ENABLE MRI Clinical Study

Expanding MRI Access for Patients with New and Existing ICDs and CRT-Ds

CLINICAL PROTOCOL

11 August 2016
Version AE

IDE # G150181

Sponsored By

Boston Scientific, CRM
4100 Hamline Avenue North
St. Paul, MN 55112 USA

Guidant Europe SA / NV,
a Boston Scientific Company
Clinical CRV Department
Green Square
Lambroekstraat 5D
1831 Diegem,
Belgium

Contact Information

[redacted]	[redacted]
[redacted]	[redacted]
Coordinating Principal Investigator	**Europe:** Prof. Aldo Rinaldi Cardiac Department 6TH Floor East Wing St Thomas' Hospital Westminster Bridge Rd SE1 7EH London UK
	Asia Pacific: Prof. Hung Fat Tse Room 1928,19/F Block K, Queen Mary Hospital 102 Pokfulam Road 852 Hong Kong
	USA: Dr. Ulrika Birgersdotter-Green The Regents of the University of California (UCSD), San Diego School of Medicine 9444 Medical Center Drive 3rd floor, Room 3-089 D La Jolla, CA 92037 USA

Original Release: 18 June 2015

Current Version: 11 August 2016

Revision History

Revision Number	Release Date	Section	Change	Reason for Change
AA	15 June 2015	N/A	Initial Release	N/A
AB	12 August 2015	All sections	Specification of MRI artifact as an Ancillary assessment. Included all Ancillary Assessments in Section 2. Clarifications and corrections throughout	Clarifications and corrections
AC	23 November 2015	Sections 2, 5, 6, 7, 9, 11, 12, 13, 17, 20, 21 and 27	Update the RA leads available for the US sites. Incorporated "For Cause" VF Induction and VF Induction Sub-Study. Adjusted sample size to accommodate an interim analysis. Administrative changes throughout document	Clarify study design and incorporate VF Induction Sub-Study
AD	17 March 2016	Sections 2, 5, 6, 10, 11, 12, 13, 20 and 21	Addition of RELIANCE 4-FRONT Lead for the U.S. Updating protocol with new MEDDEV requirements. Administrative changes.	Add an additional RV lead choice for the US and adapt to new MEDDEV guidance
AE	11 August 2016	Sections 2, 5, 9, 10, 11, 12, 13, 21 and 28	Updated exclusion criteria 5 & 6 Adding additional warnings for MRI protection mode Updated Phase I and Phase II definitions Updated MRI visit Heart Rhythm Monitoring Updated Medically Necessary MRI requirements Clarified that pre-scan time does not count	Implement additional screening steps at inclusion and the MRI visit to better detect subjects at risk of complete AV Block Updated MEDDEV requirements for AE reporting

			against the required RF and gradient intensive sequences	

Protocol Authors

Name	Title
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2. Protocol Synopsis

<table>
<tr><th colspan="2">ENABLE MRI Study</th></tr>
<tr><td>Objective(s)</td><td>The objective of this study is to collect data to confirm the safety and effectiveness of the ImageReady™ MR Conditional Defibrillation System when used in the 1.5T MRI environment under the labeled Conditions of Use (Phase I).

Additionally, the study will assess medically necessary MR scans according to the labeled Conditions of Use to provide real-world scanning data (Phase I and Phase II).

The study also aims to demonstrate the continued ability of the ImageReady MR Conditional Defibrillation System to sense and detect ventricular fibrillation (VF) post MRI scan by collecting and analyzing data from spontaneous VF episodes, “for-cause” VF inductions, and from an optional VF induction Sub-study.</td></tr>
<tr><td>Test system</td><td>ImageReady MR Conditional Defibrillation System (ImageReady System)</td></tr>
<tr><td>ImageReady MR Conditional Defibrillation System Components</td><td>
Table 2-1: ImageReady MR Conditional Defibrillation System Components
<table>
<tr><th>Device Name</th><th colspan="3">Device Model Number</th></tr>
<tr><th rowspan="2">Pulse Generators</th><th colspan="2">Phase I and II</th><th>Phase II Only *</th></tr>
<tr><th>CRT-D (IS1/DF4/IS4)</th><th>VR ICD (DF4)</th><th>DR ICD (IS1/DF4)</th></tr>
<tr><td>ORIGEN™ MINI ICD</td><td>--</td><td>D000</td><td>D002</td></tr>
<tr><td>ORIGEN EL ICD</td><td>--</td><td>D050</td><td>D052</td></tr>
<tr><td>ORIGEN X4 CRT-D</td><td>G058</td><td>--</td><td>--</td></tr>
<tr><td>INOGEN™ MINI ICD</td><td>--</td><td>D010</td><td>D012</td></tr>
<tr><td>INOGEN EL ICD</td><td>--</td><td>D140</td><td>D142</td></tr>
<tr><td>INOGEN X4 CRT-D</td><td>G148</td><td>--</td><td>--</td></tr>
<tr><td>DYNAGEN™ MINI ICD</td><td>--</td><td>D020</td><td>D022</td></tr>
<tr><td>DYNAGEN EL ICD</td><td>--</td><td>D150</td><td>D152</td></tr>
<tr><td>DYNAGEN X4 CRT-D</td><td>G158</td><td>--</td><td>--</td></tr>
<tr><td>AUTOGEN ™ MINI ICD*</td><td>--</td><td>D044</td><td>D046</td></tr>
<tr><td>AUTOGEN EL ICD*</td><td>--</td><td>D174</td><td>D176</td></tr>
<tr><td>AUTOGEN X4 CRT-D*</td><td>G179</td><td>--</td><td>--</td></tr>
<tr><td colspan="4">Right Atrial Leads and Accessories</td></tr>
<tr><td colspan="2">FINELINE™ II Sterox</td><td colspan="2">4479, 4480</td></tr>
<tr><td colspan="2">FINELINE II Sterox EZ</td><td colspan="2">4469, 4470, 4471, 4472, 4473, 4474</td></tr>
<tr><td colspan="2">Suture Sleeves for FINELINE II Leads</td><td colspan="2">6220, 6221</td></tr>
<tr><td colspan="2">INGEVITY™ MRI*</td><td colspan="2">7735, 7736, 7740, 7741, and 7742</td></tr>
<tr><td colspan="2">Suture Sleeve for INGEVITY MRI*</td><td colspan="2">6402</td></tr>
<tr><td colspan="2">IS-1 Lead Port Plug</td><td colspan="2">7145</td></tr>
<tr><td colspan="4">Right Ventricular Leads and Accessories</td></tr>
</table>
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<table>
<tr><th colspan="2">ENABLE MRI Study</th></tr>
<tr><td></td><td>
<table>
<tr><td>RELIANCE 4-FRONT™ (DF4)**; ‡</td><td>0636, 0654, 0655, 0657, 0658, 0665, 0675, 0676, 0682, 0683, 0685, 0686, 0692, 0693, 0695, and 0696</td></tr>
<tr><td>Suture Sleeve for RELIANCE 4-FRONT leads**; ‡</td><td>6403</td></tr>
<tr><td>ENDOTAK RELIANCE™ (DF4)</td><td>0265, 0266, 0275, 0276, 0282, 0283, 0285, 0286, 0292, 0293, 0295, and 0296</td></tr>
<tr><td colspan="2">Left Ventricular Leads and Accessories</td></tr>
<tr><td>ACUITY™ X4 (IS4)</td><td>4671, 4672, 4674, 4675, 4677, and 4678</td></tr>
<tr><td>Suture Sleeve for ACUITY X4 leads</td><td>4603</td></tr>
<tr><td colspan="2">Non-Implanted Components</td></tr>
<tr><td>ZOOM™ LATITUDE™ PRM</td><td>3120</td></tr>
<tr><td>ZOOM LATITUDE PRM Software Application</td><td>2868 v3.07 or later</td></tr>
</table>
* May only be used internationally outside the US
**The ACUITY X4 pacing lead and RELIANCE 4-FRONT lead may be investigational in the US during a portion or the entire duration of the study
‡ For the US, only existing RELIANCE 4-FRONT implants will be allowed
</td></tr>
<tr><td>Study Design</td><td>A prospective, non-randomized, confirmatory, global study to be conducted as an IDE in the United States, and as a post market study in Europe, Israel and Asia Pacific</td></tr>
<tr><td>Planned Number of Subjects</td><td>500 subjects will be enrolled in the study.</td></tr>
<tr><td>Planned Number of Centers / Countries</td><td>Approximately 70 sites in the United States, Europe, Israel and Asia Pacific</td></tr>
<tr><td>Primary Safety Endpoint-Phase I</td><td>MR scan-related Complication-free rate between the MR Scan and the MRI + 1 Month Visit</td></tr>
<tr><td>Primary Effectiveness Endpoints-Phase I</td><td>• Increase in RV pacing threshold from the pre-MR scan to the 1 Month post-MR scan
• Decrease in RV sensed amplitude from the pre-MR scan to the 1 Month post-MR scan
• Increase in LV pacing threshold from the pre-MR scan to the 1 Month post-MR scan</td></tr>
</table>

