

Each subject will be followed per the defined follow-up schedule or until they withdraw from the study. An End of Study eCRF must be completed when a subject completes or withdraws from the study. Subjects should be followed as standard of care by their physician after their study participation is completed.

10.12. ***Source Documents***

Table 10-3 below summarizes the source data requirements for this study. It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in Table 10-3.

Table 10-3: Source Documentation Requirements

Requirement	Disposition
Informed consent documentation process	Retain at site
Assessment of pregnancy for women of childbearing potential: method of assessment per physician discretion	Retain at site
Documentation of: • Demographics: age at implant, gender, race, ethnicity • Indication for implant • Cardiovascular medications • Subject's height and weight • Arrhythmia history • Cardiac disease history	Retain at site
Implant details regarding IPG, leads, and accessories used or signed Implant Technical Source Form	Retain at site
Printout of PSA measurements and ECG strip showing loss of capture or signed Implant Technical Source Form	Retain at site
Implant questionnaire	Retain at site
For in-clinic visits: Printout of IPG measurements and threshold results (device follow-up report and ECG programmer strip documenting LOC), for all lead pacing threshold tests	Retain at site
For remote visits: Appropriate LATITUDE report or page print of LATITUDE data or signed Technical Source Form for IPG measurements and threshold results	Retain at site
Time of pocket closure, to document time 0	Retain at site
Time of pre-discharge visit to document visit window	Retain at site
PA and lateral chest X-ray or fluoroscopic image of lead distal tip fixation, either from Implant or Pre-Discharge	Retain at site
Reportable Adverse Events, Device Deficiencies, and Protocol Deviations, if applicable	Retain at site
In the event of subject death: • Death narrative • Relevant medical records • Death certificate • Autopsy report	Submit one copy to Boston Scientific RM At ingevityplus.safety@bsci.com or uploaded to the Rave Database Retain at site

Note: If thermal paper from the device programmer is used for source documentation, signed and dated photocopies or printed pdfs should be used instead, or the strips should be electronically saved.

11. Statistical Considerations

11.1. *Endpoints*

For an INGEVITY+ lead to be eligible to contribute to endpoint analyses, it must be the final lead implanted or attempted per chamber during the initial procedure. Therefore, each subject may contribute up to two total INGEVITY+ leads to the endpoint analyses – one each for the right atrium and right ventricle. See section 11.3.1 for specifics on the analysis sets used for each endpoint analysis.

11.1.1. Primary Safety Endpoint: Lead-related Complication-Free Rate from 0 to 3 Months

Safety of the INGEVITY+ Leads will be confirmed by the lead-related complication-free rate (CFR) from lead implant through the three-month follow-up, based on complications that are related to the INGEVITY+ Lead. Lead-related complications are defined as lead-related adverse events resulting in permanent loss of pacing therapy, invasive intervention, injury, or death. Lead-related adverse events include, but are not limited to the following, based on the Advamed Industry Guidance for Uniform Reporting of Clinical Performance of Cardiac Rhythm Management of Pulse Generators and Leads[1], and in accordance with the FDA Guidance[2]:

- Cardiac perforation requiring surgical intervention
- Cardiac perforation not requiring surgical intervention
- Conductor fracture/ helix damage
- Lead dislodgment
- Failure to capture
- Oversensing
- Failure to sense (undersensing)
- Insulation breach
- Abnormal pacing impedance
- Extracardiac stimulation

Lead-related complications associated with attempted INGEVITY+ Lead implants will count toward this safety endpoint. Lead-related adverse events that are not a complication will be counted as a complication if intravenous (IV) drug therapy is necessary to treat the event. IV drug therapy that occurs concomitant but unrelated to the lead-related adverse event will not be counted as a lead-related complication. Complications involving an INGEVITY+ lead that occur as a result of a procedure unrelated to that INGEVITY+ lead will not count toward this safety endpoint. Two examples of this scenario are 1) an INGEVITY+ lead dislodgement resulting from an ablation procedure and 2) an RV INGEVITY+ lead dislodgement resulting from a repositioning of an RA lead (INGEVITY+ or other market-released).

