Optimizing Pacing Therapy by Using Multi-Programmable Pulse Generators for Cardiac Resynchronization Pacing (CRT-P)

RALLY-CRT-P

CLINICAL INVESTIGATION PLAN

Study Reference: Rally-CRT-P-02-2015

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Sponsored By

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Revision History

Revision Number	Release Date	Section	Change	Reason for Change
AA	16-Mar-2015	**NA**	**Initial release**	**NA**
AB	17-Nov-2015	Table 11-1	- Documentation of clinical assessment at 1 month follow-up as described in section 11.7 - Wording clarification POST Function/daily measurements	Correction of editorial mistake and clarification
		Section 11.4	Documentation of chronic atrial fibrillation, asthma, COPD and LVEF	Clarification
		Section 10.4, 11.5, 11.6 and 11.7	Abbreviation/ wording clarification/typo	Correction of editorial mistake
		Table 11-7	- Age ranges - Programmed value for AMPHR*80%	Clarification
		Section 11.8	Wording clarification POST Function/daily measurements	Clarification
		Section 11.9	Patients reaching 16 months follow-up	Clarification
		Table 11-8	1 month follow-up source documentation requirements	Correction of editorial mistake
		Section 13.1	Data collection - Echographic imaging	Correction of editorial mistake

Contact Information

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Investigational Sites	A list of investigational sites will be maintained and is available upon request.

2. Clinical Investigation Plan Synopsis

Rally-CRT-P	
Study Objective	The objective of this Post Market Clinical Follow-up (PMCF) is to collect data on the performance of the Ingenio 2 CRT-P devices and to document that device-related events, device malfunctions or device deficiencies (DDs) do not increase safety risks in Ingenio 2 CRT-P devices (CRT-Ps), both in general and specific to the new features and hardware of the devices.
Device	
Indications for Use	Boston Scientific (BSC) Ingenio 2 CRT-Ps (VISIONIST, VISIONIST X4,) are clinically indicated for subjects who have symptomatic congestive heart failure (CHF) including left ventricular (LV) dysfunction and wide QRS; and/or one or more of the following conditions: • symptomatic paroxysmal or permanent second- or third-degree atrioventricular (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. Atrial tracking modes are also indicated for subjects 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 (ventricular single chamber mode) intolerance (i.e., pacemaker syndrome) in the presence of persistent sinus rhythm • low cardiac output or CHF secondary to bradycardia. Adaptive-rate pacing is indicated for subjects exhibiting chronotropic incompetence and who would benefit from increased pacing rates concurrent with increases in minute ventilation (MV) and/or physical activity.

<table>
<tr><th colspan="4">Rally-CRT-P</th></tr>
<tr><td>Device Description</td><td colspan="3">The three Ingenio 2 CRT-P models to be used in this study have similar architectural platforms, closely related device features and a very similar clinical use association compared to the previously approved and marketed BSC implantable devices, Ingenio. Some enhancements have been incorporated into Ingenio 2 models, primarily at a component and engineering level rather than at a clinical level. No changes from the previous devices have been made to clinical indications, intended use or target subject population.
<table>
<tr><th>Component</th><th>Model Number</th><th>Connector Type</th></tr>
<tr><td>VISIONIST</td><td>U225</td><td>IS1</td></tr>
<tr><td>VISIONIST</td><td>U226</td><td>IS1/ LV1</td></tr>
<tr><td>VISIONIST X4</td><td>U228</td><td>IS1/ IS4</td></tr>
</table></td></tr>
<tr><td>Device Specifications</td><td colspan="3">• External case which functions as an electrode and consists of two 0.012-inch thick hermetically sealed, perimeter-welded, Grade 1 titanium case halves, backfilled with dry nitrogen / helium
• Internal electronic circuitry and SL or EL battery (encapsulated in the external case)
• Overmolded header, consisting of urethane plastic skeletal core structure
• Titanium weld ring</td></tr>
<tr><td>New Hardware Components</td><td colspan="3">• Filtered feedthru
• IS1 coil spring design
• Front liner
• Lead port identifiers</td></tr>
<tr><td colspan="4">Study Design</td></tr>
<tr><td>Study</td><td colspan="3">Prospective, non-randomized, multi-center, single group, post market clinical study</td></tr>
<tr><td>Number of Study Subjects</td><td colspan="3">62 eligible subjects</td></tr>
<tr><td>Planned Number of Centers / Countries</td><td colspan="3">10-15 investigational centers, including but not limited to: Belgium, Denmark, Finland, Germany, Netherlands, Spain. If a site does not enroll a subject within a 3-month time period, the site may be replaced at the discretion of the sponsor.</td></tr>
</table>

Rally-CRT-P	
Endpoints and Objectives	
Primary Safety Endpoint	• Evaluate and document device-related complications by assessing the device-related complication free rate (DRCFR), for study subjects, at the 3 months post-implant
Primary Effectiveness Endpoint	• LV pacing threshold measurements performed at 0.5 ms pulse width at 3 months post-implant. The pacing configuration that the physician selects for permanent programming will be compared to prospectively determined limits.
Secondary Safety Objectives	• Assessment of proper function of the PaceSafe-left ventricular automatic threshold (LVAT) feature with special attention to: o inappropriate loss of capture due to LVAT (not related to lead dislodgement, connection issue, etc.) and o devices which show retry into LVAT followed by Latitude alert • Assessment of reported events in relation to the use of the Medical Implant Communication Service (MICS) during all visits • Assessment of all reported events in relation to the Quad Lead and Header
Secondary Effectiveness Objectives	• Collection of user experience with the programmer (PRM) interface through the Product Experience Reporting at implant and during follow-up • Assessment of LV pacing at implant and follow up (pacing threshold per vector, impedance per vector, % pacing) • Assessment of battery voltage at Latitude based Close-out • Assessment of Post-Operative System Test (POST): number of out of range impedance alerts not related to mitigating factor (header connection issue, lead failure, lead dislodgement, etc.) • Assess the correlation between 6 minute walking test distance at 1 month and 3 months post-implant and for subjects with heart rate score (HRS) < 50 and ≥ 50 • The HRS changes between 1 month follow-up and 3 month follow-up will be analyzed for all subjects, for subjects with HRS < 50 and ≥ 50, and for subjects in a non-rate adaptive mode and with rate adaptive pacing: All event data may be combined with data from Ingenio 2 devices enrolled into the Gentle study.
Methodologies	
Method of Assigning Subjects to Treatment	The devices are fully commercially available and all subjects are planned to receive a CRT-P implant as part of their standard of care (SOC). The assignment of the specific Ingenio 2 device is physician's choice and will consider leads currently in place from previous devices and planned new leads (e.g., Acuity X4 and/or other LV leads).

Rally-CRT-P	
Enrollment and Follow-up Schedule	Clinic visits will occur at: • Enrollment and Consenting Clinic Visit (≤ 30 days prior to implant procedure) (required) • Implant Procedure (Day 0; all future follow ups based on this date) (required) • Pre-Discharge Clinic Visit (after pocket closure and wound coverage 0-5 days post-implant procedure) (required) • 1 month post-implant Clinic Visit (30 ± 15 days) (required) • 3 month post-implant Clinic Visit (91 ± 21 days) (required) • Latitude-based Close-out (91 - 120 days months post last enrollment) (reporting only required) • Unscheduled clinic follow-up (any clinic visit between pre-discharge and 3 month follow up which is in addition to the 1 month follow up; per center SOC or subject needs; event reporting only) • Re-implant/Revision (as needed) • During the trial unanticipated serious adverse device effects (USADEs), serious adverse device effects (SADEs), adverse device effects (ADEs), DDs, all serious adverse events (SAEs), deaths, and changes in the device system must be reported (enrollment to Closeout).
Study Duration	Enrollment is expected to take 12 months. The study will be considered complete (primary endpoint completion) after all subjects have completed the Latitude based close-out 3-4 months after the last study enrollment. All study required visits will be completed as part of regularly scheduled clinic visits. Study completion is anticipated in 2016.
Required Medication Therapy	Subjects will receive all medication per SOC according to the center.
Inclusion Criteria	1. 18 years or above, or above legal age to give informed consent specific to state and national law 2. Willing and capable of providing informed consent 3. Planned to be implanted or replaced with a VISIONIST Ingenio 2 CRT-P device 4. Planned to be implanted with a 3-lead CRT-P system 5. Planned to be connected to the remote data collection through the Latitude® system 6. Able to do a 6 minute walk test 7. Maximum sensor rate of age predicted maximal heart rate (APMHR) 80% should be clinically acceptable 8. Willing and capable of participating in all visits associated with this study at an approved clinical study center and at the intervals defined

Rally-CRT-P	
	by this CIP
Exclusion Criteria	1. Documented life expectancy of less than 12 months 2. Currently on the active heart transplant list 3. Enrolled in any other concurrent study without prior written approval from BSC, with the exception of local mandatory governmental registries and observational studies/registries that are not in conflict and do not affect the following: o Schedule of procedures for the Rally CRT-P Study (i.e., should not cause additional or missed visits) o Rally CRT-P Study outcomes (i.e., involve medications that could affect the heart rate of the subject) o Conduct of the Rally CRT-P Study per Good Clinical Practice (GCP)/ International Standard Organization (ISO) 14155:2011/ local regulations as applicable 4. In chronic atrial fibrillation 5. APMHR needs to be programmed < 80%. 6. Not planned to receive a functional atrial lead 7. Per the implanting physician's discretion, subject is not a suitable candidate to receive the study device as determined during the implant procedure 8. Women of childbearing potential who are or might be pregnant at the time of study enrollment 9. Unwilling or unable to participate in all scheduled study follow up visits at an approved study center 10. Does not anticipate being a resident of the area for the scheduled duration of the trial.
Multiple Interventions During Index Procedure	Subjects are allowed to receive any intervention during the index procedure according to the SOC of the center. Any additional interventions will be documented.
Statistical Methods	
Primary Statistical Hypothesis	DRCFR from implant through 3 months post-implant is greater than the pre-specified performance goal of 87.5% H_o: πDRCFR ≤ 87.5% H_A: πDRCFR > 87.5% Mean LV pacing threshold at 3 months post-implant is less than the pre-specified performance goal of 2.5V H_o: mean LV pacing threshold ≥ 2.5V H_A: mean LV pacing threshold < 2.5V

Rally-CRT-P	
Statistical Test Method	**Sample Size Methodology:** • Sample size for the primary safety endpoint was calculated using exact binomial methods for comparison of a single proportion to a performance goal. • Sample size for the primary effectiveness endpoint was calculated using one-sample t-test methodology for comparison of a single mean to a performance goal. **Analysis Methods:** • The DRCFR from implant will be calculated as the proportion of actively enrolled subjects without a device-related complication through 3 months after implant. The null hypothesis will be rejected and the endpoint considered met if the lower one-sided 95% confidence bound for the proportion of subjects with no device-related complication is greater than 87.5%. • Regarding mean LV pacing threshold at 3 months post-implant, the null hypothesis will be rejected and this endpoint considered met if the upper one-sided 95% confidence bound for the mean LV pacing threshold at 3-months is less than 2.5V. Further details on analytical methods can be found in Section 12.0 of the CIP.
Sample Size Parameters	DRCFR through 3 months post-implant: 62 subjects. Sample size was calculated assuming a 97.5% DRCFR, a performance goal of 87.5%, one-sided alpha level of 0.05, 80% power, and 20% attrition. Mean LV pacing threshold at 3 months post-implant: 45 subjects. Sample size was calculated assuming a mean (± standard deviation [SD]) LV pacing threshold of 1.9 ± 1.2V, a performance goal of 2.5V, one-sided alpha level of 0.05, 90% power, and 20% attrition. Based on the above sample size calculations, the minimum required sample size to statistically power the primary endpoints is 62 subjects.

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3.1. Table of Figures

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4. Introduction

The lifetime risk of developing heart failure (HF) is one in five for a person living to age 40 in the developed countries[1,2]. HF affects 1–2% of the population and causes about 5% of all medical admissions amongst adults[3]. In the US, HF affects almost 5 million patients with 500,000 new cases documented annually[4]. The one-year mortality rate for symptomatic HR has been reported at nearly 45%[5]. Quality of life is reduced more by HF than by any other chronic illness and it is an enormous burden on health and social services, accounting for approximately 2% of all health-care spending.[6]

About half of all HF cases are caused by left ventricular (LV) systolic dysfunction, which is commonly due to ischemic heart disease or dilated cardiomyopathy. Interestingly, in the early stages of heart failure, patients are more likely to die of sudden cardiac death than of pump failure[7]. Logically therefore, therapy strategies for these patients should focus on reducing the risk of sudden death as well as improving symptoms and quality of life and in addition, preventing progression of the disease.