ENABLE MRI Study	
	• Decrease in LV sensed amplitude from the pre-MR scan to the 1 Month post-MR scan
Ancillary Assessments	• Assessment of RV and LV impedances • Assessment of RA lead measurements • Assessment on MR scan effect on lead measurements • Assessment of VT/VF episodes post-MR-scan • Assessment of effect of medically necessary MR scans • Assessment of Beeper function • Assessment of programming the MRI Protection Mode • Assessment of Image Artifacts for non-medically necessary MR scans. • Collect real-world information from medically necessary MR scan(s)
Follow-up Schedule	Study procedures or clinic visits will occur at the following time periods: For patients with de novo implants, • Screening and Enrollment Visit (≤ 30 days prior to implant procedure) • Implant Procedure • Pre-Discharge Clinic Visit (3 – 72 hours post-implant) • MRI Visit (6-9 weeks post-implant) (Phase I only) • MRI + 1 Month Visit (30 ± 7 days post-MRI Visit) (Phase I only) • Every Three-month follow-ups post MR scan (recommended) • Annual device follow-ups (for 3 years): Every 12 months ± 3 months For patients with existing implants, • Screening and Enrollment Visit • MRI Visit (within 6 weeks from enrollment) (Phase I only) • MRI + 1 Month Visit (30 ± 7 days post-MRI Visit) (Phase I only) • Every Three-month follow-ups post MR scan (recommended) • Annual device follow-ups (for 3 years): Every 12 months ± 3 months
Study Duration	The study is expected to start in 2015, and last approximately 5.5 years.

Key Inclusion Criteria

1. **Phase I:** Subject is indicated per guidelines and will receive a CRT-D or ICD system consisting only of the following MR Conditional components* OR Subject is implanted with a functional and stable CRT-D or ICD system consisting only of the following MR Conditional components*

   Phase II: Subject is implanted with a functional and stable CRT-D or ICD system consisting only of the following MR Conditional components*

*** MR Conditional Components**
(refer to Table 2-1 for component model numbers):

Lead/PG	International (All Market Approved)		US	
RA Lead	INGEVITY MRI		FINELINE II Sterox/Sterox EZ	
	FINELINE II Sterox/Sterox EZ			
RV Lead	RELIANCE 4-FRONT		RELIANCE 4-FRONT[1, ‡]	
	ENDOTAK RELIANCE		ENDOTAK RELIANCE	
LV Lead	ACUITY X4		ACUITY X4 [1]	
Phase I: PG • VR ICD • CRT-D[2]	**PG Header**	**Device Name**	**PG Header**	**Device Name**
	VR ICD (DF4), CRT-D[2] (IS1/DF4/IS4)	ORIGEN INOGEN DYNAGEN AUTOGEN	VR ICD (DF4), CRT-D[2] (IS1/DF4/IS4)	ORIGEN INOGEN DYNAGEN
Phase II: PG	**PG Header**	**Device Name**	**PG Header**	**Device Name**
	VR ICD (DF4), DR ICD[2] (IS1/DF4), CRT-D[2] (IS1/DF4/IS4)	ORIGEN INOGEN DYNAGEN AUTOGEN	VR ICD (DF4), CRT-D[2] (IS1/DF4/IS4)	ORIGEN INOGEN DYNAGEN

[1] The ACUITY X4 pacing lead and RELIANCE 4-FRONT lead may be investigational in the US during a portion or the entire duration of the study

[‡] For the US, only existing RELIANCE 4-FRONT implants will be allowed

[2] Port plug 7145 must be used in DR ICDs and CRT-Ds with no atrial lead

2. Subject will receive or is implanted with an ICD or CRT-D pulse generator in the left or right pectoral region
3. Subject is able and willing to undergo an MR scan without intravenous sedation (Phase I only)
4. Subject is willing and capable of providing informed consent and participating in all testing/ visits associated with this clinical study at an approved clinical study center and at the intervals defined by this protocol
5. Subject is age 18 or above, or of legal age to give informed consent specific to state and national law

Key Exclusion Criteria

1. Subject implanted with an ICD or CRT-D pulse generator with battery at Explant status

	2. Subject has other active or abandoned implanted cardiac rhythm devices, components or accessories present such as pulse generators, leads, lead adaptors or extenders 3. Presence of metallic objects that represent a contraindication to MR imaging at the discretion of the Radiologist and impacting the ability to conduct the study protocol 4. Subject needs or will need a medically necessary MR scan, before completing the 1-month post-MR follow-up visit (Phase I only) 5. Subject with: • A history of syncope related to brady-arrhythmia • A history of syncope of unknown etiology • Sinus pauses (Pause > 2 s) • Permanent or intermittent complete AV block • Documentation of progressive AV nodal block over time • Trifascicular block (alternating bundle branch block or PR > 200 ms with LBBB or other bifascicular block) *Note: It is required to run a 12 lead ECG and a 10s rhythm strip to document this exclusion criterion. During ECG acquisition, subjects must be in either their own intrinsic rhythm or, in subjects with an existing device implant, the device must be programmed to VVI 40 ppm.* 6. Subject is not clinically capable of tolerating the absence of pacing or Resynchronization therapy support in a supine position for the duration that the pulse generator is in MRI Protection Mode, per Physician discretion 7. Subject is not clinically capable of tolerating the absence of Tachycardia therapy support for the duration that the pulse generator is in MRI Protection Mode, per Physician discretion 8. Subjects with a planned RA, RV or LV lead revision or extraction within 30 days of enrollment (Phase I only) 9. Subjects with an implanted lead that is planned to be extracted during the study implant procedure 10. Subjects currently requiring dialysis 11. Subject has a mechanical heart valve 12. Subject has a known or suspected sensitivity to dexamethasone acetate (DXA) 13. Subject is currently on the active heart transplant list 14. Subject has documented life expectancy of less than 12 months 15. Subject is enrolled in a concurrent study, with the exception of local mandatory governmental registries and observational studies/registries, without the written approval from Boston Scientific

	16. Women of childbearing potential who are or might be pregnant, and will receive an ICD or CRT-D pulse generator
VF Induction Sub-study Exclusion Criteria	In addition to meeting all of the inclusion criteria and none of the exclusion criteria of the ENABLE MRI study, subjects enrolled in the VF Induction Sub-study must also not meet any of the following VF Induction Sub-study exclusion criteria: 1. Unstable heart failure requiring hospitalization in the last 30 calendar days 2. Unable to tolerate sedation (e.g. IV sedation, general anesthesia) 3. Planned cardiac revascularization procedure 4. Right Ventricular Lead R wave is less than 5 mV

Statistical Methods

Hypotheses testing in the ENABLE MRI Study will use standard statistical methodology.