11.1.1.1. Hypotheses

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

H_0: The lead-related complication-free rate from 0 to 3 months ≤ 93%

H_a: The lead-related complication-free rate from 0 to 3 months > 93%

The performance goal was selected to ensure that the INGEVITY+ Lead has a similar safety profile in the implant through 3-month post-implant period as other market-approved pace/sense leads in the same period. The average of the complication-free rates observed in studies used to support market approval of various pace/sense leads was used to establish average market-approved lead safety. A clinically acceptable delta of 5% was then subtracted from this average of 98% to establish the performance goal of 93%.

11.1.1.2. Sample Size

A sample size of 200 leads (185 required for analysis plus 15 for attrition) is required to evaluate Primary Safety Endpoint. This sample size was calculated using the normal approximation to the binomial and confirmed via Monte Carlo simulations employing Kaplan-Meier methodology, using SAS version 9.4 with the following assumptions:

- Expected performance = 98%
- Performance goal = 93%
- Expected attrition/missing data = 7.5%
- One-sided significance level = 2.5%
- Power = 90%

The sample size for the INGEVITY+ Study is determined by this endpoint.

11.1.1.3. Statistical Methods

Data from all implanted or attempted leads at the time of endpoint analysis will be eligible for inclusion in the endpoint analysis.

The lead-related complication-free rate from date of implant (or date of attempt, for leads attempted but not implanted) through 91 days post-implant will be calculated using Kaplan-Meier methodology. The 97.5% one-sided lower pointwise confidence limit of the complication-free rate will be calculated via log-log methodology for all eligible leads contributing to the analysis and compared to the performance goal of 93%. If the lower confidence limit exceeds 93%, the null hypothesis will be rejected.

Each lead's exact follow-up time in the 91-day post-implant period will be included in the analysis via Kaplan-Meier methodology. The leads that fail to reach 91 days of follow-up (without experiencing an endpoint event prior to their end of follow-up in the period) will be censored at the time of their end of follow-up in the period. Because non-informative censoring cannot be assumed for these leads, a tipping point analysis will be performed to determine the potential effects these censored leads could have on the results if full information on each lead was present. The tipping point analysis will assign each lead that was censored prior to 91 days as either having or not having an endpoint event. All possible combinations of these leads' data will be evaluated along with the actual observed data to find the point, if any, at which the endpoint is failed. An exact binomial test will be performed for the tipping point analysis.

11.1.2. Primary Efficacy Endpoint

The Primary Efficacy Endpoint will confirm the percent of leads with an adequate mean INGEVITY+ Pacing Capture Threshold (PCT) measurement. A lead with an adequate mean INGEVITY+ PCT measurement will be referred to as a Pacing Capture Threshold Responder.

11.1.2.1. Hypotheses

H_0: Pacing Capture Threshold Responders at 3-month visit ≤ 80%

H_A: Pacing Capture Threshold Responders at 3-month visit > 80%,

where a Responder is defined by a mean PCT at 3-month visit ≤ 2 V.

The PCT measurements will be taken using a 0.4 ms pulse width. The performance goal of 80% aligns with current performance goals accepted by the FDA for leadless pacemakers and responder rates from previous RV lead studies.

11.1.2.2. Sample Size

A total of 57 measurements (3-month PCT@0.4 ms) are required to sufficiently power the Primary Efficacy Endpoint. The following assumptions were used to calculate the sample size:

- Performance goal = 80%
- Expected rate = 95%
- One-sided significance level = 2.5%
- Power = 90%

The sample size for this study was not determined by this endpoint.

11.1.2.3. Statistical Methods

All INGEVITY+ leads with a PCT measurement taken at the 3-month visit (with a 0.4 ms pulse width) will be included in the endpoint evaluation. The number of responders (PCT at 3-month visit ≤ 2 V) divided by the total number of INGEVITY+ leads included in the endpoint evaluation will be calculated. The one-sided 2.5% binomial exact lower confidence limit will be calculated and compared to the performance goal of 80%. If the lower confidence limit exceeds 80%, the null hypothesis will be rejected.