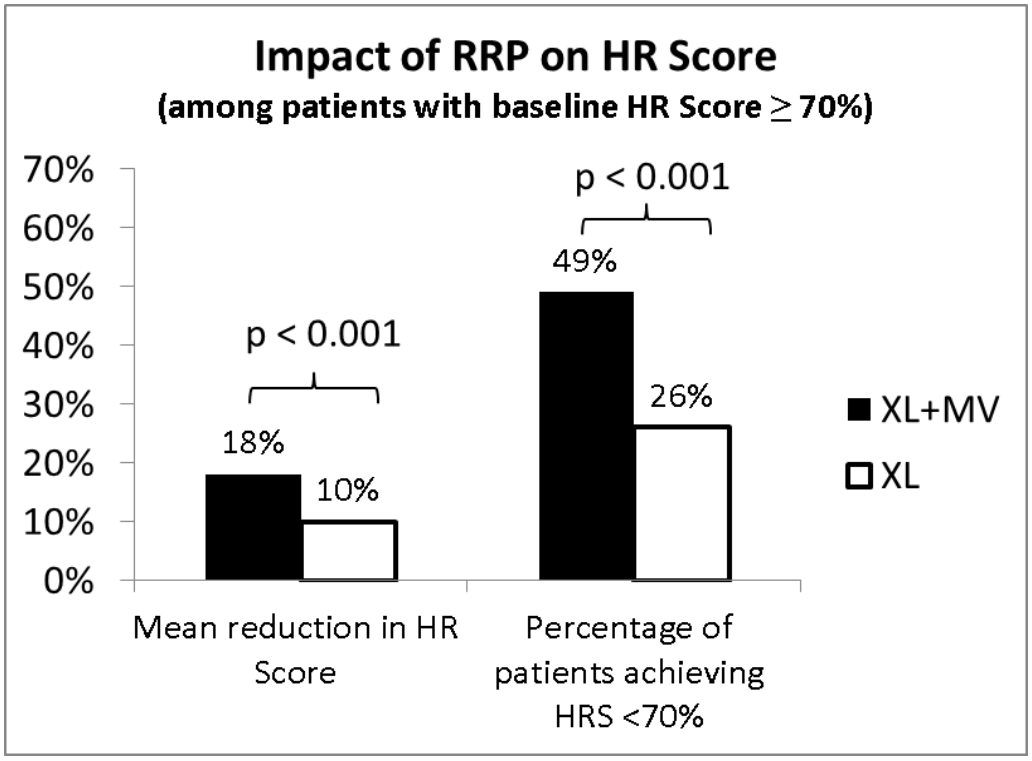
The hypothesis behind cardiac resynchronization therapy (CRT) is that prevention of the electromechanical delay that creates ventricular dyssynchrony can reduce the detrimental effects caused by the dyssynchrony such as decreased stroke volume, mitral regurgitation, increased wall stress, and delayed relaxation[8, 9, 10]. Initial, acute studies demonstrated that CRT could reduce mitral regurgitation and wall stress[11]. Larger randomized trials showed that HF patients improved in exercise tolerance, symptoms of heart failure and quality of life. In addition there was evidence of reverse remodeling of the heart as well as a reduction in HF mortality and morbidity[12, 13, 14, 15].

Cardiac resynchronization therapy pacemakers (CRT-Ps) are designed to treat both cardiac ventricles in heart failure (HF) patients who may have symptoms despite receiving the best available pharmaceutical therapy. The Ingenio 2 family includes CRT-P devices that are multi-programmable pulse generators (PGs), offering various levels of therapeutic and diagnostic functionality.

The benefits of rate responsive pacemakers (RRP) for chronotropically incompetent patients are well established, as measured using objective quantitation of exercise performance[16] and subjective symptom scores.[17] Optimal objective and subjective benefit, however, requires accurate programming of rate response parameters.[18] A heart rate score (HRS) can be significantly reduced with RRP (Figure 4-1). A blended minute ventilation (MV)+XL RRP approach is more effective than XL alone at decreasing the HRS. An HRS <70% has been associated with reduced mortality in implanted cardioverter defibrillator (ICD) and cardiac resynchronization therapy-defibrillator (CRTD) patients. These data suggest the need for prospective evaluation of HRS, and its reduction with combined XL+MV DDDR, in both pacemaker (PM) and ICD patients. One study[19] showed that patients with a baseline HRS of >70 showed statistically significant improvement in HRS when converting from DDD to DDDR pacing, as opposed to maintaining DDD pacing[20] (Figure 4-2).

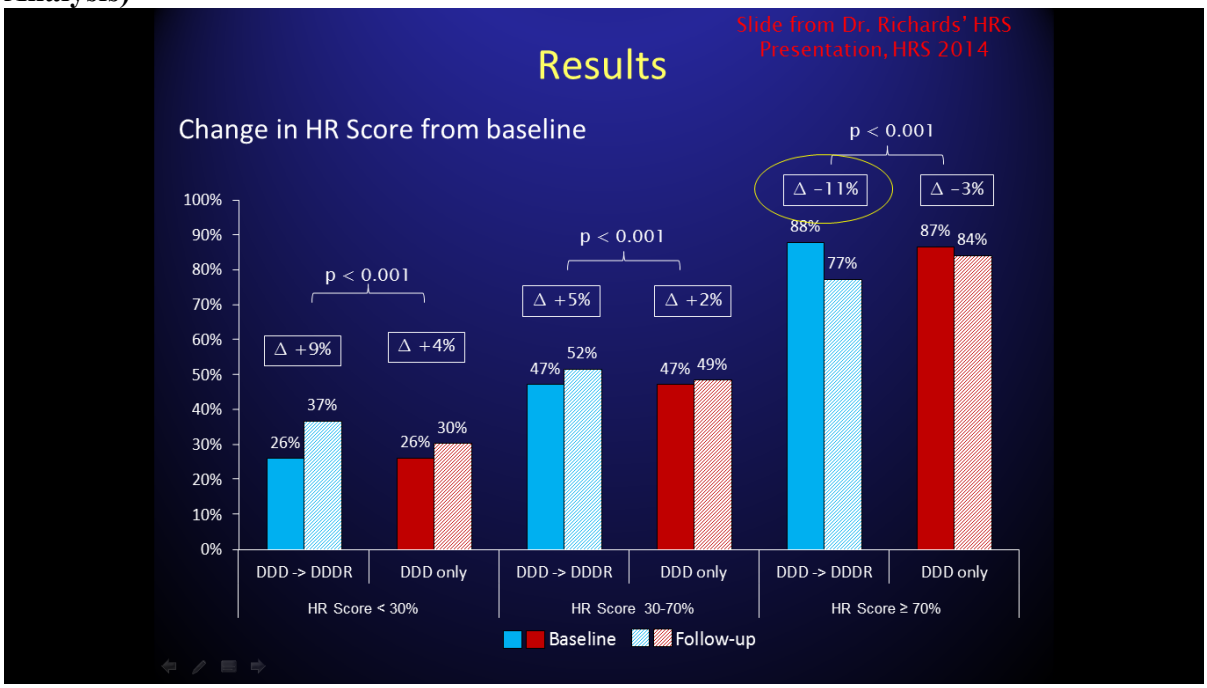
These patients decreased their HRS by 3% when staying at DDD and decreased their HRS by 11% by changed from DDD pacing to DDDR (with XL) pacing. Although these patients will not be analyzed separately in this study due to the non-randomized study design, the study will allow a better understanding of the clinical impact of optimized rate adaptive pacing driven by MV sensor in HF patients and about sensor optimization in HF patients in general, following a 6 minute walking test.

Figure 4-1: Impact of Rate Responsive Pacemakers on Heart Rate Score



Source: Sulke N, Dritsas A, Chamber J, et al. Is accurate rate response programming necessary? PACE 1990; 13:1031–1044.
HR=heart rate, HRS=heart rate score, RRP=rate response pacemaker, MV=minute ventilation, XL=accelerometer, XL+MV=blended sensor (accelerometer+ minute ventilation)

Figure 4-2: Changes in Heart Rate Score (DDD vs. DDD → DDDR: LAT Analysis)



Source: Richards, M., et al. The Addition of Minute Ventilation to DDDR Pacing Improves the Heart Rate Score, A Marker for Chronotropic Incompetence and Increased Mortality. Heart Rhythm, Vol. 11, No. 5, May Supplement 2014: p 3-33.
DDD=dual chamber pacing; DDDR=dual chamber pacing, with sensing (*recording*) ability

The Ingenio 2 CRT-Ps have similar architectural platforms, closely related device features and a very similar clinical use association compared to the previously approved and marketed BSC implantable devices, Ingenio CRT-P PGs. This approach offers several significant advantages, the key one being the well-established clinical field experience with this platform. However, some enhancements incorporated into Ingenio 2 models are primarily at a component and engineering level rather than at a clinical level (Section 5.1).

Another study, GENTLE, is currently ongoing to collect clinical data on BSC's ImageReady MR Conditional Pacing Systems involving the INGEVITY MRI lead based on observations / events. The GENTLE study will be leveraged to support the Ingenio 2 CRT-Ps as the new features and hardware are consistent between all Ingenio 2 devices (pacemakers and CRT-Ps).

However, no data are available specifically to support the Ingenio 2 CRT-Ps. Therefore, this present PMCF study intends to collect data specific to the Ingenio 2 CRT-Ps focused on documenting freedom from unanticipated adverse device effects (UADEs) and unusual occurrences of new device deficiencies (DD), in order to bridge and complement the information from other studies on safety and functionality of the Ingenio 2 platform devices.

5. Device Description

5.1. Ingenio 2 Cardiac Resynchronization Therapy Pacemakers

Ingenio 2 CRT-Ps provide device feature enhancements to commercially available Ingenio CRT-Ps manufactured by BSC. However, no changes are anticipated regarding the clinical indications, intended use, or target population for the new CRT-Ps compared to the previously marketed Ingenio devices.

There are three Ingenio 2 CRT-Ps available, 2 models of VISIONIST and the VISIONIST X4. The main device features of the 2 Ingenio 2 CRT-Ps are shown in Table 5-1. Photographs of the devices are shown in Figure 5-1; a photograph of the lead connections and setscrew locations are shown in Figure 5-2. The basic components for each device are noted in Table 5-2.

Basic device specifications include:

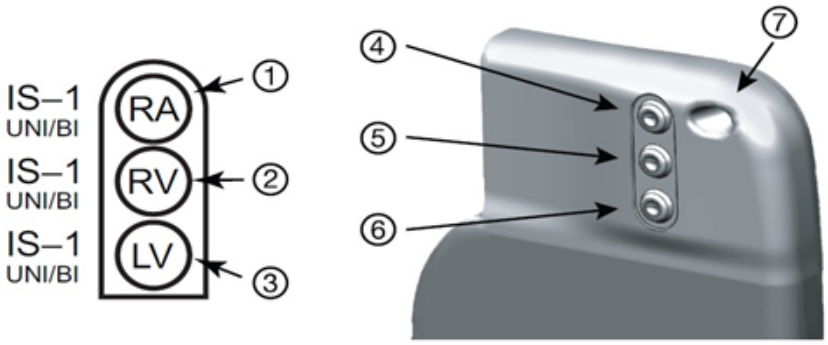
- External case which functions as an electrode and consists of two 0.012-inch thick hermetically sealed, perimeter-welded, Grade 1 titanium case halves, backfilled with dry nitrogen / helium
- Internal electronic circuitry and SL or EL battery (encapsulated in the external case)
- Overmolded header, consisting of urethane plastic skeletal core structure
- Titanium weld ring

Table 5-1: Ingenio 2 Cardiac Resynchronization Therapy Pacemakers

Product Name	Model Number	Connector Type	Device Feature Overview
VISIONIST	U225	ISI	CRT-P basic functionality plus: AP Scan, Atrial Pacing Preference / ProACT, Positive LV Offset, LV-Only Pacing, Right Rate™ MV, Pace Safe LV in IS-1 and LV-1 models
VISIONIST	U226	ISI/LV1	
VISIONIST X4	U228	ISI/IS4	

Figure 5-1: VISIONIST X4 CRT-Pacemaker

Figure 5-2: Lead Connections and Setscrew Locations



[1] RA: White [2] RV: White [3] LV: Green [4] RA [5] RV [6] LV [7] Suture Hole

Table 5-2: Device Components

Component	Model	Connector Type	Battery	Mass (g)	Vol (cc)	Dimensions (cm) (H x W x D)
VISIONIST	U225	IS1	EL	30.6	16.2	6.13 x 4.45 x 0.75
VISIONIST	U226	IS1/ LV1		31.1	16.7	6.13 x 4.45 x 0.75
VISIONIST X4	U228	IS1/ IS4		33.0	17.6	6.17 x 4.45 x 0.75

The key new features in the Ingenio 2 CRT-Ps include:

1. EasyView header with port identifiers. Increased header transparency provides enhanced visibility of the lead ports and ease of individual port identification.
2. LV quadripolar devices, providing 17 pacing configurations and 8 sensing configurations for devices compatible with IS4 LV leads
3. PaceSafe™ Left Ventricular Automatic Threshold (LVAT), which performs LV threshold testing every 21 hours and sets an output safety margin; maximum amplitude and safety margin are programmable (Section 5.1.1)
4. enhanced hardware including new battery chemistry, filtered feedthru, IS1 coil spring design, and front liner
5. enhanced diagnostic functions including Post-Operative System Test (POST), which provides an automatic device / lead check at a pre-determined time post-implant to help document proper system functionality without requiring manual system testing (Section 5.1.2)
6. Atrial Arrhythmia Reports (Section 5.1.3)
7. ECG/EGM (electrogram from device) Snapshot function (Section 5.1.4)
8. Medical Implant Communication Service (MICS) telemetry band used for radio frequency (RF) telemetry communication with the programmer (PRM) (Section 5.1.6).
9. programmable lead impedance limits for daily measurements: high impedance limit programmable between 2000 and 3000 Ω; low impedance limit programmable between 200 and 500Ω.

Upgrades from the Ingenio devices include:

- mechanical changes
    1. overmolded header, incorporating the quadripolar LV port, MICS RF antenna, and IS1 coil springs
    2. filtered feedthru, adding 2 more feedthru wires for quadripolar LV
    3. silicone rubber front liner, instead of plastic, which includes integrated desiccant.

- electrical changes
    1. analog integrated circuit (IC), with additional quadripolar LV capabilities and RF/MICS interface
    2. digital IC, with increased memory
    3. MICS RF module
    4. RC array
    5. capacitor array
    6. filtered feedthru
    7. battery upgrade to 70 mW RF power.

All X4 models used in this study allow the connection of LV quadripolar leads. Leads are commercially available (Section 5.1.5) and the ZOOM LATITUDE Programming System remains unchanged (Section 5.1.7).

5.1.1. *PaceSafe*

PaceSafe LVAT is designed to dynamically adjust the LV pacing output to ensure capture of the left ventricle using a programmable Safety Margin. LVAT will measure pacing thresholds from 0.2 V up to the programmable maximum amplitude (7.5 V maximum). The output will be at a minimum amplitude of 1.0 V up to the programmable maximum amplitude of 7.5 V (with a programmable pulse width).

PaceSafe LVAT automatically performs LV threshold testing every 21 hours and sets the pacing pulses amplitude while maintaining output safety margin. Additionally, maximum amplitude and safety margin are programmable.

PaceSafe is available in the VISIONIST devices only.

5.1.2. *Post-Operative System Test*

The POST feature provides an automatic device/lead check at a pre-determined time post-implant. This helps document proper system functionality without requiring manual system testing, which helps facilitate same-day discharge. The clinician can select the amount of time after lead attachment when automatic lead test results are desired. Any adjustments to the nominal test results time must be programmed prior to lead attachment.