	Endpoint	Assessment	Expected Value	Performance Goal	Test	Alpha Level	Power Level	Number of Subjects	Assumed Attrition	Number of Subjects with Assumed Attrition
Safety	Primary	MR Scan-Related ImageReady System Complication-Free Rate			Kaplan-Meier					
Effectiveness	Primary RV 1	Pacing Threshold - increase in pacing thresholds ≤ 0.5V (at 0.5 ms)			One-sided Exact Test for a Single Binomial Proportion					
	Primary RV 2	Sensed Amplitude –remains ≥ 5.0 mV and above 50% of the value at the MR Follow-up Visit			One-sided Exact Test for a Single Binomial Proportion					
	Primary LV 1	Pacing Threshold - increase in pacing thresholds ≤ 1V between MR Follow-up and Post-MR Follow-up Visits			One-sided Exact Test for a Single Binomial Proportion					
	Primary LV 2	Sensed Amplitude –remains ≥ 5.0 mV and above 50% of the value at the MR Follow-up Visit			One-sided Exact Test for a Single Binomial Proportion					

Abbreviations: **RV**: Right Ventricle; **LV**: Left Ventricle

3. Table of Contents

3.1 Table of Figures

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4. Introduction

Magnetic resonance imaging (MRI) is a diagnostic technique that images body parts by producing a static magnetic field followed by rapidly changing radiofrequency fields to excite hydrogen nuclei. MRI scanning is now the imaging modality of choice for many neurological and musculoskeletal conditions. In the past, implanted cardiac devices including pacemakers and implanted cardioverter-defibrillators have been contraindicated in MRI scanners [1,2]. Recent studies, though, have suggested that select patients may be safely scanned [3,4]. Medical societies in both Europe and the United States have acknowledged these findings with publication of expert opinion and guidelines on scanning patients with implanted cardiac devices[5,6].

A number of studies have reported on the relative safety of scanning patients with cardiac pacemakers or implantable cardioverter-defibrillators. Martin, et al. reported on 54 patients undergoing 62 scans. In their series, 9.4% of patients had significant pacing threshold changes, of which 1.9% required device reprogramming[3]. Nazarian, et al.[7] evaluated 55 patients undergoing 68 scans without any adverse events. In a series reported by Sommer, et al. [4], 82 patients underwent 115 scans. An increase in pacing thresholds was seen in 3.1% of leads. In a larger series, 103 patients underwent a total of 127 scans without any significant change in pacing thresholds immediately post-scan, though small changes in sensed amplitude and pacing impedances were seen[8]. In that series, no restriction was placed on landmark or on maximum SAR. When high-SAR scans (SAR greater than 2 W/kg) were evaluated separately, no significant change in pacing capture thresholds were seen, though immediately post-scan lead impedances and sensed amplitudes were lower.

More recently, preliminary results from the first 829 cases (617 pacemakers, 212 ICDs, 1620 leads) of a large, prospective, Investigational Device Exemption (IDE) study showed no deaths, device failures, generator/lead replacements, ventricular arrhythmias, or losses of capture during non-thoracic MRI at 1.5T for routine clinical care[9]. Nazarian et al [10], in a prospective non randomized trial involving 555 MRI scans from 488 patients, showed that MRI was performed safely. There was no immediate or long-term change in device variables that required system revision or reprogramming. Small changes in acute lead sensing, impedances, and capture thresholds after MRI were reported and attributed to heating at the lead–tissue interface[10].

Boston Scientific (BSC) intends to provide MR Conditional labeling to certain models of existing Implantable Cardiac Defibrillator (ICD) and Cardiac Resynchronization Therapy – Defibrillator (CRT-D) implantable pulse generators (PGs) and associated implantable leads. This combination of PGs and leads will be referred to as the ImageReady™ MR Conditional Defibrillation System (ImageReady System). The ImageReady System will have CE mark at the start of the ENABLE MRI study and commercially available in geographies that accept CE mark. The ENABLE MRI study will be used to support regulatory approval of the ImageReady System in additional geographies.

5. Device Description

The ImageReady MR Conditional Defibrillation System included in the ENABLE MRI Clinical Study, here to forward referred to as the ImageReady System, consists of:

- Certain models from the Next Generation (NG3) ICD and CRT-D family of PGs (Section 5.1 and Table 5-1)
- FINELINE II Sterox/Sterox EZ or INGEVITY MRI pace/sense lead families for the Right Atrial (RA) lead (Section 5.2 and Table 5-1)
- RELIANCE 4-FRONT™ or ENDOTAK RELIANCE DF4 defibrillation lead families for the Right Ventricle (RV) lead (Section 5.3 and Table 5-1)
- ACUITY X4 IS4 heart failure lead family for the Left Ventricle (LV) lead (Section 5.4 and Table 5-1)

The ImageReady MR Conditional Defibrillation System models will be labeled as "MR Conditional" as defined by the American Society for Testing and Materials (ASTM)[1], when used as a system and in accordance with the labeled MRI Conditions of Use.

Table 5-1: ImageReady MR Conditional Defibrillation System Components

Device Name	**Device Model Number**		
Pulse Generators	**Phase I and II**		***Phase II Only ****
	CRT-D (IS1/DF4/IS4)	**VR ICD (DF4)**	***DR ICD (IS1/DF4)***
ORIGEN™ MINI ICD	--	D000	*D002*
ORIGEN EL ICD	--	D050	*D052*
ORIGEN X4 CRT-D	G058	--	--
INOGEN™ MINI ICD	--	D010	*D012*
INOGEN EL ICD	--	D140	*D142*
INOGEN X4 CRT-D	G148	--	--
DYNAGEN™ MINI ICD	--	D020	*D022*
DYNAGEN EL ICD	--	D150	*D152*
DYNAGEN X4 CRT-D	G158	--	--
*AUTOGEN ™ MINI ICD**	--	*D044*	*D046*
*AUTOGEN EL ICD**	--	*D174*	*D176*
*AUTOGEN X4 CRT-D**	*G179*	--	--
Right Atrial Leads and Accessories			
FINELINE™ II Sterox	4479, 4480		
FINELINE II Sterox EZ	4469, 4470, 4471, 4472, 4473, 4474		
Suture Sleeves for FINELINE II Leads	6220, 6221		
*INGEVITY™ MRI**	*7735, 7736, 7740, 7741, and 7742*		
*Suture Sleeve for INGEVITY MRI**	*6402*		

[1] ASTM Standard F2503-08, "Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment" ASTM International, West Conshohocken, PA, 2008, DOI**:** 10.1520/F2503-08, www.astm.org.

Device Name	Device Model Number
IS-1 Lead Port Plug	7145

Right Ventricular Leads and Accessories	
RELIANCE 4-FRONT™ (DF4) **, ‡	0636, 0654, 0655, 0657, 0658, 0665, 0675, 0676, 0682, 0683, 0685, 0686, 0692, 0693, 0695, and 0696
Suture Sleeve for RELIANCE 4-FRONT leads**, ‡	6403
ENDOTAK RELIANCE™ (DF4)	0265, 0266, 0275, 0276, 0282, 0283, 0285, 0286, 0292, 0293, 0295, and 0296
Left Ventricular Leads and Accessories	
ACUITY™ X4 (IS4) **	4671, 4672, 4674, 4675, 4677, and 4678
Suture Sleeve for ACUITY X4 leads**	4603
Non-Implanted Components	
ZOOM™ LATITUDE™ PRM	3120
ZOOM LATITUDE PRM Software Application	2868 v3.07 or later

* May only be used internationally outside the US

**The ACUITY X4 pacing lead and RELIANCE 4-FRONT lead may be investigational in the US during a portion or the entire duration of the study

‡ For the US, only existing RELIANCE 4-FRONT implants will be allowed

5.1 Boston Scientific's ICD and CRT family of PGs

Boston Scientific's MR Conditional defibrillators are comprised of select models of the AUTOGEN, DYNAGEN, INOGEN, and ORIGEN ICD and CRT-D devices. Only single chamber (VR) and dual chamber (DR) ICD devices with a DF4 right ventricular port and CRT-D devices with IS-1/DF4/IS4 port are MR Conditional. The BSC ICD and CRT-D models used in the study are approved for commercial use, with the exception of the AUTOGEN PGs which are not commercially approved in the US at the start of the study. In the US, the AUTOGEN PGs may become approved during the study; however the devices still cannot be used in the ENABLE MRI study in the US.

The PG hardware was not changed. The PG firmware (FW) and Programmer Software Application (SW) was updated to provide MRI Protection Mode to these models. Refer to the ICD and CRT-D Reference Guide for additional information about the PGs.

5.1.1 MRI Protection Mode

MRI Protection Mode is accessible through the 3120 programmer/recorder/monitor (PRM) that has the 2868 software application (see Section 5.5). Prior to the patient undergoing an MRI scan, the PG must be programmed to the MRI Protection Mode using the PRM.