To assess the potential impact missing data could have had on the analysis results, a tipping point analysis will be conducted that will include all implanted INGEVITY+ leads. The tipping point analysis will assign each lead with missing data as either being a PCT responder or a PCT non-responder. All possible combinations of these leads' data will be evaluated along with the actual observed data to find the point, if any, at which the endpoint is failed.

11.1.3. Secondary Efficacy Endpoint 1: Sensed Amplitude in the RA and RV

The efficacy of the INGEVITY+ Leads will be further be established by demonstrating that the leads provide clinically acceptable sensing amplitudes at three months post-implant.

11.1.3.1. Hypotheses

The following hypotheses will be used to evaluate Secondary Efficacy Endpoint 1 for each of the right-sided chambers:

Atrial leads

H_0: P-wave sensed amplitude at three months post-implant ≤ 1.5 mV

H_a: P-wave sensed amplitude at three months post-implant > 1.5 mV

Ventricular leads

H_0: R-wave sensed amplitude at three months post-implant ≤ 5 mV

H_a: R-wave sensed amplitude at three months post-implant > 5 mV

11.1.3.2. Sample Size for Secondary Effectiveness Endpoint 1

This endpoint will be evaluated separately for each of the two heart chambers. A sample size of 13 atrial leads (11 required for analysis plus 2 for attrition) and 9 ventricular leads (8 required for analysis plus 1 for attrition) is required for Secondary Effectiveness Endpoint 1. This sample size was calculated using a one-sample t-test, using SAS version 9.4 with the following assumptions:

Atrial leads:

- Expected performance = 3.5 ± 2.0 mV
- Performance goal = 1.5 mV
- Expected attrition/missing data = 10%
- One-sided significance level = 5%
- Power = 90%

Ventricular leads:

- Expected performance = 12 ± 6 mV
- Performance goal = 5 mV
- Expected attrition/missing data = 10%
- One-sided significance level = 5%
- Power = 90%

Note that the sample size for the study is not determined by this endpoint.

11.1.3.3. Statistical Methods for Secondary Efficacy Endpoint 1

All sensed amplitude data collected at the three-month follow-up visit that is available at the time of analysis will be included in the endpoint analyses.

Endpoint analysis will be performed separately for each heart chamber. A one-sided one-sample t-test will be performed, using an alpha equal to 5%. If the t-test is deemed to be inappropriate based on the data, then a data transformation or a non-parametric test will be performed. If the p-value for the one-sided test is less than 0.05, the null hypothesis will be rejected.

11.1.4. Secondary Efficacy Endpoint 2: Pacing Impedance

The efficacy of the INGEVITY Leads will further be established by demonstrating that the leads provide clinically acceptable pacing impedance at three months post-implant.

11.1.4.1. Hypotheses

The following hypotheses will be used to evaluate Effectiveness Endpoint 3 for each of the lead fixation types:

H_0: Pacing impedance $\leq 300\ \Omega$, or Pacing impedance $\geq 1300\ \Omega$

H_a: $300\ \Omega <$ Pacing impedance $< 1300\ \Omega$

11.1.4.2. Sample Size for Secondary Effectiveness Endpoint 2

A sample size of 15 leads (13 required for analysis plus 2 for attrition) is required for Effectiveness Endpoint 3. This sample size was calculated using a one-sample t-test, using SAS version 9.4 with the following assumptions:

- Expected performance = $650 \pm 400\ \Omega$
- Performance goals = $300\ \Omega$ and $1300\ \Omega$
- Expected attrition/missing data = 10%
- One-sided significance level = 5%
- Power = 90%

Note that the sample size for the study is not determined by this endpoint.