If enabled, automatic intrinsic amplitude, impedance, and pace threshold testing will be attempted one hour prior to the desired test results time. Left ventricular automatic threshold (LVAT) function is available for bipolar electrodes only; thresholds for X4 leads will need to be tested manually.

Upon interrogation, status of the testing (scheduled to run; in-progress; complete) will be provided on the Summary dialog and Summary screen for the first 48 hours following lead attachment. Test results can be printed on Quick Notes and Follow-Up Reports.

5.1.3. *Atrial Arrhythmia Reports*

The following Reports are provided:

- AT / AF percent
- total time in AT / AF counters
- AT / AF burden
- right ventricular (RV) rate during AT / AF
- pacing percent
- heart rate
- activity level
- respiratory rate trends
- longest AT / AF
- fastest right ventricular sensed event (RVS) rate in AT / AF
- most recent episode information.

A timeline history of interrogations, programming, and counter resets for 1 year are also collected.

5.1.4. *ECG/EGM Snapshots*

Up to 6 unique traces of the ECG / EGM display can be stored at any time by pressing the Snapshot button. The traces are 10 seconds pre-activation and 2 seconds post-activation. A 10 second trace will automatically be stored at the end of Pace Threshold tests, which counts as one of the 6 snapshots.

5.1.5. *Leads*

All commercially available BSC leads can be used and are strongly recommended. Leads of other manufacturers may be used, if commercially available. In the atrial channel only bipolar leads are acceptable.

5.1.6. *ZIP Telemetry*

All investigational devices used in this study will incorporate the capability of interrogating the device via ZIP telemetry operating on a RF telemetry band utilizing MICS frequency, in addition to telemetry by wand telemetry.

The PRM communicates with the pulse generator using telemetry wand. For study devices the PRM can also use wand-less ZIP telemetry which allows two way RF communication as an additional option. ZIP telemetry operates with a transmit frequency of 402 to 405MHz (MICS) and RF communication is enabled by Zoom Wireless Transmitter.

When Zip telemetry is ready for use a message will display on the PRM screen indicating that the wand can be removed.

5.1.7. *Programming System*

Programming and interrogation of the investigational devices used in this study is accomplished using the approved and commercially available BSC / Guidant Model

3120 ZOOM Latitude Programming System and approved Model 2869 Application Software.

5.2. Ingenio 2 CRT-P Indications for Use

The Ingenio 2 CRT-Ps are indicated for patients who have symptomatic congestive heart failure (CHF) including LV dysfunction and wide QRS, and/or one or more of the following conditions:

- symptomatic paroxysmal or permanent second- or third-degree atrioventricular (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.

Atrial tracking modes are also indicated 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 (ventricular single chamber mode) intolerance (i.e., pacemaker syndrome) in the presence of persistent sinus rhythm
- low cardiac output or CHF secondary to bradycardia.

Adaptive-rate pacing is indicated for patients exhibiting chronotropic incompetence and who would benefit from increased pacing rates concurrent with increases in MV and/or physical activity.

Please refer to the Instructions for Use (IFU) for the most complete labeling instructions.

5.3. Ingenio 2 CRT-P Contraindications

BSC Ingenio 2 CRT-P devices have the following contraindications:

- in patients who have a separate ICD with transvenous leads
- unipolar pacing or use of the MV/Respiratory Sensor with a subcutaneous ICD (S-ICD) is contraindicated because it may cause inappropriate therapy or inhibition of appropriate S-ICD therapy.
- MV is contraindicated in patients with both unipolar atrial and ventricular leads
- single-chamber atrial pacing is contraindicated in patients with impaired AV nodal conduction
- atrial tracking modes are contraindicated in patients with chronic refractory atrial tachyarrhythmias (atrial fibrillation or flutter), which might trigger ventricular pacing.
- asynchronous pacing is contraindicated in the presence (or likelihood) of competition between paced and intrinsic rhythms.

Please refer to the IFU for the most complete labeling instructions.

6. Study Objective

The objective of this post market clinical follow-up (PMCF) is to collect data on the performance of the Ingenio 2 CRT-P devices and to document that device-related events, device malfunctions or DDs do not increase safety risks in Ingenio 2 CRT-Ps, both in general and specific to the new features and hardware of the devices.

7. Endpoints

7.1. Primary Safety Endpoint

The primary safety endpoint of this study is to:

- evaluate and document the device-related complications by assessing the device-related complication free rate (DRCFR) at the 3 months post-implant.

Device-related complication is defined as complication (an AE that resulted in death, serious injury, a correction using invasive intervention, or permanent loss of device functions) assessed as related to the device.

7.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is:

- LV pacing threshold measurements performed at 0.5 ms pulse width at 3 months post-implant

The pacing configuration selected for permanent programming will be compared to prospectively determined limits.

7.3. Secondary Safety Objectives

The secondary safety objectives for this study are:

- Assessment of proper function of the PaceSafe-LVAT feature with special attention to:
  - inappropriate loss of capture due to LVAT (not related to lead dislodgement, connection issue, etc.) and
  - devices which show retry into LVAT followed by Latitude alert
- Assessment of reported events in relation to the use of MICS during all visits
- Assessment of all reported events in relation to the Quad Lead and Header.

7.4. Secondary Effectiveness Objectives

The secondary effectiveness objectives for this study include:

- Collection of user experience with the PRM interface through the Product Experience Reporting at implant and during follow-up
- Assessment of LV pacing at implant and follow up (pacing threshold per vector, Impedance per vector, % pacing)
- Assessment of battery voltage at Latitude based Close-out visit, for all devices. A battery voltage of ≤ 75% of expected power level (based on the theoretical power consumption calculation in respect to the programmed parameters) will be investigated further.
- Assessment of POST: number of out of range impedance alerts not related to mitigating factor (header connection issue, lead failure, lead dislodgement, etc.)
- Assessment of the correlation between 6 minute walking test distance at 1 month and 3 months post-implant and for subjects with an HRS < 50 and ≥ 50
- The HRS changes between 1 month follow-up and 3 month follow-up will be analyzed for all subjects, for subjects with HRS < 50 and ≥ 50, and for subjects in a non-rate adaptive mode and with rate adaptive pacing.

All event data may be combined with data from Ingenio 2 devices enrolled into the Gentle study.

8. Design

This study is prospective, non-randomized, multi-center, single-group PMCF study.

8.1. Scale and Duration

Sixty-two eligible subjects planned for implant with an Ingenio 2 CRT-P will be enrolled in this study from 10-15 investigational centers, including but not limited to: Belgium, Denmark, Finland, Germany, Netherlands, and Spain. If a site does not enroll a subject within a 3-month time period, the site may be replaced by the discretion of the sponsor.

Enrollment is expected to take approximately 12 months. Subjects will be followed for 3 to 16 months after implant with a median follow-up time of 1 year. All study required visits will be completed as part of a regularly scheduled clinic visit.

The study will be considered complete (primary endpoint completion) after all subjects have completed the Latitude based Close-out 3 to 4 months (91 – 120 days) after last study enrollment. The analysis is planned for 2016. Study completion is anticipated in 2016.

8.2. Treatment Assignment

This study is a non-randomized non-blinded post-market study intended to evaluate the Ingenio 2 CRT-P (VISIONIST) device in a clinical setting. All enrolled subjects will receive an Ingenio 2 CRT-P and the treatment assignment will be based on an "all-comers" consecutive basis. The study devices are fully commercially available and all subjects are planned to receive a CRT-P implant. The assignment of the specific Ingenio 2 device will be determined by the physician; all leads currently in place from previously implanted devices and planned new leads (e.g., Acuity X4 and/or other LV leads) are to be allowed.

8.3. Justification for the Study Design

The primary objective of this study is to gather data to establish the chronic safety, performance and effectiveness of Ingenio 2 CRT-P and to obtain "standard" clinical data on the device use in the clinical setting. In order to obtain a "real world" picture of the CRT-P, the study Inclusion/Exclusion Criteria and follow-up schedule has been written generally enough to allow for study center specific standard of practice that should accurately capture the device use in a "standard" clinical setting. Additionally, by requiring study centers to follow their specific standard of practice, risk to the subject is minimized because the treatment received by the subject will be similar to the treatment the subject would receive if not participating in the study. For this same reason, device implantation is not randomized as it will be determined by the study doctor, based on implanted leads already in place and other medical factors.

Determination of sample size is provided in Section 12.3.

9. Subject Selection

9.1. Study Population and Eligibility

Inclusion and Exclusion criteria are listed in Sections 9.2 and 9.3 below.

Subjects who are enrolled but later determined to not fulfill all inclusion and exclusion criteria after an attempted 3-lead device system implant will be considered to have incurred a Clinical Investigation Plan (CIP) deviation. These subjects will not be included in the planned data analysis but will be followed until the end of the study. Subjects who were intended to be implanted with a Visionist device, or who did not receive a Visionist device after an attempted implant should be withdrawn 30 days after the unsuccessful attempt if all pending events are closed. Once it has been

determined that a subject did not fulfill any inclusion/exclusion criteria, only observational data will be collected for that subject at any visit attended.

9.2. Inclusion Criteria

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

Table 9-1: Inclusion Criteria

1. 18 years or above, or above legal age to give informed consent specific to state and national law
2. Willing and capable of providing informed consent
3. Planned to be implanted or replaced with a VISIONIST Ingenio 2 CRT-P device
4. Planned to be implanted with a 3-lead CRT-P system
5. Planned to be connected to the remote data collection through the Latitude® system
6. Able to do a 6 minute walk test
7. Maximum sensor rate of APMHR 80% should be clinically acceptable
8. Willing and capable of participating in all visits associated with this study at an approved clinical study center and at the intervals defined by this CIP.

9.3. Exclusion Criteria

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

Table 9-2: **Exclusion Criteria**

1. Documented life expectancy of less than 12 months
2. Currently on the active heart transplant list
3. Enrolled in any other concurrent study without prior written approval from BSC, with the exception of local mandatory governmental registries and observational studies/registries that are not in conflict and do not affect the following:
    - Schedule of procedures for the Rally CRT-P Study (i.e., should not cause additional or missed visits)
    - Rally CRT-P Study outcomes (i.e., involve medications that could affect the heart rate of the subject)
    - Conduct of the Rally CRT-P Study per Good Clinical Practice (GCP)/ International Standard Organization (ISO) 14155:2011/ local regulations as applicable
4. In chronic atrial fibrillation
5. Age predicted maximal heart rate (APMHR) needs to be programmed < 80% for clinical reasons at time of enrollment.
6. Not planned to receive a functional atrial lead
7. Per the implanting physician's discretion, subject is not a suitable candidate to receive the study device as determined during the implant procedure
8. Women of childbearing potential who are or might be pregnant at the time of study enrollment
9. Unwilling or unable to participate in all scheduled study follow up visits at an approved study center
10. Does not anticipate being a resident of the area for the scheduled duration of the trial.

10. Subject Accountability

10.1. Point of Enrollment

Subjects will only be enrolled in this study if they meet all eligibility criteria and provide written informed consent. If a subject doesn't meet all eligibility criteria prior to the implant procedure (e.g., no attempt of Rally CRT-P implant is planned) the subject will be withdrawn from the study; any points of ineligibility must be clearly documented in the enrollment/screening log. These subjects will be considered consent ineligible as discussed in Section 10.3, and will not count towards the enrollment ceiling. Any subject that signs consent and meets all Inclusion Criteria and does not meet any Exclusion Criteria will be enrolled followed in the study. If a subject signs consent and meets all eligibility criteria but does not receive the Rally CRT-P implant (for example: anesthesia complications, Visionist CRT-P device was finally not implanted, etc.), the subject will be followed for 30 days for safety reasons and will then be withdrawn from the study (Section 9.1).

10.2. Withdrawal

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

withdrawal is due to problems related to investigational device safety or performance, the Investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal include physician discretion, subject choice to withdraw consent, loss to follow-up, or death. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to future treatment. All applicable case report forms should be completed up to the point of subject withdrawal. Subjects who are "lost-to-follow-up" should have 3 documented failed phone call attempts to contact the subject as well as a certified letter sent to the subject without a response prior to study withdrawal or termination. Sites should also contact their municipal registries (as available in the geography) to determine if the subject may have expired. A death note will need to be provided together with the Serious Adverse Event (SAE) event discription on the Adverse Event (AE) form. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. All open AEs should be closed or documented as chronic or continuing at the end of the study. Data collected up to the point of subject withdrawal may be used. A Study Withdrawal Case Report Form (CRF) should be completed at this time. A retrospective cancelling of subject data collection should be expressed explicitly by the subject so that all data can be removed from the database.

Subjects who do not receive an LV lead or an atrial lead will be followed until the Latitude based Close-out.

10.3. Subject Status and Classification

Consent ineligible subject

A study subject who has signed informed consent but is found to not meet eligibility criteria will be considered a consent ineligible subject and will not count towards the enrollment ceiling. There are no follow-up or AE reporting requirements for consent ineligible subjects. The original signed Informed Consent must be maintained in the center's administrative file.

Active enrolled subject

A study subject who meets the eligibility criteria as per Section 9.2 and Section 9.3 and has signed and dated the Subject ICF is considered actively enrolled in the study. These subjects are followed in accordance with the CIP follow-up schedule and included in the foreseen study analysis. The original signed Subject ICF and any applicable documentation must be maintained in the center's subject file. All applicable eCRFs per the CIP must be completed.

10.4. Enrollment Controls

The study is planned to enroll a maximum of 30 device replacements, and a maximum of 10 subjects with a known indication for rate adaptive pacing which doesn't allow non-rate adaptive pacing between pre-discharge and one month follow up.

Each center may enroll up to a maximum of 20 Rally CRT-P study subjects in order to mitigate any bias from a single center in the final study analysis.

If a center wishes to exceed these limits, the center must obtain prior approval from the sponsor or sponsor's delegated representative.

Once 62 subjects have been enrolled and registered in the trial database, all centers will be informed that enrollment has closed. After closure of enrollment has been communicated, centers must obtain approval from the sponsor or the sponsor's delegated representative for all remaining subjects who are consented but not implanted or enrolled into the study database.