Adherence to the MRI Conditions of Use must be verified prior to each scan to assess the patient's eligibility and readiness for an MR scan (see Section 6).

At the start of the study, in international geographies, the 'MRI Protection Mode' will have CE mark and be available for commercial use.

In the US, a programmer key (dongle) is required to interrogate the VR ICDs and CRT-Ds to access the investigational 'MRI Protection Mode'.

NOTE: MRI Protection Mode may become approved in the US during the study. If this occurs, then the dongle will no longer be needed to access MRI Protection Mode.

In the MRI Protection Mode, the following features and functions are suspended:

- Bradycardia sensing/pacing
- Cardiac Resynchronization Therapy
- Tachycardia detection and therapy
- PaceSafe™** automatic threshold(s)
- Daily diagnostics (Lead Impedance, Intrinsic Amplitude, Pace Threshold)
- Motion and respiratory sensors
- Magnet detection
- RF telemetry
- Battery voltage monitoring
- Beeper is disabled

** Only available internationally outside the US

NOTE: In MRI Protection Mode there is no pacing and no antitachycardia therapy available.

During MRI Protection Mode, the patient will not receive pacing until the PG is returned back to normal operation. Additionally, the system will not detect ventricular arrhythmias and the patient will not receive anti-tachycardia pacing (ATP) or shock defibrillation therapy until the pulse generator is programmed back to normal operation.

Refer to the *BSC ImageReady MR Conditional Defibrillation System MRI Technical Guide*[2], here to forward referred to as the *BSC MRI Technical Guide*, for additional information regarding MRI Protection Mode.

5.1.1.1 Beeper Feature

[redacted]

[2] The *BSC MRI Technical Guide* is investigational in the US, at the start of the study. This may become approved in the US during the study.

5.1.1.2 MRI Protection Mode Time-out Function

The MRI Protection Mode Time-out function allows the user to choose the length of time the PG remains in the MRI Protection Mode before returning to previous settings. MRI Protection Mode is programmed using the PRM. The Time-out feature has programmable values of OFF, 3, 6, 9 and 12 hours. At the conclusion of the programmed duration the PG returns to the previously programmed therapy parameters and settings. MRI Protection Mode may also be exited manually at any time during the time-out period. If the MRI Protection Time-out value is programmed to OFF, the patient will not receive Bradycardia pacing, Cardiac Resynchronization Therapy, or Tachycardia therapy until the PG is programmed out of MRI Protection Mode and back to previous operation.

Refer to the *BSC MRI Technical Guide* for additional information on the MRI Protection Mode Time-out Function.

5.2 Boston Scientific's Right Atrial Leads and Accessories

The FINELINE II Sterox/Sterox EZ (referred to as FINELINE II) and INGEVITY MRI leads are steroid-eluting, bipolar endocardial pacing leads designed for atrial or ventricular use for chronic pacing, and are compatible with PGs that accept IS-1[3] connectors. The FINELINE II and INGEVITY MRI lead families consist of passive fixation and active fixation leads. A radiopaque suture sleeve is pre-loaded on the INGEVITY MRI leads, and is also available in a slit form as an accessory (Table 5-1). Suture sleeves for FINELINE II leads are also

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

available as accessories (Table 5-1). In the ENABLE MRI study, the FINELINE II and INGEVITY MRI leads will be used in the right atrium. Refer to the Physician's Lead Manuals for additional information about the leads.

Boston Scientific's Right Atrial lead and accessory models that are included in the ImageReady System and allowed for the study are listed in Table 5-1.

The FINELINE II leads are approved for commercial use and may be used as part of the ImageReady System in the ENABLE MRI study at all study centers in Europe, Israel , Asia Pacific and the US.

The INGEVITY MRI leads have CE mark and may be used in the ENABLE MRI study at centers in Europe, Israel and Asia Pacific. The INGEVITY MRI leads will not be used in the US.

5.3 Boston Scientific's Right Ventricular Leads and Accessories

The RELIANCE 4-FRONT (DF4) and ENDOTAK RELIANCE (DF4) leads are steroid-eluting, ventricular endocardial cardioversion/defibrillation and pace/sense leads with an ISO standard DF4[4] terminal connector design. Passive and active fixation models are available in both lead families. Refer to the Physician Lead Manuals for additional information about the leads.

Boston Scientific's Right Ventricular lead and accessory models that are included in the ImageReady System and allowed for the study are listed in Table 5-1.

Internationally, the RELIANCE 4-FRONT (DF4) and ENDOTAK RELIANCE (DF4) leads are approved for commercial use. In the US, the ENDOTAK RELIANCE (DF4) leads are approved for commercial use and may be used in the study. The RELIANCE 4-FRONT (DF4) lead will be investigational in the US during a portion or the entire duration of the ENABLE MRI study. Only patients with existing RELIANCE 4-FRONT (DF4) leads from another Boston Scientific-sponsored IDE study (NAVIGATE X4 Study, NCT02071173, G130222) will be allowed to participate in the US.

5.4 Boston Scientific's ACUITY X4 Quadripolar LV Lead and Accessories

The ACUITY X4 quadripolar coronary venous leads are intended for chronic left ventricular pacing and sensing. These steroid-eluting leads have an IS4[5] four-pole connector. A variety of pace/sense configurations are possible with the four distal electrodes that can function as cathodes (all four electrodes) or anodes (all except E1, the most distal electrode) when used with a compatible pulse generator. See Figure 5.4-1 below for a picture of the ACUITY X4 leads as well as the layout of the electrodes on the lead. Refer to the Physician Lead Manuals for additional information about the leads.

[4] DF4 refers to the international standard ISO 27186:2010
[5] IS4 refers to the international standard ISO 27186:2010.

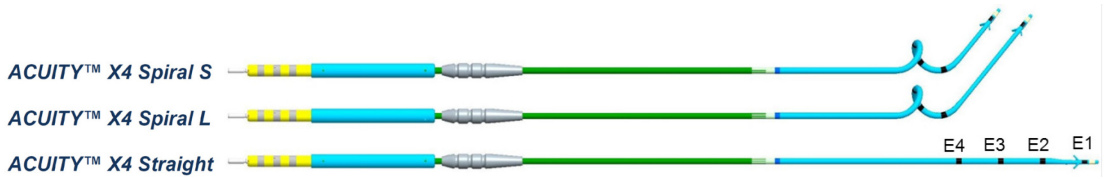


Figure 5.4-1: ACUITY X4 Leads and Electrode Placement

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

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

Boston Scientific's ACUITY X4 quadripolar left ventricular lead and accessory models are included in the ImageReady System and are allowed for the study (see Table 5-1).

Internationally, the ACUITY X4 leads are approved for commercial use. In the US, the ACUITY X4 leads may be investigational at the start of the study. If the ACUITY X4 lead becomes approved for commercial use in the US, the lead will no longer be tracked as an investigational lead. Any investigational ACUITY X4 leads used in the ENABLE MRI study will be reconciled in a report following approval.

5.5 Programming System

The programming system consists of the commercially approved 3120 Zoom LATITUDE PRM and 2868 programmer software application (Table 5-2).

The PRM is MR Unsafe and must remain outside the MRI site Zone III (and higher) as defined by the American College of Radiology Guidance Document for Safe MR Practices[6]. Under no circumstances should the PRM be brought into the MRI scanner room, the control room, or the MRI site Zone III or IV areas.

In the US, a programmer key (dongle) is required to interrogate the VR ICDs and CRT-Ds to access the investigational 'MRI Protection Mode'. A programmer key is only available for use by a BSC representative. Therefore a BSC representative will need to be present any time the investigational 'MRI Protection Mode' is needed to be accessed (i.e., all MR scans). A programmer key is not required for device interrogation. It is anticipated that the ImageReady System will become approved for commercial use in the US during the course of the study. If this occurs, then a programmer key will no longer be needed to access the MRI Protection Mode.

[6] Kanal E, et al., American Journal of Roentgenology 188:1447-74, 2007.