11.1.4.3. Statistical Methods for Secondary Effectiveness Endpoint 2

All pacing impedance data collected at the three-month follow-up visit that is available at the time of analysis will be included in the endpoint analysis.

Two one-sided t-tests (TOST) will be performed, using an alpha equal to 5% for each test. If the TOST is deemed to be inappropriate based on the data, a data transformation or a non-parametric test will be performed. If both of the p-values for the two one-sided tests are less than 0.05, the null hypothesis will be rejected.

11.2. *Ancillary Analysis*

- Summary of turn count for all implanted and attempted leads
- Summary of the implant questionnaire including:
  - Lead handling
  - Lead maneuverability
- Summary of accessories used

- Summary of lead-related Adverse Events
- Summary of lead-related device deficiencies, including extension/retraction issues

11.3. *General Statistical Methods*

11.3.1. Analysis Sets

For an INGEVITY+ lead to be eligible to contribute to endpoint analyses, it must be the final lead implanted or attempted per chamber during the initial procedure. Therefore, each subject may contribute up to two total INGEVITY+ leads to the endpoint analyses – one each for the right atrium and right ventricle. These leads will be called 'endpoint leads' in this section. The following analysis sets will be used for each endpoint.

Endpoint	Analysis Sets
Primary Safety Endpoint	All endpoint leads
Primary Efficacy Endpoint	All endpoint leads with 3-month visit PCT data
Secondary Efficacy Endpoint 1	All implanted endpoint leads with 3-month visit sensed amplitude measurements
Secondary Efficacy Endpoint 2	All implanted endpoint leads with 3-month visit pacing impedance measurements

11.3.2. Control of Systematic Error/Bias

Selection of subjects will be made from the investigator's usual patient load. All patients meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study.

11.3.3. Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to implant or attempt more than 20% of the maximum number of subjects, without approval from BSC.

11.4. *Data Analyses*

11.4.1. Interim Analyses

Analyses of adverse events and device deficiencies will occur at frequent intervals during the course of the study. Results of these analyses will be reviewed by the BSC Medical Safety Group to evaluate the safety of the subjects under study.

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

11.4.2. Subgroup Analyses

Analyses will be performed for each endpoint to determine whether significant differences exist in primary endpoint results between subgroups. The list of subgroups (with applicable definitions in parentheses) includes, but is not necessarily limited to:

- Sex (Female vs. Male)
- BMI (Obese vs. Non-Obese)
- Age (< 65 years vs. ≥ 65 years)
- Race (Black or African heritage vs. other races)
- Lead Chamber (Right Atrium vs. Right Ventricle)
- Pulse generator type (pacemaker vs. CRT-P)
- Pacing Capture Threshold Test Type (In-office vs. Auto-threshold) – applicable to Primary Efficacy Endpoint only

Female sex and minority races are considered under-represented group in most cardiovascular device clinical studies. Any efforts to maximize subject retention would be targeted to the under-represented group as well. The study's inclusion and exclusion criteria are not expected to have a negative effect on the recruitment or retention of the said populations.

A log-rank test will be performed to assess differences in Primary Safety endpoint results by subgroup. A Pearson's chi-square test will be performed to assess the differences in Primary Effectiveness endpoint results by subgroup. A test for significance at the 15% level will be performed. For each subgroup variable in which a significant difference exists, the results for each subgroup will be presented separately. BSC does not plan to seek labeling for these subgroups based on these analyses.

11.4.3. Pooling Analysis

For both primary endpoints, data from the right atrial and right ventricular leads will be pooled for analysis, based on the expected similarity in results across chambers. The assumption of poolability across chambers will be assessed through the subgroup analysis described in Section 11.4.2.

11.4.4. Multivariable Analyses

Univariable analyses of various baseline covariates and their relationship to each endpoint are outlined in Section 11.4.2. For each endpoint, all baseline characteristics found to be significantly associated with the outcome will be included as covariates in a multivariable regression model. The impact of each baseline characteristic's subgroups will be presented along with the multivariable model results.