11. Study Methods

11.1. Data Collection

Details for data collection are shown in Table 11-1. Data collection will take place at the following time points:

- Required visits
    - Enrollment and Consenting Clinic Visit (≤ 30 days prior to implant procedure; required)
    - Implant Procedure (Day 0; all future follow ups based on this date; required)
    - Pre-Discharge Clinic Visit (after pocket closure 0-5 days post-implant procedure; required)
    - 1 month visit (30 days ± 15 days post-implant procedure; required)
    - 3 month Clinic Visit (91 ± 21 days post-implant procedure; required)
    - Latitude-based Close-out (91 – 120 days post last enrollment; reporting only required)
- Optional visits
    - Re-implant/Revision (as needed)
    - Any unscheduled visits or additional interim visits

In clinic visits that occur outside the specified visit window will be classified as "Unscheduled Visits". CIP visits that occur outside the specified visit window will be documented as a CIP deviation.

All data collected according to the Data Collection Requirements (Table 11-1) and specified in Sections 11.2 to 11.10 is to be appropriately noted in the eCRF.

Table 11-1: Data Collection Requirements

Procedure/Assessment	Enrollment and Consenting Clinic Visit (required) (≤ 30 days prior to implant procedure)	Implant Procedure (required) (Day 0) Re-implant/ Revision (as needed)	Follow- Up Visits				
			Pre-discharge Visit (required) (0-5 days post-implant procedure)	1 Month Visit (required) (30 ± 15 days post-implant procedure)	3 Month Visit (required) (91 ± 21 days post-implant procedure)	Unscheduled Visit (optional) (according to Center SOC or subject needs)	Latitude-based Close-out[1] (required) (91-120 days post last enrollment)
Informed Consent Form, including informed consent signature and date	X	--	--		--	--	--
Subject information, medical/device history	X	--	--		--	--	--
Clinical assessment	X			O	O	--	--
Implant of CRT-P and implant measurements		X					
12 lead ECG recording	SOC				SOC		
12 lead ECG recording upload	X	--			X	--	--
ECG 10s device based			X		X		
LV pacing threshold for all available vectors			X		X	--	
LVAT function (programming and documenting)		X	X		X	--	
LVAT data report			X		X	--	
Device assessment/interrogation **Leads (impulse, threshold, sensing amplitude)** **MICS** **Header**		X	X	X	X	--	
Manual confirmation ofPOST function/daily measurements		X	X	--	X	--	
Device programming			X	X	X		

Procedure/Assessment	**Enrollment and Consenting Clinic Visit** (required) (≤ 30 days prior to implant procedure)	**Implant Procedure** (required) (Day 0) Re-implant/ Revision (as needed)	**Follow- Up Visits**				
			Pre-discharge Visit (required) (0-5 days post-implant procedure)	**1 Month Visit** (required) (30 ± 15 days post-implant procedure)	**3 Month Visit** (required) (91 ± 21 days post-implant procedure)	**Unscheduled Visit** (optional) (according to Center SOC or subject needs)	**Latitude-based Close-out**[1] (required) (91-120 days post last enrollment)
6 minute walking test				X	X		
Device data collection (electronically) and electronic upload			X	X	X		
Manual threshold and device testing		X	X	X	X	--	
Current/concomitant medications[2]	X		X	X	X		
Adverse device events[3] **and SAEs**	--	X	X	X	X	X	X
Latitude report on device data collection; battery status/diagnostic report			X	X	X	X	X

ECG=electrocardiogram; HF=heart failure; O=optional; POST=Post-Operative System Test; SAE=serious adverse event; SOC=standard of care; X=required; --=not required

1. A 12 month post-implant data collection will be done, but will be done remotely and does not require a site visit
2. Only heart failure medication classes (Beta blockers, ACE inhibitors, diuretics, etc.); currently being administered or changes to administration of.
3. To include collection of all USADEs, SADEs, ADEs, DDs; collection of all SAEs

11.2. Study Candidate Screening

After approval by the Investigator's Ethics Committee (EC) and the sponsor or delegated representative, the Investigator will follow standard of care (SOC) practices to screen subjects for inclusion in the study. Subjects are considered enrolled after they have met all inclusion criteria, none of the exclusion criteria, and provided written informed consent in accordance with applicable regulatory agency and EC requirements.

11.3. Informed Consent

During the Enrollment and Consenting Visit (Section 11.4) a qualified center representative will review the consent with a potential subject. The subject will be encouraged to ask any questions about the study. All questions from the subject should be addressed prior to the subject signing the informed consent. If the subject signs the informed consent, a signed copy should be provided to the subject and the original should be filed in the medical records. Documentation of the consent process by the person obtaining consent should be filed in the subject study file. Study personnel should explain to the subject that even if the subject agrees to participate in the study and signs the study Informed Consent Form (ICF), the implant procedure may demonstrate that the subject is not a suitable candidate for the study. No study-specific data collection of any procedure should be conducted prior to consent.

11.4. Enrollment Visit (≤ 30 days prior to implant procedure; required)

Prior to initiating any study procedures, the Investigator must ensure that appropriate informed consent has been documented (Section 11.3).

The data collection at enrollment includes: subject information and medical history; subject status and clinical assessment per SOC; and details on previously/currently implanted devices.

Baseline data that are not caught in the hospital records must be queried and documented with a Note to File.

Subject information and medical history

- **Demographic data:** age at time of consent; gender.
- **Additional rhythm disease:** information will be collected on additional relevant rhythm diseases: atrio-ventricular block; sinus node dysfunction; paroxysmal/chronic atrial fibrillation; chronotropic incompetence.
- **Subject etiology:** ischemic cardiomyopathy; idiopathic cardiomyopathy; valvular; cardiomyopathy; hypertrophic cardiomyopathy; congenital heart disease; infiltrative disease; neuromuscular disease (including myotonic dystrophy and Kearns-Sayre syndrome).
- **Associated diseases/risk factors:** hypertension, diabetes, renal disease, chronic pulmonary disease, peripheral artery disease, COPD, asthma, other known malignancies (tumor, lymphoma or leukemia), other chronic diseases.

- **Other subject history:** previous stroke; previous myocardial infarction; previous hospitalization for heart failure; previous ablation (AV node, atrial fibrillation or atrial flutter).
- **Current/concomitant medication:** documentation of current/concomitant medication classes being administered for treatment of heart failure

History of implanted devices

- **Pacemaker, ICD, etc. data**: Implant date, number of years implanted, model and manufacturer
- **Pacing lead data**: cardiac chamber (atrial and ventricular), number of years implanted and lead-model and manufacturer

Baseline subject status and clinical assessment

- **Clinical assessment data**: weight, height, blood pressure, New York Heart Association (NYHA) class, Left Ventricular Ejection Fraction (<1 year old).
- **Electrocardiogram (data collection and document upload in e.g. pdf format):** date (maximum 1 month before enrollment); rhythm (normal sinus rhythm, junctional rhythm, atrial fibrillation, paced); resting heart rate; intrinsic QRS width; intrinsic PR interval, intrinsic QT interval; QRS morphology (normal, right bundle branch block (RBBB), left bundle branch block (LBBB), other conduction disorders). The Investigator should classify the nature of the subjects intrinsic intra-ventricular conduction delay (e.g. LBBB, RBBB, or non-specific) per the World Health Organization Guidelines. These guidelines can be found in Appendix B: Ventricular Conduction Delay Definitions.

11.5. Implant Procedure (Day 0; required); Re-implant/Revision Procedures (as needed)

Subjects that meet all of the entry criteria and consent to the procedure are eligible. All subjects will be implanted, per center SOC procedure, with one of 3 Rally CRT-P models; selection of subject appropriate device will be at the discretion of the Investigator based on appropriate medical considerations. All future follow-ups will be based on this date.

Subjects that need re-implant or revision procedures, as determined by the Investigator, will undergo the same procedures as described for Day 0. The reason for re-implant/revision is to be documented in the eCRF.

While the Investigator should follow the center's SOC procedures and the IFU, it is important to ensure that the pulse generator has good contact with the surrounding tissue of the implantation pocket, and then suture it in place to minimize device migration (Figure 5-2).

In addition, two strategies are recommended for device configuration and programming:

1) Non-apical, non-septal-pacing vector, AV optimization, Echocardiographic optimization, QLV optimization any acceptable pacing threshold and no PNS
2) Non apical pacing vector, no further optimization, good pacing threshold and no PNS.

All standard lead/device components are to be assessed during and/or after implant.

The following data elements will be captured DURING the index procedure:

- Procedure time skin to skin, number of LV lead repositioning attempts
- Model and serial number of all implanted and active devices
- Final LV pacing configuration: impedance and threshold
- Final sensing configuration LV-R-wave
- Artifacts during sensing post-implant (ADE reporting)
- Confirmation /assessment of MICS, lead insertion, header
  (all lead insertion difficulties or ball seal problems (including but not limited to: missing springs, dislodged springs, etc.) must be reported as an event. The subject impact should be documented in the event description.
- Bipolar sensing amplitude for right atrial (RA) and right ventricle (RV) electrodes should be measured and recorded
- Occurrence of any device-related event (unanticipated serious adverse device effect [USADE], ADE, DD) or SAEs unrelated to the device

The implant procedure will be noted in the eCRF as intended, attempted or successful.

MICS should be used for any device interrogation. Any DDs (including but not limited to: drop-outs during use of MICS, threshold test taking too long, loss of STAT Pace, etc.) are to be reported. The subject impact should be documented in the event description.

Details on the occurrence of any USADE, SADE, ADE, DD, SAE or device-related malfunction are to be recorded.

Implant data shall be documented as indicated in Table 11-2 and Table 11-3.

Table 11-2: Implant Procedure Assessments

Pacing configuration	Pacing Threshold at 0.5 ms*	Impedance In Ω	Sensing Amplitude
E1 – unipolar (PSA)			
E2 – unipolar (PSA)			
E3 – unipolar (PSA)			
E4 – unipolar (PSA)			
Final minimum measurements after pocket closure			
Final RA lead measurements			
Final RV lead measurements			
Final LV – lead configuration E… to …..			

* 0.4 can be used as a standard setting, per Investigator discretion; to be documented in the eCRF
eCRF=electronic Case Report Form, LV=left ventricle, PSA=Pacing System Analyzer, RA=right atrium

Table 11-3: Post-pocket Closure Sensing Assessments

Sensing Configuration V – V During Smart Delay with Pacing Configuration	V-V timing in ms
E1	
E2	
E3	
E4	

The POST function is to be switched on POST-IMPLANT for device interrogation. Confirmation of all measurements via POST will be noted in the eCRF, with follow-up manual confirmation of:

- pacing threshold for all 3 electrodes
- pacing threshold of at least 3 of the possible 17 LV vectors per configuration on unipolar, bi-polar and extended bipolar
- impedance for all 3 electrodes
- intrinsic signal (p-wave, r-wave)
- all vectors of LV lead.

A DD report is to be submitted for any parameter that does not function appropriately.

11.6. Pre-discharge Clinic Visit (0-5 days post-implant procedure; required)

A device assessment will be performed in order to document the proper device function and any adverse device events or SAEs that may have occurred since the implant procedure. Current medication classes prescribed shall be documented, and device interrogation performed according to SOC practices.

At this visit, a BiV-paced post-implant 10s programmer ECG recording is required to be uploaded to the study database for core lab review (should be manually measured as SOC). Channels to be used include:

- RA (RAS/RAP)
- RV (RVS/RVP)
- LV (left ventricular sensed event [LVS]/left ventricular pressure [LVP])
- surface ECG.

In general, device based measurements at this visit are to include the PR interval over multiple intervals; RVS to LVS timing for each LV electrode; thresholds; and impedances and amplitude measurement.

In addition to all automatic POST measurements, manual testing should be done of all leads (impulse, threshold, sensing amplitude) and output programming. All out of range alerts from POST should be documented on the event page regardless of the direct subject impact. Any subject impact is also to be documented in the event description.

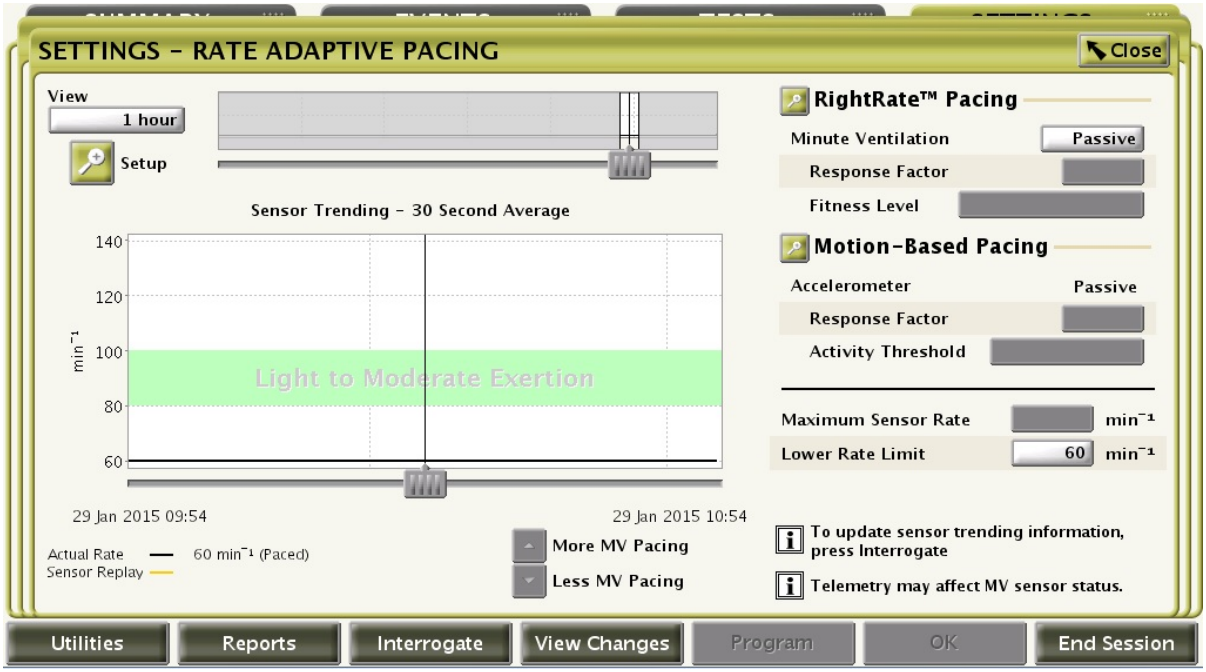
Output programming should be tested via LVAT and manually, the functionality of MICS confirmed and the PRM interface rating is to be documented. Pre-discharge device assessments as noted in Table 11-4, Table 11-5 and Table 11-6 are to be documented.