Table 5-2: Programming System (Non-implanted Components) for ImageReady MR Conditional Defibrillation System

Device Name	Device Model Number	MR Status
ZOOM LATITUDE PRM	3120	MR Unsafe
ZOOM LATITUDE PRM Software Application	2868 v3.07 or later	N/A

6. Conditions of Use

The following MRI Conditions of Use must be satisfied as listed here and in the *BSC MRI Technical Guide*[7]. Where differences exist between the *BSC MRI Technical Guide* and the ENABLE MRI Study protocol, they are noted, and the protocol extends the *BSC MRI Technical Guide.*

The intended MRI Conditions of Use for the ImageReady System consist of the following items.

6.1 Cardiology

1. Patient is implanted with an ImageReady MR Conditional Defibrillation System (see Section 5).
2. No other active or abandoned implanted devices, components. or accessories present such as lead adaptors, extenders, leads, or pulse generators
3. Pulse generator is in MRI Protection Mode during scan
4. As soon as MRI Protection Mode is programmed, the patient must be continuously monitored by pulse oximetry and electrocardiography (ECG). Ensure backup therapy is available (external rescue).
5. Patient is judged to be clinically capable of tolerating no Tachycardia protection and no Bradycardia** support (including CRT) for the entire duration in which the pulse generator is in MRI Protection Mode

   **Note: For Phase I of the ENABLE MRI Study, pace-dependence will be defined as no underlying heart rhythm when paced at VVI 40. Label the ECG strip with the subject ID#, date, time, and Visit name.
6. Patient does not have elevated body temperature or compromised thermoregulation at time of scan
7. Pulse generator implant location restricted to left or right pectoral region

[7] The *BSC MRI Technical Guide* is investigational in the US, at the start of the study. This may become approved in the US during the study.

8. At least six (6) weeks have elapsed since implantation and/or any lead revision or surgical modification of the MR Conditional Defibrillation System
9. No evidence of a fractured lead or compromised pulse generator-lead system integrity

6.2 Radiology

1. MRI magnet strength RF field Maximum spatial gradient MRI equipment specification	1.5 T only Approximately 64 MHz 20T/m (2,000 G/cm) Horizontal, 1H proton, closed bore scanners only
2. Specific Absorption Rate (SAR) limits for the entire active scan	Normal Operating Mode[a]: • Whole body averaged, ≤ 2.0 watts/kilogram (W/Kg) • Head, ≤ 3.2 W/Kg
3. Maximum specified gradient slew rate	≤ 200 T/m/s per axis
4. The use of receive-only coils is not restricted. Local transmit-only coils or local transmit/receive coils may be used, but should not be placed directly over the defibrillation system. 5. Patient in supine or prone position only 6. Patient must be continuously monitored by pulse oximetry and electrocardiography (ECG) for the entire duration in which the pulse generator is in MRI Protection Mode. Ensure backup therapy is available (external rescue). [a.] *As defined in IEC 60601-2-33, 201.3.224, 3rd Edition.*	

7. Objectives

The objective of the study is to collect data to confirm the safety and effectiveness of the ImageReady MR Conditional Defibrillation System when used in the 1.5T MRI environment under the labeled Conditions of Use.

Additionally, the study will assess medically necessary MR scans according to the labeled Conditions of Use to provide real-world scanning data.

The study also aims to demonstrate the continued ability of the ImageReady MR Conditional Defibrillation System to sense and detect VF post MRI scan by collecting and analyzing data from spontaneous VF episodes, “for-cause” VF inductions, and from an optional VF induction Sub-study.

8. Endpoints (Phase I only)

For details around Phase I endpoints, see Section 13.1.

8.1 Primary Safety Endpoint

- MR Scan-related ImageReady System Complication-Free Rate between the MR Scan and the MRI + 1 Month Visit

8.2 Primary Effectiveness Endpoints

- Primary RV Effectiveness Endpoint 1: Increase in RV pacing threshold (at 0.5 ms) from the pre-MR scan to the 1 Month post-MR scan
- Primary RV Effectiveness Endpoint 2: Decrease in RV Sensed Amplitude from the pre-MR scan to the 1 Month post-MR Scan
- Primary LV Effectiveness Endpoint 1: Increase in LV pacing threshold (at 0.5 ms) from the pre-MR scan to the 1 Month post-MR Scan
- Primary LV Effectiveness Endpoint 2: Decrease in LV Sensed Amplitude from the pre-MR scan to the 1 Month post-MR Scan

9. Design

The ENABLE MRI Study is a prospective, non-randomized, confirmatory, global study conducted as an IDE in the United States, and as a post market study in Europe, Israel and Asia Pacific.

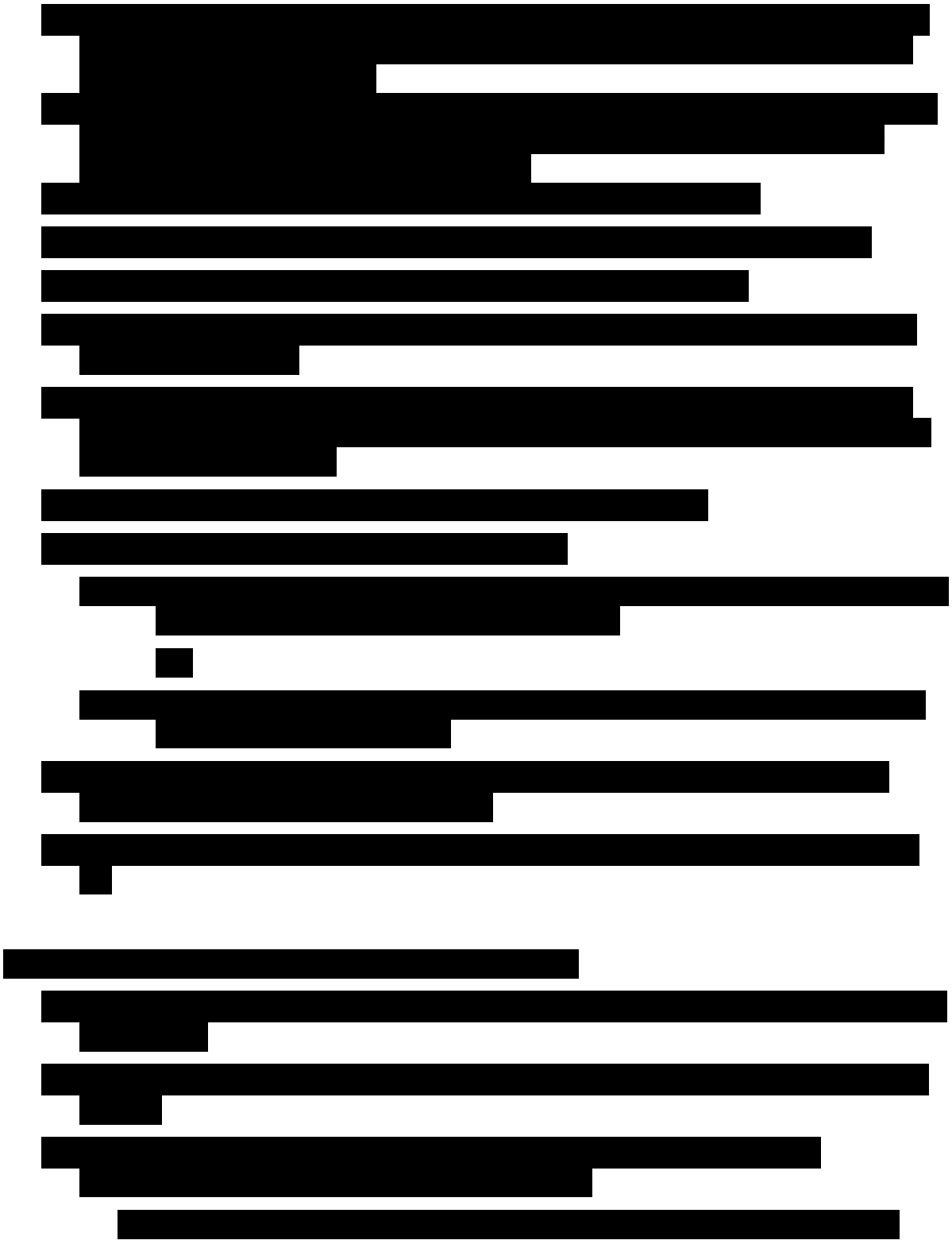
The study will be conducted in two phases as described in Section 9.1.