11.4.5. Impact of Repeated Measures

As stated in Section 11.3.1, each subject in the study can contribute up to two leads to the endpoint analyses. To investigate the potential impact of repeated measures on the endpoint

results, analyses will be performed for each primary endpoint comparing a model adjusted for repeated measures to one unadjusted for repeated measures. Results from both models – accounting and not accounting for repeated measures – will be presented.

11.4.6. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in the SAP 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. Data Management

12.1. *Data Collection, Processing, and Review*

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

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

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

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

12.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

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

13. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

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

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

14. Compliance

14.1. *Statement of Compliance*

This study will be conducted in accordance with the requirements of this protocol, US Title 21 CFR Part 11, Part 50, Part 54, Part 56, Part 814.82(a)(2) and ISO14155, Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and applicable country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB, and the US FDA (regulatory authority) has been obtained, as appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB or regulatory authority shall be followed, as appropriate.

14.2. *Investigator Responsibilities*

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

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

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

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

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.

- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

14.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a site, the sub-investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

14.3. *Institutional Review Board*

The investigational site will obtain the written and dated approval/favorable opinion of the IRB for the clinical investigation before recruiting subjects and implementing all subsequent amendments if required.

A copy of the written IRB approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the INGEVITY+ study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the ICF will be IRB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

Annual IRB approval and renewals will be obtained throughout the duration of the study as required by applicable local laws or regulations or IRB requirements. Copies of the study reports and the IRB continuance of approval must be provided to the sponsor.

14.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this

information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

14.4.1. Role of Boston Scientific Representatives

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

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

Typical tasks may include the following:

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

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

- Observing testing or medical procedures to provide information relevant to protocol compliance

- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following:

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

15. Monitoring

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

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

16. Potential Risks and Benefits

16.1. *Directions for Use*

Please refer to the INGEVITY+ lead and BSC pacemaker, or CRT-P Physician's Manual for an overview of anticipated adverse (device) effects, and risks associated to the commercial device(s).

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

This clinical study does not involve additional risks to study subjects since it is an observational study collecting data that is consistent with approved device labeling and 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 INGEVITY+ lead and BSC pacemaker, or CRT-P Physician's Manual for reference.

As described in the INGEVITY+ Physician's Lead Manual, possible adverse events associated with pulse generator and/or lead implant include:

- Air embolism
- Allergic reaction
- Arterial damage with subsequent stenosis
- Bleeding
- Bradycardia
- Breakage/failure of the implant instruments
- Cardiac perforation
- Cardiac tamponade
- Chronic nerve damage
- Component failure
- Conductor coil fracture
- Death
- Electrolyte imbalance/dehydration
- Elevated thresholds
- Erosion
- Excessive fibrotic tissue growth
- Extracardiac stimulation (muscle/nerve stimulation)
- Fluid accumulation
- Foreign body rejection phenomena
- Formation of hematomas or seromas
- Heart block
- Hemorrhage
- Hemothorax
- Inability to pace
- Inappropriate therapy (e.g., shocks and antitachycardia pacing [ATP] where applicable, pacing)
- Incisional pain
- Incomplete lead connection with pulse generator
- Infection including endocarditis
- Lead dislodgment
- Lead fracture
- Lead insulation breakage or abrasion
- Lead tip deformation and/or breakage
- Malignancy or skin burn due to fluoroscopic radiation
- Myocardial trauma (e.g., tissue damage, valve damage)
- Myopotential sensing
- Oversensing/undersensing
- Pericardial rub, effusion
- Pneumothorax
- Pulse generator and/or lead migration
- Syncope
- Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
- Thrombosis/thromboemboli
- Valve damage

- Vasovagal response
- Venous occlusion
- Venous trauma (e.g., perforation, dissection, erosion)

For a list of potential adverse events associated with MRI scanning, refer to the appropriate ImageReady MR Conditional Pacing System or Defibrillation System MRI Technical Guide.