Device programming (Figure 11-1) should include selection of final LV pacing/sensing vectors; Smart delay should be used to determine paced and sensed AV delays and

confirmation of LV-RV offset. All subjects are to be programmed to a non-rate adaptive pacing mode from the time of discharge until the 1 month follow-up visit (e.g., DDD). Accelerometer and/ or MV Sensor might be programmed ON for subjects *with previous device implants (e.g., pacemaker) with a known need for rate adaptive pacing*. If a rate adaptive pacing mode is programmed, reasons must be documented in the eCRF. Pacing Rate and AV delay should be programmed at the physician's discretion so that subjects receive a maximum of ventricular pacing rate to assure optimal CRT therapy.

To obtain an accurate MV baseline, the MV sensor will be calibrated automatically or can be calibrated manually. A new, manual calibration should be performed if the pulse generator is removed from the pocket following implant, such as during a lead repositioning procedure, or in cases where the MV baseline may have been affected by factors such as lead maturation, air entrapment in the pocket, pulse generator motion due to inadequate suturing, external defibrillation or cardioversion, or other patient complications (e.g., pneumothorax).

Figure 11-1: Pre-Discharge Programming Screen



The LATITUDE data collection system will be set up at discharge (± 5 days). A weekly interrogation frequency should be programmed until 3 month follow up. After 3 month follow up the interrogation might be less frequent but not less than monthly. Inability to set up or program the data collection system will be considered a CIP deviation.

After the final programming (DDD pacing mode) and setting rate adaptive pacing (MV sensor) to “passive”, the final data interrogation must be saved as data file and stored in the subject binder. The file should be uploaded as a ZIP file into the study database.

Additional details to be documented in the eCRF:

- final LV pacing vector
- SMART delay optimization used (YES/NO)
- programmed AV delay
- how accelerometer was programmed at the end of pre-discharge (ON/Passiv)
- how MV sensor was programmed at the end of pre-discharge (ON/Passiv)
- programmed pacing mode

All information is to be saved to a disc at the end of the visit.

XL and MV sensors should be in the passive mode.

Chronotropic incompetent subjects (e.g. rate trend shows all time < 100 bpm) may receive benefit from the use of available rate response functions.

All current/concomitant heart failure medication classes (Beta blockers, angiotensin-converting-enzyme [ACE] inhibitors, diuretics, etc.) at baseline and at time of discharge are to be noted in the eCRF; any changes made to these medications during hospitalization are also to be noted in the eCRF.

Details on the occurrence of any USADE, SADE, ADE, DD, SAE or device-related malfunction which have occurred since the implant procedure are to be recorded.

Table 11-4: Pre-discharge Device Assessments

Pacing configuration	Pacing Threshold at 0.5 ms	Impedance in Ω
E1 – unipolar (Can) (device based)		
E2 – unipolar (Can) (device based)		
E3 – unipolar (Can) (device based)		
E4 – unipolar (Can) (device based)		
E1 – Ext Bipolar (device based)		
E2 – Ext Bipolar (device based)		
E3 – Ext Bipolar (device based)		
E4 – Ext Bipolar (device based)		
Bipolar E1 →E2 (device based)		
Bipolar E1 →E3 (device based)		
Bipolar E1 →E4 (device based)		
Bipolar E2 →E3 (device based)		
Bipolar E2 →E4 (device based)		
Bipolar E3 →E2 (device based)		
Bipolar E3 →E4 (device based)		
Bipolar E4 →E2 (device based)		
Bipolar E4 →E3 (device based)		
RV Threshold (bipolar)		
RV Threshold Unipolar (optional)		
RA Threshold (bipolar)		
RA Threshold Unipolar (optional)		

Table 11-5: Pre-discharge Sensing Assessments

Sensing Configuration V – V during Smart Delay with Pacing Configuration	V-V timing in ms
E1	
E2	
E3	
E4	

Table 11-6: Sensing Configuration

LV Sensing Configuration	R-Wave in mV
LV - E1	
LV - E2	
RV Sensing	
RA Sensing	

11.7. 1 Month Clinic Visit (30 ± 15 days post-implant procedure; required)

Clinical assessments may be done at this visit, if the assessment is part of the center's SOC procedures. All subjects are to be programmed to a non-rate adaptive pacing mode until this visit.

Prior to the initial device interrogation, subjects will do a 6 minute brisk walk, in a non-rate adaptive pacing mode. Data to be collected in association with the walk include:

- age predicted maximal heart rate
- heart rate prior to and at the conclusion of the walk
- maximum heart rate
- distance walked (in meters)
- any symptoms experienced.

All subjects shall be "interrogated" after the 6 minute walk test and the data must be saved prior to any re-programming.

Chronotropic incompetent subjects (e.g., rate trend in the device for the previous 24 hours [including the 6 minute walk test] shows all time < 100 bpm) may receive benefit from the use of MV sensor.

If, after the walking test, the maximum heart rate is < 100 bpm or < 80% of the age predicted heart rate ([220-age]*80%), the MV sensor should be programmed on (e.g., DDDR); the maximum sensor rate should be at 80% of the age predicted maximal heart rate (APMHR).

The accelerometer should be programmed to "Passiv" during the course of the study until the Latitude close out follow up. In case the accelerometer needs to be turned on for clinical reasons an event and corrective action need to be documented in the study database.

Rate adaptive pacing during this study should be triggered by the MV Sensor only.

Subjects with a maximum heart rate < 80% of their respective age predicted maximum ([220-age]*80%) after the 6 minute walk will receive sensor optimization, per the Optimization Guidelines:

- The maximum sensor rate should be programmed to: APMHR * 80% (Table 11-7)
- The maximum sensor rate should not be programed below 110 bpm
- The programming of the MV "Response Factor" should be programmed (based on the result of the sensor modulation after 6 minute walk; starting at nominal 8).
- The resulting HR frequency in the sensor response modulation (especially in the 2nd part of the 6 minute walk) should result in a minimum of 70% of APMHR so that an appropriate HR can be achieved during future exercises.

A screen shot for the pacing configuration is shown in Figure 11-2.

Figure 11-2: One Month Follow up Programming Screen

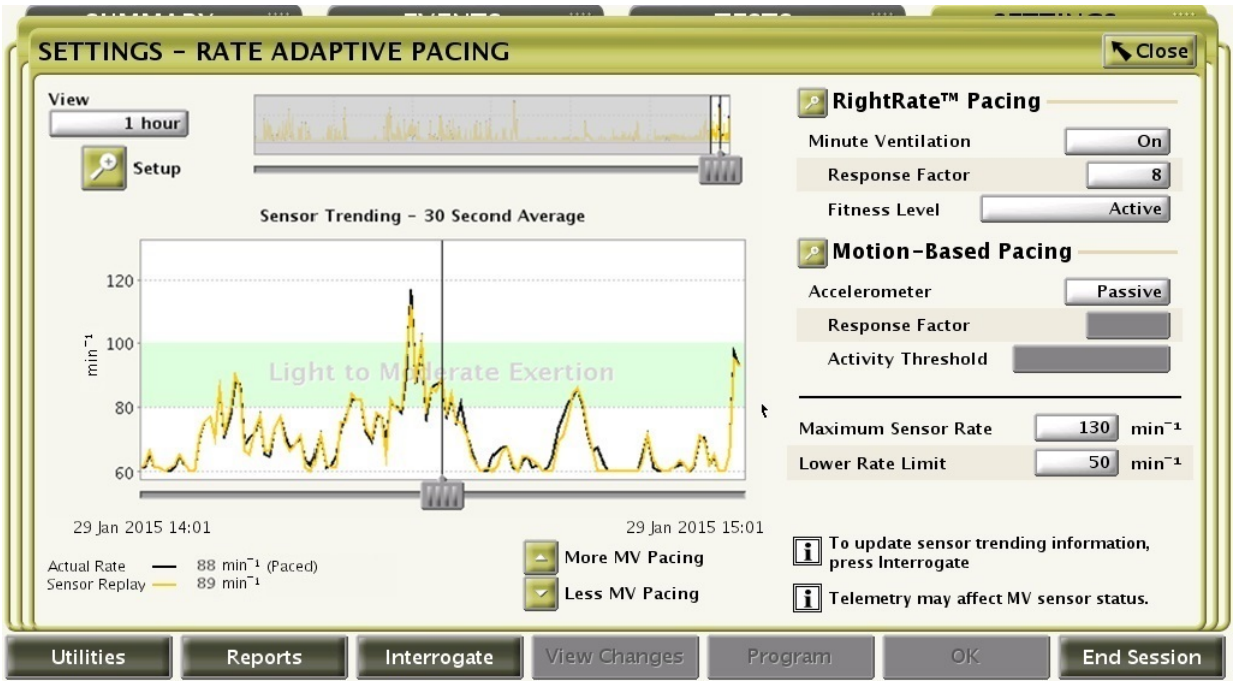


Table 11-7 provides an overview of the age dependent values as guidance for hall walk sensor adjustments to achieve optimal pacing rates, if clinically acceptable.

Table 11-7: Age Predicted Heart Rates (100%, 80%, 70%)

Age			APMHR	APMHR*80%	Programmed Value for APMHR*80%	APMHR*70%
55	to	59	165	132	130	116
60	to	64	160	128	130	112
65	to	69	155	124	125	108
70	to	74	150	120	120	105
75	to	79	145	116	115	101
80	to	84	140	112	110	98
85	to	89	135	108	110	95

APHR=age predicted heart rate, APMHR=age predicted maximal heart rate

MICS should be used for device interrogation. Events including (but not limited to) drop-outs during use of MICS, threshold test taking too long, loss of STAT Pace, etc. are required to be reported. The subject impact should be documented in the event description.

After final programming and sensor optimization, counters must be cleared and the final data interrogation can be saved for the clinical records as data file; the data does not need to be submitted as part of this study.

All current/concomitant heart failure medication classes, including changes to medications, are to be noted in the eCRF.

Details on the occurrence of any USADE, SADE, ADE, DD, SAE or device-related malfunction which have occurred since the previous visit are to be recorded.

Subjects will have their device performance, nominal alerts and diagnostic data downloaded remotely via the Latitude system by the BSC Latitude team during this visit timeframe. The subject device memory file will be collected. The following will be collected from the Latitude report by the core lab:

- Identify the atrial histogram. Report the “10 bpm bin” with **most paced beats by number** and report the %AP.
- Identify the atrial histogram. Report the “10 bpm bin” with **most sensed beats by number** and report %AS.

- HRS calculated from %AP and %AS.

11.8. 3 Month Clinic Visit (91 ± 21 days post-implant procedure; required)

Clinical assessments may be done at this visit, if the assessment is part of the center's SOC procedures.

The subject should have a vigorous 6 minute walk, to be done in the mode programmed at the 1 month follow up visit (e.g., DDDR for chronotropic incompetent patients and DDD for patients who clinically don't need rate adaptive pacing). Data to be collected in association with the walk include:

- age predicted heart rate
- heart rate prior to and at the conclusion of the walk
- maximum heart rate
- distance walked (in meters)
- any symptoms experienced.

MICS should be used for device interrogation. In case of but not limited to: e.g. drop-outs during use of MICS, or threshold test taking too long, loss of STAT Pace, etc. it is required to report all those events. The subject impact should be documented in the event description.

All subjects will be "interrogated" after the 6 minute walk test and the data must be saved prior to any re-programming.

The initial data interrogation the data file must be saved and stored in the subject binder. The file must be uploaded as a ZIP file into the study database.

If the HRS is still > 70 the response factor may be increased by 1.

A BiV-paced post-implant 10s programmer ECG recording is required to be uploaded to the study database for core lab review.

Subjects will have their device performance, nominal alerts and diagnostic data downloaded remotely via the Latitude system by the BSC Latitude team during this visit timeframe.

The final programming will be collected via the Latitude database and does not need to be uploaded.

The following will be collected from the Latitude report by the core lab:

- Identify the atrial histogram. Report the "10 bpm bin" with **most paced beats by number** and report the %AP.
- Identify the atrial histogram. Report the "10 bpm bin" with **most sensed beats by number** and report %AS.

- HRS calculated from %AP and %AS.

This visit is intended to evaluate the confidence interval (CI) using the HRS; confirm device diagnostics; and document subject symptoms. In particular all "trending" information should be noted. The BiV testing routine should document the PR interval over multiple intervals; RVS to LVS timing for each LV electrode; selection of final LV pacing/sensing vectors; use of Smart Delay to determine paced and sensed AV delays; and confirmation of LV-RV offset.

Output programming should be tested via LVAT and manually, the functionality of MICS confirmed and the PRM interface rating is to be documented. All daily measurement assessments should be confirmed manually.

All current/concomitant heart failure medication classes, including changes to those medications, are to be noted in the eCRF.

Details on the occurrence of any USADE, SADE, ADE, DD, SAE or device-related malfunction which have occurred since the previous visit are to be recorded.

11.9. Latitude based Close-out (91 - 120 days after the study is closed for enrollment; required)

Each subject will be followed up for 3 to 16 months (the maximum time in the study for any subject) following the implant procedure. Each subject should have a remote Latitude based Close-out (Latitude Report) collected within 3 to 4 months (91 - 120 days) after the date the study is closed to enrollment. All centers will be notified of this date. For subjects reaching 16 months, the Latitude based Close-out will be performed before reaching 16 months in the study, since 16 months is the maximum time in the study for any subject.

Subjects will not need to come to the study facility for any study procedures, but any clinical assessments done as part of center SOC should be documented on the eCRF.

During the remote Close-out, RV and LV pacing configuration and pacing threshold and battery voltage should be documented in the eCRF. Battery longevity will be monitored and documented. All device alerts will be reviewed and should correspond to the facility event reporting (e.g. SADE, ADE, SAE; DD for confirmed alert; or DD for false positive alert).