A subset of subjects enrolled into Phase I of the ENABLE MRI study may be eligible to participate in the VF induction Sub-study as described in section 11.2.8.

9.1 Scale and Duration

The ENABLE MRI Study will be conducted in two phases to enroll 500 subjects at approximately 70 investigational centers in the United States, Europe, Israel and Asia-Pacific.

[redacted]



[redacted]

All subjects enrolled in this study must be followed according to the investigational plan unless Boston Scientific notifies the Investigator to the contrary or Boston Scientific has officially closed the study. The duration of the study is expected to be approximately 5.5 years.

9.2 Justification for the Study Design

The ENABLE MRI Study is being conducted to collect data to support pre-market regulatory agency submissions for approval of the ImageReady System for use in the 1.5T MRI environment (Phase I), in geographies where prospective clinical data is required. The study data will also be used to support worldwide post-market requirements in certain geographies.

The study is designed with one interim analysis to support regulatory submissions.

The study also aims to demonstrate the continued ability of the ImageReady™ MR Conditional Defibrillation System to sense and detect VF post MRI scan by collecting and analyzing data from spontaneous VF episodes, "for-cause" VF inductions, and from the VF induction Sub-study.

Phase I and Phase II data will be used to evaluate VT/VF sensing after an MR scan, potential influence of multiple MR scans on the ImageReady System, Beeper functionality after MR scans, and programming of the MRI Protection Mode (see Section 13.2 on ancillary analysis).

Data from the FINELINE II leads will be used to support regulatory approval in geographies that do not already have market approval of FINELINE II as an MR Conditional lead.

10. Subject Selection

10.1 Study Population and Eligibility

Subjects enrolled in the ENABLE MRI Study shall be selected from the investigators general patient population indicated for an ICD or CRT-D implantation. The Investigator is responsible for screening potential subjects and selecting those who meet the eligibility criteria for the study as described in Sections 10.2 and 10.3.

Patients who consent to be part of the VF induction Sub-study also have to be evaluated for the VF Sub-study exclusion criteria at the time of their consent. Subjects enrolled into the ENABLE MRI Study who will receive a de novo device may be enrolled into the Sub-study up to 14 calendar days after the implant procedure.

10.2 Inclusion Criteria

Subjects who meet all of the following criteria (Table 10-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion are met (Table 10-2).

Note: All study subjects enrolled prior to protocol version AE implementation will need to be assessed for the current Inclusion and Exclusion Criteria. More details are provided in Section 11.1.

For Inclusion criterion #1, "functional and stable CRT-D or ICD system" will be defined as follows:

- Lead impedances for the RA, RV and LV leads are within the acceptable ranges per device labeling (please refer to the Physician Guide for details)
- No evidence of lead fracture or lead dislodgement
- No evidence of PG malfunction (i.e. error code)

Table 10-1: Inclusion Criteria

<table>
<tr><td>Inclusion Criteria</td><td>
1. Phase I: Subject is indicated per guidelines and will receive a CRT-D or ICD system consisting only of the following MR Conditional components* (OR) Subject is implanted with a functional and stable CRT-D or ICD system consisting only of the following MR Conditional components*
Phase II: Subject is implanted with a functional and stable CRT-D or ICD system consisting only of the following MR Conditional components*

*MR Conditional Components
System must consist only of these PGs and leads listed below (refer to Table 5-1 for component model numbers):
<table>
<tr><th>Lead/PG</th><th colspan="2">International
(All Market Approved)</th><th colspan="2">US</th></tr>
<tr><td>RA Lead</td><td colspan="2">INGEVITY MRI
FINELINE II Sterox/Sterox EZ</td><td colspan="2">FINELINE II Sterox/Sterox EZ</td></tr>
<tr><td>RV Lead</td><td colspan="2">RELIANCE 4-FRONT
ENDOTAK RELIANCE</td><td colspan="2">RELIANCE 4-FRONT[1, ǂ]
ENDOTAK RELIANCE</td></tr>
<tr><td>LV Lead</td><td colspan="2">ACUITY X4</td><td colspan="2">ACUITY X4 [1]</td></tr>
<tr><td>Phase I: PG
• VR ICD
• CRT-D[2]</td><td>PG Header
VR ICD (DF4), CRT-D[2] (IS1/DF4/IS4)</td><td>Device Name
ORIGEN
INOGEN
DYNAGEN
AUTOGEN</td><td>PG Header
VR ICD (DF4), CRT-D[2] (IS1/DF4/IS4)</td><td>Device Name
ORIGEN
INOGEN
DYNAGEN</td></tr>
<tr><td>Phase II: PG</td><td>PG Header
VR ICD (DF4), DR ICD[2] (IS1/DF4), CRT-D[2] (IS1/DF4/IS4)</td><td>Device Name
ORIGEN
INOGEN
DYNAGEN
AUTOGEN</td><td>PG Header
VR ICD (DF4), CRT-D[2] (IS1/DF4/IS4)</td><td>Device Name
ORIGEN
INOGEN
DYNAGEN</td></tr>
<tr><td colspan="5">[1] The ACUITY X4 and the RELIANCE 4-FRONT leads may be investigational in the US during a portion or the entire duration of the study
[ǂ] For the US, only existing RELIANCE 4-FRONT implants will be allowed
[2] Port plug 7145 must be used in DR ICDs and CRT-Ds with no atrial lead</td></tr>
</table>
2. Subject will receive or is implanted with an ICD or CRT-D pulse generator in the left or right pectoral region

3. Subject is able and willing to undergo an MR scan without intravenous sedation (Phase I only)*

*Oral sedation may be used, if necessary, based on medical discretion

4. Subject is willing and capable of providing informed consent and participating in all testing/ visits associated with this clinical study at an approved clinical study center and at the intervals defined by this protocol

5. Subject is age 18 or above, or of legal age to give informed consent specific to state and national law
</td></tr>
</table>

10.3 Exclusion Criteria

Subjects who meet any one of the following criteria (Table 10-2) will be excluded from this clinical study.

Table 10-2: Exclusion Criteria

Exclusion Criteria	1. Subject implanted with an ICD or CRT-D pulse generator with battery at Explant status
	2. Subject has other active or abandoned implanted cardiac rhythm devices, components or accessories present such as pulse generators, leads, lead adaptors or extenders
	3. Presence of metallic objects that represent a contraindication to MR imaging at the discretion of the Radiologist and impacting the ability to conduct the study protocol
	4. Subject needs or will need a medically necessary MR scan, before completing the 1-month post-MR follow-up visit (Phase I only)
	5. Subject with: • A history of syncope related to brady-arrhythmia • A history of syncope of unknown etiology • Sinus pauses (Pause > 2 s) • Permanent or intermittent complete AV block • Documentation of progressive AV nodal block over time • Trifascicular block (alternating bundle branch block or PR > 200 ms with LBBB or other bifascicular block) *Note: It is required to run a 12 lead ECG and a 10s rhythm strip to document this exclusion criterion. During ECG acquisition, subjects must be in either their own intrinsic rhythm or, in subjects with an existing device implant, the device must be programmed to VVI 40 ppm.*
	6. Subject is not clinically capable of tolerating the absence of pacing or Resynchronization therapy support in a supine position for the duration that the pulse generator is in MRI Protection Mode, per Physician discretion
	7. Subject is not clinically capable of tolerating the absence of Tachycardia therapy support for the duration that the pulse generator is in MRI Protection Mode, per Physician discretion
	8. Subjects with a planned RA, RV or LV lead revision or extraction within 30 days of enrollment (Phase I only)
	9. Subjects with an implanted lead that is planned to be extracted during the study implant procedure
	10. Subjects currently requiring dialysis
	11. Subject has a mechanical heart valve
	12. Subject has a known or suspected sensitivity to dexamethasone acetate (DXA)
	13. Subject is currently on the active heart transplant list

	14. Subject has documented life expectancy of less than 12 months
	15. Subject is enrolled in a concurrent study, with the exception of local mandatory governmental registries and observational studies/registries, without the written approval from Boston Scientific.
	16. Women of childbearing potential who are or might be pregnant, and will receive an ICD or CRT-D pulse generator *NOTE: Pregnancy tests are required as part of standard routine clinical practice at all centers whenever female patients of child bearing potential are exposed to x-ray radiation as part of the implant procedure.*

10.3.1 VF Induction Sub-study Exclusion Criteria

In addition to meeting all of the inclusion criteria and none of the exclusion criteria of the ENABLE MRI Study, subjects enrolled in the VF Induction Sub-study must not meet any of the following VF Induction Sub-study exclusion criteria.