16.3. *Risk Minimization Actions*

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

16.4. *Anticipated Benefits*

Subjects enrolled in this clinical study may not receive any direct benefit from their participation; however, medical science and future patients may benefit from their participation in this clinical study.

The potential benefits the subject may receive from the INGEVITY+ Lead would be the same if they did not enroll in this study.

17. Safety Reporting

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

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

- All Serious Adverse Events
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- All INGEVITY+ Lead Related Adverse Events
- All Cardiac Related Adverse Events
- All INGEVITY+ Lead Procedure Related Adverse Events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

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

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

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of one (1) specific SAE (see Table 17-1 for AE definitions).

Refer to Directions for Use for the known risks associated with the commercial device(s).

17.2. *Definitions and Classification*

Adverse event definitions are provided in Table 17-1. Administrative edits were made on the safety definitions from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 17-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the study medical device. **NOTE 1**: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or intentional abnormal use of the study medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

Table 17-1: Safety Definitions

Term	Definition
	NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of the study medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

17.3. ***Relationship to Device(s)***

The Investigator must assess the relationship of the reportable AE to the device, therapy/stimulation or procedure. See criteria in Table 17-2:

Table 17-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the study device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

Table 17-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
	- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the study device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable;

Table 17-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
	- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

17.4. *Investigator Reporting Requirements*

The communication requirements for reporting adverse events and device deficiencies to BSC are as shown in Table 17-3.

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

Table 17-3: Investigator Reporting Requirements

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

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (MEDDEV 2.12/2 : GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Product Deficiency section of the Adverse Event eCRF with all available new and updated information.	• Within 2 business days of first becoming aware of the event. Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of sponsor
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	

17.5. ***Boston Scientific Device Deficiencies***

All lead deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. The device(s) should be returned to BSC for analysis. Instructions for returning the device(s) will be provided in the site initiation visit slides. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency, would be recorded as an adverse event on the appropriate eCRF.

17.6. ***Reporting to Regulatory Authorities / IRBs /Investigators***

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

The Principal Investigator is responsible for informing the IRB and regulatory authorities of UADEs and SAEs as required by local regulations.

17.7. ***Subject Death Reporting***

A subject death during the study should be reported to Boston Scientific RM as soon as possible, preferably within three (3) calendar days of center notification. The center's IRB must be notified of any deaths in accordance with that center's IRB policies and procedures.

Notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death and is signed by the principal Investigator or authorized co-Investigator. The details listed below should be addressed in the death narrative, in order for BSC to understand the circumstance surrounding the death: A death narrative in the local language is acceptable, if accompanied by a translation in English (signed by a translator. The death narrative must include all of the following, if available:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Rhythm at the time of death, if known (include any available documentation)
- Whether the death was related to the pulse generator, lead/catheter, clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Device status and/or activity at the time of death (device recipients only – pacing and defibrillation, active or inactive)
- Whether the patient had worsening heart failure
- Any other circumstances surrounding the death
- Approximate time interval from the initiating event to death (temporal course)
- Investigator or sub-investigator signature and date

Any information listed above that is unavailable or unknown must be specified as unavailable or unknown, as applicable, in the narrative. Also submit the following documentation:

If the subject expired in the hospital:

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

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

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

Whenever possible, the IPG should be interrogated. Leads and related Boston Scientific RM system components (e.g., IPGs) should be removed intact and returned promptly to Boston Scientific RM for analysis.

The INGEVITY+ Clinical Events Committee (CEC) must review information regarding subject deaths (see Section 19.2).

18. Informed Consent

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

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

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

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

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

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

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

learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local IRB , as appropriate.

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

19. Committees

19.1. *Safety Monitoring Process*

The BSC Medical Safety group reviews unmonitored data as soon as the event is reported, on a continuous basis. During scheduled monitoring activities, clinical research monitors will support this continuous review through their review of source document and other data information. The BSC Medical Safety group includes healthcare professionals with expertise in Cardiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

19.2. *INGEVITY+ Clinical Events Committee (CEC)*

A CEC is an independent group of individuals with pertinent expertise that reviews and adjudicates important 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 subject death from any cause.