Subjects will have their device performance, nominal alerts and diagnostic data downloaded remotely from the Latitude BSC team during this visit timeframe.

Once the subject completes the Latitude based Close-out, participation in this study has been completed. In case of premature termination of the study, data collection will stop accordingly.

If a device-related event (USADE, SADE, ADE) is ongoing at the time of study completion, the subject may be asked to remain enrolled in the study and provide additional information regarding the event until the event is resolved. The physician will provide treatment for any ongoing events according to SOC regardless of whether the subject agrees to continue participating in the study.

11.10. Unscheduled or Interim Visits outside of Study Visit Windows

Should the subject be hospitalized or have an unscheduled or additional interim ambulatory/in clinic visit (e.g., related to center SOC, HF, resynchronization therapy, or antiarrhythmic therapy, or a visit with study personnel for any reason), the Investigator is responsible for notifying the sponsor. For Unscheduled Visits (outside of study visit schedule for any reason) an Unscheduled Follow-up eCRF should be completed in order to document this visit. The visit should be documented. If the visit was necessary due to an event which was serious or related to the device the Event-report eCRF must be completed. The occurrence of any event (USADE, SADE, SAE, ADE or DD, including but not limited to: drop-outs during use of MICS, threshold test taking too long, loss of STAT Pace, etc.) must be reported. The subject impact should be documented in the event description.

11.11. Source Documents

Table 11-8 summarises all source data requirements for this CIP. Most source documents will be filed in the subject's hospital chart since all procedures will follow SOC.

Some device measurements (e.g. 17 pacing vectors, 6 minute walk test, etc.) need to be documented on Worksheets which should be filed in the patient binder. Some source documents (e.g., 10s programmer ECG strips, device data memory file) will also be kept in the patient binder after the upload into the study database. Where copies of the original source document and printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation study team (Research Coordinator or Investigator who is authorized per the delegation log). Other copies and measurements outside SOC as well as the patient consent form should be kept in the subject binder.

All personal information should be removed from all documents prior uploading into the study database and replaced by the study ID. In case this is not possible the database administrator will anonymize data as required.

Table 11-8: Source Documentation Requirements

Requirement	Disposition
Subject Consent Form	**1-Retain subject file, 2-study binder, 3-Subject copy**
Enrollment and Baseline Data	Retain in subject hospital file
Implant Measurement Worksheet	Subject binder
Implant Procedure Medical Records	Retain in subject hospital file
Pre-discharge Clinic Visit Data	Retain in subject hospital file and Subject binder
1 and 3 month Clinic Visit Data	Retain in subject hospital file and Subject binder
Interim and Unscheduled Visit Data	Retain in subject hospital file
Latitude report Close-out Data	Latitude database and pdf - Report in Study Database
Device Event Data	Retain in subject hospital file and report into the study database
Protocol (CIP) Deviation	Report in Study Database
Study Withdrawal Worksheet	Subject binder
12-lead ECG e-Recording	Retain in subject hospital file and copy upload to study database
10s Programmer ECG Recording	Subject binder, upload to study database
Device Interrogation and Print-outs	Retain in subject hospital file
6 minute walk test results documented on the worksheet	Retain in subject hospital file or in the subject binder
Latitude device and alert data	Latitude database and copy upload into study database

12. Statistical Considerations

12.1. Primary Safety and Effectiveness Endpoints

12.1.1. *Primary Safety Endpoint*

The primary safety endpoint for this study is to:

- evaluate and document the device-related complications by assessing the DRCFR at 3 months post-implant.

Safety will be evaluated by the DRCFR from implant through 3-months post-implant, based on complications that are related to the Ingenio 2 CRT-P device. A device-related complication is an AE that resulted in death, serious injury, a correction using invasive intervention or permanent loss of device functions, and that was assessed as related to the device. Device-related complications that may count against the primary safety endpoint are outlined in Section 18.1 and Section 18.2 of this CIP.

12.1.1.1. Hypotheses

The null and alternative hypotheses are as follows:

H_0: The DRCFR from 0-3 months ≤ 87.5%

H_A: The DRCFR from 0-3 months > 87.5%

The null hypothesis (H_0) will be rejected if the lower one-sided 95% confidence bound for the DRCFR is greater than the performance goal of 87.5%.

12.1.1.2. Statistical Methods

When the final study subject reaches the 3 Month required follow-up visit, the primary safety analysis will be performed based on exact binomial methods for the estimation of the DRCFR, including the exact lower one-sided 95% confidence bound. Subjects that die/withdraw or are lost-to-follow-up prior to the 3-month endpoint evaluation (≤ 91 + 21 days post-implant or post-implant attempt) and have not experienced device-related complications will be excluded from the analysis. The sample size was adjusted to account for up to 20% attrition to ensure there would be a sufficient number of evaluable subjects through 3-months.

The primary safety endpoint will evaluate the DRCFR through 3-months post-implant (or implant attempt), calculated using exact binomial methods. The null hypothesis will be rejected and the endpoint considered met if the lower one-sided 95% confidence bound for the DRCFR at 3-months is greater than 87.5%.

12.1.2. *Primary Effectiveness Endpoint*

The primary effectiveness endpoint of this study is:

- LV pacing threshold measurements performed at 0.5 ms pulse width at 3 months post-implant

The pacing configuration that the physician selects for permanent programming will be compared to prospectively determined limits.

12.1.2.1. Hypotheses

The null and alternative hypotheses are as follows:

H_0: The mean LV pacing threshold at 3 months ≥ 2.5V

H_A: The mean LV pacing threshold at 3 months < 2.5V

The null hypothesis (H_0) will be rejected if the upper one-sided 95% confidence bound for the mean LV pacing threshold is less than the performance goal of 2.5V.

12.1.2.2. Statistical Methods

When the final study subject reaches the 3 Month required follow-up visit, the primary effectiveness analysis will be performed based on one-sample t-test methodology for the

comparison of the mean LV pacing threshold, including the upper one-sided 95% confidence bound. Implanted subjects with available LV pacing threshold at the 3-month endpoint evaluation (91 days ± 21 days post-implant) will be included in the analysis. The sample size was adjusted to account for up to 20% attrition to ensure there would be a sufficient number of evaluable subjects at 3-months.

The primary effectiveness endpoint will evaluate the mean LV pacing threshold at 3-months post-implant, and comparison will be performed using one-sample t-test methodology. The null hypothesis will be rejected and the endpoint considered met if the upper one-sided 95% confidence bound for the mean LV pacing threshold at 3-months is less than 2.5V.

12.2. Secondary Safety and Effectiveness Objectives

To further characterize the safety, performance, and effectiveness of the Ingenio 2 CRT-P device, the following outcomes will also be summarized for all implanted and attempted subjects.

12.2.1.1. Secondary Safety Objectives

- Assessment of proper function of the PaceSafe-LVAT feature with special attention to:
    - inappropriate loss of capture due to LVAT (not related to lead dislodgement, connection issue, etc.) and
    - devices which show retry into LVAT followed by Latitude alert
- Assessment of reported events in relation to the use of MICS during all visits
- Assessment of all reported events in relation to the Quad Lead and Header

12.2.1.2. Secondary Effectiveness Objectives

- Collection of user experience with the PRM interface through the Product Experience Reporting at implant and during follow-up
- Assessment of LV pacing at implant and follow up (pacing threshold per vector, impedance per vector, % pacing)
- Assessment of battery voltage at the Latitude based Close-out visit, for all devices. A battery voltage ≤ 75% of expected power level (based on the theoretical power consumption calculation in respect to the programmed parameters) will be investigated further.
- Assessment of POST: number of out of range impedance alerts not related to mitigating factor (header connection issue, lead failure, lead dislodgement, etc.)
- Assessment of the correlation between 6 minute walking test distance at 1 month and 3 months post-implant and for subjects with HRS < 50 and ≥ 50.
- The HRS changes between 1 month follow-up and 3 month follow-up will be analyzed for all subjects, for subjects with HRS < 50 and ≥ 50, and for subjects in a non-rate adaptive mode and with rate adaptive pacing.

All event data may be combined with data from Ingenio 2 devices enrolled into the Gentle study.

12.3. Sample Size

The minimum required sample size to evaluate the primary endpoints and account for up to 20% attrition is 62 (Table 12-1).

Table 12-1: Endpoint Sample Size Estimates

Endpoint	Measurement	Hypotheses[1]	Expected Performance	Power	Number of Subjects needed for analysis	Number of Subjects to be enrolled for ≤ 20% attrition
Primary Safety Endpoint	DRCFR from 0 to 3 months	H_0: DRCFR ≤ 87.5% H_A: DRCFR > 87.5%	97.5%	80%	49	62
Primary Effectiveness Endpoint	LV pacing threshold at 3 months	H_0: mean ≥ 2.5V H_A: mean < 2.5V	1.9 ± 1.2V	90%	36	45

[1] Hypothesis test based on a one-sided alpha level of 0.05.
LV=left ventricular; DRCFR=device-related complication free rate

Sample sizes were calculated employing exact binomial methods (primary safety endpoint) and one-sample t-test methodology (primary effectiveness endpoint) in nQuery 6.0.

The following assumptions were used for the calculation of sample sizes:

- Primary Safety Endpoint
  - Expected DRCFR = 97.5% (determined from prior comparable BSC devices)
  - Performance goal = 87.5% (clinically accepted delta of 10%, subtracted from expected DRCFR)
  - Test significance level (α) = 0.05 (one-sided)
  - Power = 80%
- Primary Effectiveness Endpoint
  - Expected mean (± standard deviation [SD]) LV pacing threshold = 1.9 ± 1.2V (based on prior BSC LV lead performance)
  - Performance goal = 2.5V (used in prior BSC led approval studies)
  - Test significance level (α) = 0.05 (one-sided)
  - Power = 90%

12.4. General Statistical Methods

12.4.1. *Analysis Sets*

All subjects where implant with the Ingenio 2 CRT-P device was successful will be included in the primary endpoints analyses. For the DRCFR primary endpoint, subjects where the Ingenio 2 CRT-P device was attempted but not successfully implanted will also be included. Nevertheless, for the DRCFR primary endpoint, subjects that die/withdraw or are lost-to-follow-up prior to the 3-month endpoint evaluation (91 days post-implant or post-implant attempt) and have not experienced device-related complication will be excluded from the analysis.

12.4.2. *Descriptive Statistical Methods*

Descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for the primary endpoints. Unless otherwise stated, all statistical testing will be one-sided and will be performed using a significance (alpha) level of 0.05.

Continuous variables as a minimum will be described by number of non-missing observations (n), arithmetic mean (Mean), SD, minimum (Minimum), median (Median), and maximum (Maximum). One additional decimal point for mean and median and 2 additional decimal points for SD will be used.

Categorical variables will be presented using the number of non-missing observations (n) or the number of subjects in the population (N) as applicable and percentages (%). Percentages will be rounded to one decimal place. Unless otherwise stated, two-sided 90% CIs will be provided when relevant. The two-sided 90% CI will be presented as it provides:

- the one-sided 95% lower limit when the upper bound is ignored to assess superiority.
- the one-sided 95% upper limit when the lower bound is ignored to assess superiority.

12.4.3. *Number of Subjects per Investigative Site*

Approximately 10 investigational centers will enroll 62 subjects. If a center does not enroll a subject within a 3-month time period, the site may be replaced at the discretion of the sponsor.

12.5. Data Analyses

12.5.1. *Interim Analyses*

No interim analyses are planned.

12.5.2. *Subgroup Analyses*

No subgroup analyses are planned due to the small number of subjects included in this evaluation.

12.5.3. *Other Analyses*

Descriptive statistics of subject demographic and baseline characteristics will be presented.

12.5.4. *Changes to Planned Analyses*

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

13. Data Management

13.1. Data Collection, Processing, and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. The time periods for recording study data (enrollment, implant data, etc.) is specified in the site guidelines.

The clinical database will reside on a production server hosted by AptivAdvantage. All changes made to the clinical data will be captured in an electronic audit trail and available for review by BSC or its representative. The associated database has been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.
The Investigator provides his/her electronic signature on the appropriate electronic Case Report Forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

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

All ECG readings should be uploaded to the study database for core lab review. Refer to the Core Lab Manual of Operations for more details.

13.2. Data Retention

The Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with International Conference on Harmonization (ICH)/GCP guidelines. Documents must be retained for at least 2 years after the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the

Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

13.3. Core Laboratories

All ECG readings should be uploaded to the study database for core lab review. Refer to the Core Lab Manual of Operations for more details.

14. Amendments

If a CIP revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., EC) of the revised CIP must be obtained prior to implementation.

15. Deviations

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

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using on the EDC eCRF and a CIP Deviation Worksheet should also be completed and filed in the subject file. Sites may also be required to report deviations to the EC, per local guidelines and government regulations.

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

16. Compliance

16.1. Statement of Compliance

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

16.2. Investigator Responsibilities

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

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

- prior to beginning the study, sign the Investigator Agreement and CIP Signature page documenting his/her agreement to conduct the study in accordance with the CIP.
- provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- make no changes in or deviate from this CIP, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved CIP 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 eCRFs and in all required reports.
- record, report, and assess (seriousness and relationship to the device/procedure) every observed DD.
- report to BSC, per the CIP requirements, all USADEs, SADEs, ADEs, DDs; all SAEs; documentation of freedom from UADEs and device-related malfunctions.
- report to the EC and regulatory authorities any SAEs and DDs that could have led to a SADE, if required by the national regulations or this CIP or by the EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- allow and support regulatory authorities and the EC when performing auditing activities.
- ensure that informed consent is obtained in accordance with this CIP and local EC requirements.
- provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of a device event, as described in the ICF.

- inform the subject of the nature and possible cause of any device events experienced.
- inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment.
- ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

16.2.1. *Delegation of Responsibility*

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

16.3. Ethics Committee

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

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

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

16.4. Sponsor Responsibilities

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

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

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

16.4.1. *Role of Boston Scientific Representatives*

Boston Scientific personnel may provide technical support to the Investigator and other health care personnel (collectively HCP) as needed during implant, testing required as part of hospital SOC, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including PRMs, 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, and assist with the conduct of testing.