Table 10-3: VF Induction Sub-Study Exclusion Criteria

VF Induction Sub-Study Exclusion Criteria	1. Unstable heart failure requiring hospitalization in the last 30 calendar days 2. Unable to tolerate sedation (e.g. IV sedation, general anesthesia) 3. Planned cardiac revascularization procedure 4. Right Ventricular Lead R wave is less than 5 mV

11.Subject Accountability

11.1 Screening and Point of Enrollment

11.1.1 Subjects enrolled under previous protocol versions

All subjects enrolled under previous protocol versions will need to be re-consented. The exclusion criterion #5 will need to be evaluated for these patients:

- Subjects not having performed the MRI visit:
    - If these subjects meet the updated exclusion criterion #5, they should be withdrawn from the study and classified as consent ineligible subjects. These withdrawn subjects will not count against the enrollment ceiling.
    - If these subjects do not meet the updated exclusion criterion #5:
        - They will continue as part of Phase I and will undergo the non-diagnostic study required MR scan
        - If they refuse to undergo the non-diagnostic study required MR scan (Phase I), they will automatically be rolled onto Phase II unless they

chose to withdraw from the study. These withdrawn subjects will not count against the enrollment ceiling.

- Subjects having performed the MRI visit:
    - If these subjects do not meet the updated exclusion criterion #5, they will continue in the study and attend visits as required per protocol. These subjects are counting toward the enrollment ceiling.
    - If these subjects meet the updated exclusion criterion #5, this should be documented in the subject's file. These subjects can remain enrolled in the study. In case of withdrawal, if possible, such subjects should not be withdrawn prior to the MRI + 1 month to ensure safety follow-up within 30 days post MRI. These subjects are counting toward the enrollment ceiling.

11.1.2 Subjects enrolled under protocol rev AE and future revisions

11.2 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.

For US subjects: 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 until the implanted investigational devices are approved by the FDA or the device is explanted.

Reasons for withdrawal include, but are not limited to:

- Subject who does not receive a Boston Scientific ImageReady MR Conditional Defibrillation System (no follow-up requirements)
- Subject who receive only a partial Boston Scientific ImageReady MR Conditional Defibrillation System (see section 11.3.4 for follow-up requirements)
- Subjects that have a PG or lead changeout that is not a Boston Scientific ImageReady MR Conditional Defibrillation System component (See Section 5)
- Subjects in Phase I who refuse to undergo the study require MR scan and are not willing to be rolled into Phase II
- Subjects already enrolled with previous protocol versions, who have not performed the MRI visit and who meet the updated exclusion criterion #5
- Subjects who fail the heart rhythm monitoring requirements at the MRI visit
- Physician discretion
- Subject choice to withdraw consent
- Lost to follow-up
- Death

While study withdrawal is discouraged, subjects may withdraw from the ENABLE MRI study and/or the VF Induction Sub-study at any time, with or without reason, and without prejudice to further treatment.

All applicable case report forms up to the point of subject withdrawal and a "Subject Status" form must be completed. Subjects who are "lost-to-follow-up" should have documented attempts to contact them prior to completion of the "Subject Status" form.

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

11.3 Subject Status and Classification

Subjects enrolled in the ENABLE MRI study will be placed into one of six classifications, as defined below.

If a subject receives the PG or lead(s) listed in **Section 5** after enrollment, they will be treated as a de novo. De novo subjects are classified based on sections 11.3.1to 11.3.5.

11.3.1 Intent

Intent refers to a subject who has been enrolled, but does not have the lead(s) or PG introduced into their body. There are no follow-up requirements for intent subjects. The

original informed consent form (ICF) and screening documentation for intent subjects should be maintained in the Center's files.

11.3.2 Consent ineligible

Consent ineligible refers to a subject who signed the ICF but meets exclusion criteria #3 or #5. As applicable, all adverse events need to be reported up to the point of withdrawal. There are no follow-up requirements for consent ineligible subjects. The original informed consent form (ICF) and screening documentation for consent ineligible subjects should be maintained in the Center's files. These subjects do not count towards the enrollment ceiling.

11.3.3 Attempt

Attempt refers to a subject who 1) has been enrolled in the Study, 2) has had anesthesia administered in preparation for the surgical implant procedure, 3) has had the lead(s) and/or PG introduced into the subject's body, but 4) is not successfully implanted with any portion of the ImageReady System during the implant procedure (meaning the subject is not successfully implanted with either the PG or lead(s)).

Attempt subjects must be followed 30 ± 7 days post-attempted ImageReady System implant to assure there are no associated adverse events, or to assure the resolution of any adverse events associated with the attempted ImageReady System implant.

11.3.4 Partial Implant

Partial Implant refers to a subject who is implanted with a component of the ImageReady System during the implant procedure, but does not end up with a complete ImageReady System. Due to the fact that these subjects do not have a full ImageReady System, according to the Conditions of Use in the *BSC MRI Technical Guide*, they shall not receive the MR Scan for the ENABLE MRI study.

- **For US subjects: If investigational leads were implanted, the subjects must be followed for safety.** These subjects must be followed at each time point required for the study until the implanted investigational leads are approved by the FDA or the device is explanted.
- **If there were no investigational leads implanted,** Partial Implant subjects must be followed 30 ± 7 days post- ImageReady System implant to assure there are no associated adverse events, or to assure the resolution of any adverse events associated with the ImageReady System implant, then withdrawn from the study.

11.3.5 Implant

Implant refers to a subject who is successfully implanted with the ImageReady System per the study protocol. These subjects are followed in accordance with the follow-up schedule and included in all analyses of safety and performance.

11.3.6 Existing Implant

Existing Implant refers to a subject who has a complete ImageReady System implanted prior to enrollment, per the study protocol. These subjects are followed in accordance with the follow-up schedule and included in all analyses of safety and performance.

11.4 Enrollment Controls

A total of 500 subjects at up to 70 investigational centers will be enrolled in this study.

11.5 End-of-Study Action Plan

Boston Scientific Corporation reserves the right to terminate the study, or discontinue implanting at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to the protection of subjects. In the event of this occurrence, BSC will communicate to the investigators of the ENABLE MRI Clinical Study. The investigators will be responsible for communicating any information necessary to the subjects. BSC will support the physicians by providing recommendations for ensuring the safety of the subjects and the handling of any investigational components of the ImageReady System in the US until those components are approved by the FDA, which may include, but are not limited to:

- Standard of care procedures
- More frequent follow ups of the subject than per standard procedures
- Longer term follow up (beyond length of initial consent)
- Explantation of RELIANCE 4-FRONT or ACUITY X4 leads upon careful risk-benefit analysis
- Other possible actions

If it becomes apparent that any of the investigational products will not be FDA-approved, a communication and study action plan for the subjects with those unapproved devices will be implemented.

12.Study Methods

12.1 Data Collection

A detailed list of procedures, testing and data collected required at the study visits are presented in Table 12-1. The table also has the study visits that are needed per study phase and per implanted device status.

- For Phase I subjects there will be a non-diagnostic study required MR scan (during the MRI visit)
- For Phase I subjects, the MRI and the MRI + 1 Month visits are required.
- For VF Induction Sub-Study subjects, VF Induction testing will be performed at the MRI + 1 Month Visit
- For "for cause" VF induction subjects, VF Induction testing will be performed ideally at the MRI + 1 Month Visit or up to 14 calendar days later
- For de novo implants (phase I), the Implant and Pre-discharge visits are required.