Committee members will include practitioners of Electrophysiology (EP), and/ or Cardiology, as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above. CEC responsibilities, qualifications, membership, and committee procedures are outlined in the CEC charter.

20. Suspension or Termination

22.1 Premature Termination of the Study

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

22.1.1 Criteria for Premature Termination of the Study

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

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

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

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

22.3 Requirements for Documentation and Subject Follow-up

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

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

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific. Boston Scientific should be notified as soon as possible for any changes related to the Principal Investigator status to ensure no gaps in study oversight.

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

22.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 2 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

21. Publication Policy

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

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

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

22. Abbreviations and Definitions

22.1. *Abbreviations*

Abbreviations are shown in Table 22-1.

Table 22-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AV	Atrioventricular
BSC	Boston Scientific
CEC	Clinical Events Committee
CFR	Complication Free Rate
CRO	Contract Research Organization
CRT-P	Cardiac Resynchronization Therapy - Pacemaker

Table 22-1: Abbreviations	
Abbreviation/Acronym	**Term**
DXA	Dexamethasone Acetate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EP	Electrophysiology
ETFE	Ethylene tetrafluoroethylene
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Health Care Professional
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
IS-1	International Standard-1
IROX	Iridium Oxide
ISO	International Standard Organization
LOC	Loss of Capture
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
mV	Millivolts
Ω	Ohms
PA	Posterior-Anterior
PAS	Post-Approval Study
PLM	Physician's Lead Manual
PSA	Pacing System Analyzer
PTFE	Polytetrafluoroethylene
RA	Right atrium/ atrial
RM	Rhythm Management
RV	Right ventricle/ ventricular
SA	Sinoatrial
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TOST	Two one-sided t-tests
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
V	Volts

22.2. ***Definitions***

Terms are defined in Table 22-2.

Table 22-2: Definitions	
Term	**Definition**
Lead-related adverse event	Lead-related adverse events include, but are not limited to the following, based on the Advamed Industry Guidance for Uniform Reporting of Clinical Performance of Cardiac Rhythm Management of Pulse Generators and Leads[1] and in accordance with the FDA Guidance[2]: • Cardiac perforation requiring surgical intervention • Cardiac perforation not requiring surgical intervention • Conductor fracture/ helix damage • Lead dislodgment • Failure to capture • Oversensing • Failure to sense (undersensing) • Insulation breach • Abnormal pacing impedance • Extracardiac stimulation
Lead-related complication	Lead-related complications are defined as lead-related adverse events resulting in permanent loss of pacing therapy, invasive intervention, injury or death.
Observation	An adverse event that was transient or reversible and corrected with non-invasive interventions, such as reprogramming or oral medications, or else resolved with no intervention or monitoring.
Pacing impedance	An assessment of the opposition to the flow of current by the pacing system; measured in ohms (Ω).
Pacing threshold	An assessment of the minimum electrical stimulation required to consistently initiate cardiac depolarization; measured in Volts (V).
Permanent Atrial Fibrillation (AF)[3]	When a patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.
Persistent AF[3]	Continuous AF that is sustained > 7 days.
Sensed amplitude	An assessment of how well the lead senses the heart's intrinsic electrical activity; measured in millivolts (mV).
Source Data	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical study.
Source Document	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, radiographs, records kept at the investigation site, and at the laboratories involved in the clinical study.

23. Bibliography

[1] Industry Guidance for Uniform Reporting of Clinical Performance of Cardiac Rhythm Management of Pulse Generators and Leads, (21 May 2009). https://www.advamed.org/sites/default/files/resource/081709_advamedfinalguidanceforuniformreportingleadsandpgs21may09.pdf. Visited 07 August 2019.

[2] Guidance for Industry: Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions. November 1, 2000.

[3] January, CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: Executive Summary. Journal of the American College of Cardiology. 2014; 64(21): 2246-2280.