Typical tasks may include the following:

- interrogating the device or programming device parameters to Investigator-requested settings as well as operating investigational equipment
- performing lead diagnostic testing using a Pacing System Analyzer (PSA) or PRM 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 PSAs, PRMs, and other equipment.

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

- observing testing or medical procedures to provide information relevant to CIP compliance
- reviewing collected data and study documentation for completeness and accuracy.

Boston Scientific personnel will not do the following:

- practice medicine
- provide medical diagnosis or treatment to subjects
- discuss a subject's condition or treatment with a subject without the approval and presence of the HCP
- independently collect critical study data (defined as primary or secondary endpoint data)
- enter data in electronic data capture systems.

16.5. Insurance

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

17. Monitoring

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

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and

relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

18. Potential Risks and Benefits

18.1. Potential Lead Implantation Adverse Events

This study is following the Visionist Instructions for Use as well as the hospital standard of care and will therefore not increase the risks for the subject. All subjects are planned to receive a CRT-P implant as part of the SOC treatment, therefore there are no additional procedural risks at implant or regular follow-up to the subject for being included in this study.

The Ingenio 2 CRT-P Visionist device is fully commercially available and subjects that will be enrolled in the Ingenio 2 CRT-P PMCF Study are following a standard implant in the hospital. During the study, procedures and follow up visits will be scheduled following the Visionist Instructions for Use and the hospital standard of care.

Device data at predefined time points will be collected from the central Latitude database. Given the well-established clinical field experience with this pacing platform no additional risks are expected if compared to implantation and follow up procedures associated to any commercially available CRT-P device. Residual risks are mitigated by appropriate subject selection according to the criteria of the present CIP and by using SOC procedure and management deserved to subjects indicated for CRT-P.

Based on the literature and on previous experience with pacemakers, Table 18-1 includes an alphabetical list of device-related events associated with implantation of a PG and/or lead system. As the devices in this study are all approved devices no additional device-related events are anticipated.

Table 18-1: Potential Adverse Events and Potential Adverse Device Effects for CRT-Ps

• Air embolism	• Lead fracture
• Allergic reaction	• Lead insulation breakage or abrasion
• Bleeding	• Lead perforation
• Bradycardia	• Lead tip deformation and/or breakage
• Cardiac tamponade	• Local tissue reaction
• Chronic nerve damage	• Loss of capture
• Component failure	• Myocardial infarction (MI)
• Conductor coil fracture	• Myocardial necrosis
• Death	• Myocardial trauma (e.g., tissue damage, valve damage)
• Electrolyte imbalance/dehydration	• Myopotential sensing
• Elevated thresholds	• Oversensing/undersensing
• Erosion	• Pacemaker-mediated tachycardia (PMT)
• Excessive fibrotic tissue growth	• Pericardial rub, effusion
• Extracardiac stimulation (muscle/nerve stimulation)	• Pneumothorax
• Fluid accumulation	• Pulse generator migration
• Foreign body rejection phenomena	• Shunting current during defibrillation with internal or external paddles
• Formation of hematomas or seromas	• Syncope
• Heart block	• Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
• Inability to pace	• Thrombosis/thromboemboli
• Inappropriate pacing	• Valve damage
• Incisional pain	• Vasovagal response
• Incomplete lead connection with pulse generator	• Venous occlusion
• Infection including endocarditis	• Venous trauma (e.g., perforation, dissection, erosion)
• Lead dislodgment	• Worsening heart failure

Subjects may develop psychological intolerance to a pacemaker or CRT-P and may experience the following:

- dependency
- depression
- fear of premature battery depletion
- fear of device malfunction.

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

- allergic reaction to contrast media
- breakage/failure of implant instruments
- prolonged exposure to fluoroscopic radiation
- renal failure from contrast media used to visualize coronary veins.

18.2. Risks Associated with the Study Devices

There are no known incremental risks that are associated with the study device beyond those mentioned in Section 18.1 related to study participation.

Atrial arrhythmia reporting, POST, and snapshot ECG / EGM display were evaluated and no new risks were identified.

18.3. Risks associated with Participation in the Clinical Study

During the first month of study participation, subjects who did not require rate response programming at pre-discharge due to known clinical reasons will not have the benefits of rate adaptive pacing. However, if the study doctor feels this programming causes significant limitations for the subject, sensor optimization may be done 15 days after implant or earlier.

There are no other known specific additional risks to the subject over and above the risks mentioned in the Section 18.1.

18.4. Possible Interactions with Concomitant Medical Treatments

The implanted leads contain steroid for the purpose of helping to reduce tissue inflammation response at the distal electrode. There are no data that show there are any drug interactions with this local steroid, or with any other portion of the implanted system.

18.5. Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this CIP, 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 CIP.

18.6. Anticipated Benefits

Subjects will be implanted with the Ingenio 2 CRT-P, which incorporates the following new features:

1) MICS telemetry band used for Radio Frequency (RF) telemetry communication (wireless at any time) with the PRM which may support faster implant and follow up procedures.
2) LV Quadripolar devices, providing 17 pacing/sensing configurations for devices compatible with IS-4 LV leads to optimize CRT and avoid invasive procedures due to phrenic nerve stimulation or inability to deliver CRT
3) PaceSafe™ LVAT for bipolar leads, allowing automatic LV threshold testing for optimized energy consumption and effective CRT.
4) enhanced hardware including new battery chemistry, filtered feedthru, IS1 coil spring design, front liner, and lead port identifiers for optimized longevity and handling
5) enhanced diagnostic functions including POST, which provides an automatic device / lead check at a pre-determined time post-implant to help document proper system functionality without requiring manual system testing, Atrial Arrhythmia Reports, and Snapshot, which provides the ability to store traces of the ECG / EGM display for optimized therapy and procedures
6) All study subjects will receive a Visionist device which has an MV sensor which allows rate adaptive pacing based on MV.
7) The sensor optimization (required by the CIP) may lead to better therapy outcome or reduced mortality (HRS 2014).
8) All subjects in the study are planned to receive a Latitude system for remote subject follow up associated to a complex alert system which may lead to optimized subject care and was shown to be associated to reduced mortality (Altitude data)

In addition, the study specifies a detailed evaluation of chronothropic incompetence of the subject, to be followed by sensor optimization. This sensor optimization in HF subjects could be associated with better HF treatment outcome.

18.7. Risk to Benefit Rationale

Subjects enrolled in the Rally CRT-P study will not be exposed to any additional testing, visits or risks as compared to subjects who are routinely implanted with any clinically approved PG system and not enrolled in this study. Standard device interrogation and testing that will be performed in the present study are part of SOC procedures specified in the Visionist Instructions for Use and the hospital SOC that occurs for each subject implanted with a PG who are followed-up under standard clinical practice.

The 6 minute walking test will be used to identify chronotropic incompetent subjects as well as optimization of the MV sensor, and is routinely used for HF patients as well as for sensor

optimization. The study requires connecting all devices with the remote monitoring system Latitude which allows closer follow up by the Investigator due to automatic alerts, diagnostic data collected by the device and system performance. The sensor optimization and use of the Latitude system specified in this CIP are widely underutilized although often associated with clinical patient benefits.

Even if electronic devices such as PG are subject to random component failures that cannot be predicted, those risks are not affected by this CIP and would be equally applicable to all subjects implanted with a market released PG system. Risks can be minimized through adherence to the guidelines for subject selection, close monitoring of the subject's physiologic status during visits and by promptly supplying BSC with all pertinent information required by this CIP.

19. Safety Reporting

19.1. Definitions and Classification

Definitions are provided in Table 19-1. Administrative edits were made to combine definitions from ISO 14155-2011 and medical device guidance (MEDDEV) 2.7/3 12/2010.

The only events that are to be reported as part of this study are any device associated events (ADEs, SADEs, USADEs, and DDs; ISO-14155) and SAEs (MEDDEV). Events such as flue, nose infection, etc. will not be reported; "AEs" as defined in Table 19-1 will not be reported.

Table 19-1: Adverse Event Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the CIP). NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Table 19-1: Adverse Event Definitions

Term	Definition
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Abbreviations: ASADE=Anticipated Serious Adverse Device Effect; CIP=Clinical Investigation Plan; EC=Ethics Committee; SAE=Serious Adverse Event; SADE=Serious Adverse Device Effect; USADE=Unanticipated Serious Adverse Device Effect,

*Per 21 Code of Federal Regulations 803.3(bb):

1) Serious injury means an injury or illness that:
    i) Is life-threatening;
    ii) Results in permanent impairment of a body function or permanent damage to body structure; or

iii) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

2) Permanent means, for purposes of this subpart, irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

**Invasive interventions are those in which treatment necessary to correct the AE is delivered by cutting or piercing of the skin or placing an instrument in a body cavity to provide therapy. Examples of invasive interventions (complication) include:

- Surgical revision of a lead
- Electrophysiology study in which an ablation is performed
- Angiogram in which angioplasty or stent placement is performed
- Intravenous medications
- Blood transfusions
- Intubation to provide respiratory support
- Chemical (pharmacologic) cardioversion with IV sedation (considered a complication due to the IV antiarrhythmic medication used for the cardioversion)

***Permanent loss of device function is where a malfunction occurs in a manner which results in compromised therapy:

- **Malfunction**: failure of a device to meet its performance specifications, to perform its essential function, or otherwise perform as intended. “Performance specifications” include claims made in the labeling of the device. (i.e., device is not functioning within labeling)

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should be recorded as an SAE, and should include a detailed description of circumstances and expected cause.

Any event (USADE, SADE, SAE, ADE, DD) experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

Refer to the BSC Physician’s Lead Manual for the known risks associated with the study devices.

All device-related adverse events will be evaluated at least monthly during the trial and might be extracted from the Rally CRT-P database in order to pool those data with other available data sets (e.g. trials). Pooling of those datasets on product performance on a broader sample size will be done especially to support safety aspects of all medical devices in this trial.

19.2. Safety Trigger

Device malfunctions or unintended device behavior, that are either unanticipated or occurring in a higher rate than anticipated, and have or could result in serious injury, will be considered towards the trial safety review.

For rate calculations the small size of this trial precludes this being the sole source of events. The event rate will be determined from the denominator of the entire sold (implanted) device base with a numerator of all similar events in the entire post market experience reported.

As a comparison for all calculated event rates in the trial the calculated event rate from regular vigilance reporting will be used. This constantly updated event rate is provided to the notifying body or authorities, and can be used as reference.

19.3. Relationship to Study Devices

The Investigator must assess the relationship of the AE to the study device as related or unrelated (Table 19-2).

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

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

19.4. Investigator Reporting Requirements

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

Table 19-3: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Serious Adverse Event including: • Unexpected Serious Adverse Device Effects • Serious Adverse Device Effects • Adverse Device Effects • Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if: a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Event Reporting eCRF page with all available new and updated information. Provide all relevant source documentation (unidentified) for reported event.	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 when documentation is available

Abbreviations: eCRF=electronic Case Report Form

19.5. Boston Scientific Device Deficiencies

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

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are to be reported in the eCRF but are not to be classified as AEs. However, an *AE that results from a device failure or malfunction* would be recorded on the appropriate AE eCRF page.

Any Investigational DD that might have led to a SAE 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.

Device deficiencies are to be reported from the study center to BSC or the study database within 24 hours of Investigator awareness. Device deficiencies will be evaluated at least monthly during the trial and might be extracted from the Rally CRT-P database in order to pool those data with other available data sets (e.g. trials). Pooling of datasets on product performance on a broader sample size will be done especially to support safety aspects of all medical devices in this trial.

19.6. Reporting to Regulatory Authorities / ECs / Investigators

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

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

19.7. Subject Death Reporting

A subject death during the study should be reported to BSC within 1 business day of center notification. Data entry into EDC shall suffice to fulfill notification requirement. The center's EC must be notified of any deaths in accordance with that center's EC policies and procedures.

Other required information for death events include a detailed narrative (death letter) that provides information describing the circumstances surrounding the death, signed by the principal Investigator or authorized co-Investigator. A death narrative in the local language is acceptable.

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 pacemaker, lead/catheter, clinical investigation, procedure, or subject condition
- whether or not the death was witnessed
- device status and/or activity at the time of death
- whether the subject had worsening heart failure
- any other circumstances surrounding the death
- approximate time interval from the initiating event to death (temporal course)
- Investigator or co-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., report of medical history and physical examination, 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 BSC)
  - death certificate (if available).

Death narratives and supporting documents should be submitted to the BSC Safety department.

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that informed consent is obtained prior to any data collection.

The obtaining and documentation of informed consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local EC and/or Regulatory authority body, as applicable. The ICF must be approved by the center's EC.

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

The process of obtaining Informed Consent shall:

- 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 and by the Investigator 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 center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements. Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject 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 CIP, a change in Principal Investigator, administrative changes, or following annual review by the EC. The new version of the ICF must be approved by the EC. BSC approval is required if changes to the revised ICF are requested by the center's EC. The EC will determine the subject population to be re-consented.

Study personnel should explain that even if a subject agrees to participate in the study and signs an Informed Consent form, the Index Procedure may demonstrate that the subject is not a suitable candidate for the study. The ICF will note that the transmission of confidential subject data, such as copies of source documents, will be required and that by signing the consent, the subject gives permission for his/her confidential subject data to be transmitted to the sponsor.

21. Committees

21.1. Safety Monitoring Process

To promote early detection of safety issues, and consistent coding across projects an internal BSC Event Review Team (Technical Services, Clinical CRM, Medical Safety, and assigned persons from ICON plc.) will provide at least monthly review and an overview of all events reported in the study database.

Specific tasks will include:

- Safety Event Reconciliation (event coding) by BSC.
- In addition to the event review and coding by the study team, every event reported in the EDC system will generate an automated e-mail to the following departments within BSC:
    - Event Analysis, Medical Safety, Technical Services and Regulatory personnel

- These immediate notifications are sent for Vigilance reporting purposes for trial independent follow up. Every review will be entered into the BSC Systems for Event Analysis and Technical services.
- Technical Services will have access to all subjects in the Rally CRT-P database to obtain immediate additional information after e-mail notification.

Procedures for Event Coding

- Event Coding will be handled by the Boston Coding Team represented by Clinical Safety, BSC-Project Management, ICON-Project Management and Technical Services.
- During Event review a four digit classification code will be used to classify each reported event.
- The classification codes will be entered into the EDC module for AE coding for each event. The role of 'Boston Coding Investigator' has been created within the Coding Team. The Coding Investigator will enter the Classification Code Number and Team AE review date for all reported events. Team members assigned to this role will have "read only" access to the rest of the eCRF.

Review and coding will be done to support device hazard analysis and monitoring of event rates. This process requires dynamic collection (as soon as the event is reported) of unmonitored data.

During scheduled monitoring visits, clinical research monitors and locally responsible FCS will support the dynamic reporting process through their review of source document information.

21.2. Technical Review Committee

Technical Review will be performed by BSC's Technical Service department to evaluate any technical issues (device-related AEs and DDs) with the device experienced during the trial. All device-related reporting will be reviewed independently from event analysis.

22. Suspension or Termination

22.1. Premature Termination of the Study

BSC reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of

subjects. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

22.2. Criteria for Premature Termination of the Study

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

- the occurrence of USADEs or unusual trends of SAE or SADEs 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 BSC to suspend or discontinue development of the device.

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

Any Investigator or EC in the Rally-CRT-P Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to BSC. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

22.4. 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 centers by BSC. The EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an EC terminates participation in the study, participating Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by BSC. In the event an Investigator terminates participation in the study, study responsibility will be transferred to a Co-Investigator, if possible. In the event there are no opportunities to transfer Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

The Investigator must return all documents to BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.5. Criteria for Suspending/Terminating a Study Center

BSC reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after center initiation, or if the center has multiple or severe CIP violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of Investigator participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and regulatory authorities, as applicable,

should be notified. All subjects enrolled in the study at the center will continue to be followed according to standard clinical practice of the center. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

23. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. BSC 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 Investigators and/or Scientific 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.

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25. Abbreviations and Definitions

25.1. Abbreviations

Abbreviations are shown in Table 25-1.

Table 25-1: Abbreviations

Acronym/Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
APMHR	Age Predicted Maximal Heart Rate
ASADE	Anticipated serious adverse device effect
AV	Atrioventricular
BSC	Boston Scientific
CHF	Congestive Heart Failure
CI	Confidence interval
CIP	Clinical Investigation Plan
CRF	Case Report Form

Acronym/Abbreviation	Term
CRT	Cardiac Resynchronization Therapy
CRT-D	CRT Defibrillator
CRT-P	CRT Pacemaker
CRO	Contract Research Organization
CRM	Cardiac Rhythm Management (a business division of Boston Scientific)
DD	Device deficiency
DRC(FR)	Device-related complication (free rate)
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGM	Electrogram (from device)
GCP	Good Clinical Practice
HF	Heart Failure
HCP	Health Care Professional
HRS	Hearth Rhythm Society
ICD	Implantable Cardioverter-Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
ISO	International Standard Organization
LBBB	Left bundle branch block
LV	Left ventricle/ ventricular
LVAT	Left ventricular automatic threshold
LVS	Left ventricular sensed event
MEDDEV	Medical Device Guidance
MICS	Medical Implant Communication Service
MV	Minute ventilation
PG	Pulse generator
PMCF	Post Market Clinical Follow-up
PRM	Programmer
PSA	Pacing System Analyzer
RA	Right atrial/atrium
RALLY CRT-P	Optimizing pacing therapy by using multi-programmable pulse generators for cardiac resynchronization pacing (CRT-P)
RBBB	Right bundle branch block
RF	Radio Frequency
RRP	Rate Response Pacemaker
RV	Right ventricle/ ventricular
RVS	Right ventricular sensed event
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard deviation
S-ICD	Subcutaneous Implantable Cardioverter-Defibrillator
SOC	Standard of Care
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
XL	Accelerometer

25.2. Definitions

Terms are defined in there are no direct benefits to subjects with participation to this PMCF study.

Table 25-2: Definitions

Term	Definition
Attempt	Refers to a subject who 1) has been enrolled in the CRT-P Study, 2) has had anesthesia administered in preparation for the surgical implant procedure, 3) has had the Visionist CRT-P device introduced, but 4) is not successfully implanted with the Visionist CRT-P. Attempt subjects must be followed 30 ± 7 days post-attempted implant to assure there are no associated adverse events, or to assure the resolution of any adverse events associated with the attempted implant.
Cardiac Perforation	Penetration of the lead tip through the myocardium to the pericardium or beyond (including micro-perforation), either clinically suspected by chest x-ray, fluoroscopy or, intra-cardiac electrogram and/or confirmed by echocardiogram, CT or visually at operation.
Cardiac Tamponade	Also known as pericardial tamponade is an acute type of pericardial effusion in which hemodynamic compromise results and urgent intervention is required. This will be considered a serious adverse device event (SADE).
Complication	An adverse event that resulted in: death, serious injury, a correction using invasive intervention, or permanent loss of device functions.
Conductor Fracture/Lead Fracture	A mechanical break/ disruption within the lead conductor (includes connectors, coils and/or electrodes) observed visually, electrically or radiographically.
Device-related Complication	A complication (an AE that resulted in death, serious injury, a correction using invasive intervention, or permanent loss of device functions) assessed as related to the device.
Elevated Pacing Thresholds	At implant, pacing thresholds for the permanently programmed electrode that are greater than 3.0 volts and at follow-up pacing thresholds for the permanently programmed electrode that are either: (1) An observed increase of 2-fold over the first chronic threshold; or (2) An observed threshold greater than 3.5 volts. Please note that these elevations in pacing threshold values may be physiologic, pathologic or device-related.
Extracardiac Stimulation (e.g., phrenic, diaphragm)	Clinical observation of inadvertent muscle/nerve stimulation other than cardiac muscle.
Hematoma	If a hematoma requires invasive intervention to evacuate the hematoma, it will be considered a serious adverse event.
High Pacing Impedance	Pacing impedance is considered abnormal based on lead model and measurement range of the device.

Table 25-2: Definitions

Term	Definition
High Shock Impedance	Shock impedance is considered abnormal based on lead model and measurement range of the device.
High Shock Impedance when attempting to deliver a shock	High shock impedance is considered abnormal based on lead model and measurement range of the device when attempting to deliver a shock.
Inappropriate shock due to over-sensing	Shock delivered due to over-sensing resulting from either physiologic or non-physiologic causes.
Inappropriate shock	Shock delivered by the device which is not appropriate therapy/treatment per the device programming.
Infection	If oral antibiotics are prescribed for treatment of an infection, it will be considered as an adverse event. If intravenous (IV) antibiotics are required for treatment of the infection, then it will be considered a serious adverse event. Any confirmed pocket sepsis or lead endocarditis requiring device system (generator and lead) extraction will be considered a serious adverse event.
Intent	Refers to a subject who has been enrolled, but does not undergo an implant procedure of a Visionist CRT-P device. The original ICF and screening documentation for intent subjects should be maintained in the center's files. There are no follow-up visit requirements for intent subjects.
Intermittent Sensing	Intermittent loss of sensing or failure to detect intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity settings.
Lead Abrasion	Upon returned product analysis, leads are analyzed for abrasion. Known examples of lead abrasion occur 1) proximal abrasions associated with lead-on-lead or lead-on-PG contact in the pocket; 2) mid-lead insulation damage caused by clavicle flex-fatigue or crush, suture or suture sleeve, insulation wear in the area of vein insertion and 3) distal region wear due to lead-on-lead (intracardiac), lead-on-heart valve or lead-on-another anatomy contact.
Lead Insulation Breach	A disruption or break in lead insulation observed visually, electrically or radiographically.
Lead Migration/Dislodgment	Radiographic and electrical evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing and/or lead performance. [redacted] dislodgement is not included.
Lead Revision / Reposition	An invasive procedure that involves manipulation of the lead(s) to modify the anatomical implanted location of the intra-thoracic portion of the lead.
Loss-of-Capture	Intermittent or complete failure to stimulate cardiac stimulation (atrial or ventricular) at programmed output delivered outside of the cardiac refractory period.

Table 25-2: Definitions

Term	Definition
Low Pacing Impedance	Pacing impedance is considered abnormal based on lead model and measurement range of the device.
Low Shock Impedance	Shock impedance is considered abnormal based on lead model and measurement range of the device.
Low shock impedance when attempting to deliver a shock	Low shock impedance is considered abnormal based on lead model and measurement range of the device) when attempting to deliver a shock.
Normal Battery Depletion	For pulse generators , the condition when a) a device is returned with no associated complaint and the device has reached its elective replacement indicator(s) with implant time that meets or exceeds the nominal (50 percentile) predicted longevity at default (labeled) settings, or b) the device is returned and the device has reached it elective replacement indicator(s) with implant time exceeding 75% of the expected longevity using the longevity calculation tool available at the time of product introduction, calculated using the device's actual use conditions and settings.
Other, Lead related	Specific proprietary attributes of a lead, such as sensors which affect a leads ability to perform as designed and remain in service.
Other, Pulse Generator/Header related	Specific proprietary attributes of a pulse generator/header, which affect a device's ability to perform as designed and remain in service.
Oversensing	The occurrence of cardiac or non-cardiac events being misinterpreted as cardiac depolarization, (e.g., T waves, multiple counting, skeletal muscle potentials and extra-cardiac electromagnetic interference (EMI)).
Pacing Impedance Changes	Pacing impedance changes are considered clinically significant if the value changes by more than a 2:1 ratio from the previous value.
Pain	A pain requiring oral medication is not considered serious. Pain requiring IV analgesics or results in prolonged hospitalization will be considered a complication.
Pneumothorax	Is a collection of air in the pleural space, causing the lung to collapse. It will be considered a serious adverse event if invasive intervention is needed for treatment.
Pocket Revision	Assuming that the subject continues to participate in the study, a pocket revision is an invasive procedure that involves modification in some manner to the extra-thoracic device pocket and/or lead(s) therein. There is no repositioning of the lead(s) tip in the heart.

Table 25-2: Definitions

Term	Definition
Possible Malfunction	May be considered if neither of the two listed below occurred. a) **Malfunction with compromised therapy, PG** – The condition when a device is found to have "malfunctioned" in a manner that compromised pacing or defibrillation therapy (including complete loss or partial degradation) while implanted and in service. Therapy is considered to have been compromised if no therapy is available or critical subject protective pacing or defibrillation therapy is not available b) **Malfunction without compromised therapy, PG** - The condition when a device is found to have "malfunctioned" in a manner that did not compromise pacing or defibrillation therapy while implanted and in service. Therapy is not compromised as long as critical patient protective pacing or defibrillation therapies are available. Changes in device setting that occur as intended by design (i.e. Power-on-reset (POR)) that do not result in loss of critical patient protective therapies but are reported as reasons for explant shall be classified as malfunctions without compromised therapy.
Shock Impedance Changes	Shock impedance changes are considered clinically significant if the value changes by more than a 2:1 ratio from the previous value.
Significant r-wave amplitude decrease over 2 weeks or less	A decrease in r-wave value is considered clinically significant if the value changes by more than a 2:1 ratio over the course of two (2) weeks or less.
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 (original records or certified copies).
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.
Suspected Lead Fracture	May be manifested by abnormal device measurements (i.e. RV lead impedance, thresholds, inappropriate shocks) which may be caused as a result of conductor/lead fracture. Investigators are requested to complete a through lead assessment; confirm through visual, radiographic and electrical analysis, and are strongly recommended to return the lead to for analysis.
Suspected Lead Abrasion	May be manifested by abnormal device measurements (i.e. RV lead impedance, thresholds) which may be as a result of unknown lead abrasion type (which are not already defined above). Investigators are requested to complete a through lead assessment; and strongly recommended to return the lead to for analysis.

Table 25-2: Definitions

Term	Definition
Twiddler's Syndrome	A complication of pacemaker treatment, in which repeated torsional pocket forces applied to the generator cause rotation and, by a ratchet mechanism, lead retraction. This may potentially result in lead displacement and loss of device function.
Undersensing	Complete or intermittent loss of sensing or failure to detect the intended intrinsic cardiac signals (atrial or ventricular) during non-refractory periods at programmed sensitivity.

26. Appendices

APPENDIX A: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must

always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimise the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be

sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorised representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
• Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive

placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extrem care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix B. Six-Minute Walk Test

The six-minute walk test is a self-paced sub-maximal exercise test that has proven useful as an outcome measure for patients with congestive heart failure (CHF). Previous studies have shown that this test is well tolerated by individuals and is more closely related to the patient's daily activities than maximal exercise testing.

The walking test should be conducted in an enclosed corridor on a course approximately 100 feet (30.5 meters) long. The length should be marked in either feet or meters to allow easy measurement of the distance walked. The corridor should not be heavily transited and should be free of obstacles and distractions. Chairs should be placed at either end of the course so that patients may rest when needed.

Instructions

The patient is to take nothing by mouth except for clear liquids for at least two hours prior to the test. Prescribed medications should be taken as usual. Patients should be advised not to smoke for at least two hours prior to exercise. Patients should also be advised to wear suitable footwear.

Patients are instructed to walk the marked course from end to end at their own pace, covering as much distance as possible in six minutes. Patients may slow down or stop to rest if necessary, but should be instructed to resume walking when they feel they are able to do so. The aim is that at the end of the test, the patient believes that they could not have walked any further in the six minutes.

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

> "The purpose of this test is to determine how far you can walk in six minutes. You will start here and go to the chair at the end of the hall, turn around, and walk back. After arriving back at the starting point, you will go back and forth again. Go back and forth as many times as you can in the six-minute period. If necessary, stop and rest and stay there until you can start again. However, the most important thing about the test is that you cover as much distance as possible during the six-minute period."
>
> "I will let you know when each minute has passed. When I say 'STOP' after 6 minutes, please stand right where you are."

"Do you have any questions about the test?"

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

"Are you ready?"

"Start when I say 'GO'."

Walking Protocol

The walk test should be performed after completing the physical assessment of the patient. Patient safety is the highest priority, and the walk test should not be initiated if the physician, coordinator or patient have concerns regarding the patient's ability to perform the test. If the patient begins the walk test, and concerns arise regarding their ability to continue, stop the test.

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