Table 12-1: Data Collection Schedule

Procedure / Assessment	Screening and Enrollment	Phase I: De novo implants only		Phase I only		Every Three-Month Visits***	Every Annual Visits*	Additional Visits	Medically necessary MRI
		Implant	Pre-Discharge	MRI Visit	MRI + 1 Month Visit				
Timeframe	De novo: ≤ 30 days prior to Implant Existing implant	Implant	3-72 hours from Implant	De novo: 6-9 weeks from Implant Δ Existing implant: within 6 weeks from Enrollment Δ	30 ± 7 days from MRI Visit	90 ± 30 days from MRI Visit	De novo: 365±90 days* from implant Existing implant: 365±90 days* from Enrollment	--	--
Informed consent form and process, including informed consent signature and date	**X****	--	--	--	--	--	--	--	--
12 lead ECG & 10s rhythm strip	**X (document exclusion #5)**	--	--	**X Pre MRI (HR monitoring)**	--	--	--	--	**X Pre MRI (HR monitoring)**
Demographics	**X**	--	--	--	--	--	--	--	--
Physical assessment	**X**	--	--	--	--	--	--	--	--
Medical History, Comorbidities, Cardiac Disease History, Medications	**X**	--	--	--	--	--	--	--	--
ICD/CRT-D system implant	--	**X**	--	--	--	--	--	--	--
Device Evaluation (includes pace thresholds, intrinsic amplitudes, impedances, RV shock impedance)	--	**X**	**X**	**X Pre & Post**	**X**	**X**	**X**	**O**	**O**

Procedure / Assessment	Screening and Enrollment	Phase I: De novo implants only		Phase I only		Every Three-Month Visits***	Every Annual Visits*	Additional Visits	Medically necessary MRI
		Implant	Pre-Discharge	MRI Visit	MRI + 1 Month Visit				
Timeframe	De novo: ≤ 30 days prior to Implant Existing implant	Implant	3-72 hours from Implant	De novo: 6-9 weeks from Implant Δ Existing implant: within 6 weeks from Enrollment Δ	30 ± 7 days from MRI Visit	90 ± 30 days from MRI Visit	De novo: 365±90 days* from implant Existing implant: 365±90 days* from Enrollment	--	--
VF Induction Testing ("for-cause" or VF Sub-study)	--	--	--	--	X****	--	--	--	--
Beeper Assessment	--	--	--	**X Pre & Post**	--	--	--	--	**X Pre & Post**
Save All	--	--	--	**X**	**X**		**X**	**O**	**O**
Printout of device settings and history	--	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
MRI Conditions of Use	--	--	--	**X**	--	--	--	--	**X**
DICOM file from MR scanner	--	--	--	**X**	--	--	--	--	**O**
Adverse Events	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Legend: X = Required; -- = Not required/ Not applicable; O = Optional; Δ Must be at least 6 weeks after any required surgical interventions to the ImageReady System;

* Annual visits will occur at 365 ± 90, 730 ± 90 and 1095 ± 90 days after implant (if de novo) or from enrollment (if existing implant) respectively.

** The informed consent process and subject signature of the informed consent form will occur before the implant procedure begins.

*** The first Every 3-month visit will occur 90 ± 30 days after MRI visit. Subsequent Every 3-month follow-up visits will be scheduled every three months (90 days ± 30 Days) from the previous scheduled study follow-up. If this visit is done, then the data is required.

**** The "for-cause" VF inductions may be performed up to 14 calendar days after the MRI + 1 Month Visit

12.2 Study Candidate Screening

Boston Scientific will collect information to document potential subjects who are considered as potential study candidates but are determined not to meet inclusion criteria prior to signing informed consent.

12.3 Informed Consent

All subjects who complete the informed consent process, sign and date the informed consent form will be evaluated for the following criteria:

- Radiologist approval to undergo MRI scan if metal objects in body (exclusion criterion #3)
- 12 lead ECG and 10s rhythm strip (either from the ECG machine or the BSC PRM) (exclusion criterion #5)

Source documentation for both of these exclusion criteria need to be retained in the patient medical file.

Subjects who meet these exclusion criteria will be considered Consent ineligible and will not count toward the enrollment ceiling.

Subjects who do not meet these exclusion criteria will be considered enrolled in the ENABLE MRI study and will count toward the enrollment ceiling.

In addition, subjects who meet none of the exclusion criteria for the VF Induction Sub-study and undergo the VF Induction Sub-Study informed consent process, sign, and date the ENABLE MRI VF Induction Sub-study informed consent form are considered enrolled in the Sub-study.

For Phase I de novo implants: Enrollment may occur up to 30 days prior to the implant procedure.

A summary of the data collected at enrollment is described in Table 12-1. The following assessments will be performed at Enrollment.

12.4 Screening and Enrollment Visit

The data to be collected at enrollment includes:

- Signed and dated informed consent to participate in the ENABLE MRI study
- Patient demographic data
- Physical assessment including height, weight and vital signs
- Medical history, comorbidities, cardiac disease history and medications.

Subjects who consent to participate in the VF Induction Sub-study will provide written informed consent.

A summary of the data collected at enrollment is described in Table 12-2.

Provide the subject with an EC/IRB approved ENABLE MRI Study identification card. The subject should be instructed to show the card at every hospitalization and ER visit.

12.4.1 Screening and Enrollment Source Data Requirements

Source data requirements at Screening and Enrollment are described in Table 12-2.

Table 12-2: Screening and Enrollment Source Documentation Requirements

Source Documentation Requirement	Disposition
Informed consent form and process, including informed consent signature and date. 12 leads ECG and 10s rhythm strip to document exclusion criterion #5 Completed Radiologists Technical Source Form (applicable for subjects with metallic implants only) VF Induction Sub-Study informed consent and process, including informed consent signature and date, if applicable	Retain at center
Demographics, including age, gender, race/ethnicity, etc.	
Physical assessment, including weight and height	
Medical History, Comorbidities, Cardiac Disease History, Medications	
Adverse Events	

12.5 Implant

For Phase I de novo subjects, the implant procedure will occur either on the same day as enrollment, after the subject signs and dates the informed consent form, or up to 30 days later.

The ImageReady System should be implanted and tested per standard procedures and in accordance with the Physician's Manuals for the associated PG and lead(s). To satisfy the MRI Conditions of Use (see Section 6), the PG must be implanted in the left or right pectoral (subcutaneous or sub-muscular) regions.

The implant procedure end time is defined as the time of device pocket closure. Record the end time in the electronic data capture (EDC) system.

Investigators will follow standard of care or standard center practices for the implant of the ICD/CRT-D system.

- For the VR ICD system, an ENDOTAK RELIANCE (DF4) or RELIANCE 4-FRONT RV[8] lead must be successfully implanted unless the subject already has an existing functional ENDOTAK RELIANCE (DF4) or RELIANCE 4-FRONT RV lead.
- For the CRT-D system:
    - In the right atrium, a FINELINE II or INGEVITY[9] RA lead or Port plug 7145 must be successfully implanted unless the subject already has an existing functional FINELINE II or INGEVITY[9] MRI RA lead or Port plug 7145.
    - In the right ventricle, an ENDOTAK RELIANCE (DF4) or RELIANCE 4-FRONT RV[8] lead must be successfully implanted unless the subject already has an existing functional ENDOTAK RELIANCE (DF4) or RELIANCE 4-FRONT RV lead
    - In the left ventricle, an ACUITY X4 LV lead must be successfully implanted unless the subject already has an existing functional ACUITY X4 LV lead.
- A DF-4 or IS-4 port plug cannot be used in place of the RV or LV lead.

A summary of the data collected at implant are described in Table 12-1.

12.5.1 Device Evaluation

All implanted leads will be evaluated through the implanted PG using the test parameters listed in Table 12-3:

- Manual pacing threshold tests, as defined in sections 12.5.1.1, 12.5.1.2 and 12.5.1.3.
- Sensing amplitude
- Impedance
- Shock impedance (RV lead only)

Record the measurements in the EDC system.

[8] No de-novo RELIANCE 4-FRONT implants will occur in the US
[9] INGEVITY is only available internationally outside of the US

Table 12-3: Test Parameters

Description	**RA Threshold Test**	**RV Threshold Test**	**LV Threshold Test**
Test Type	Amplitude	Amplitude	Amplitude
Pulse Width (ms)	0.5	0.5	0.5
Cycles per Step	3 (minimum)	3 (minimum)	3 (minimum)
Pacing Lead Configuration	Not Programmable	Not Programmable	Per HCP **For MRI and MRI + 1 Month visits:** The same LV Pacing Configuration must be used for threshold testing
Impedance Tests	**RA Impedance Test**	**RV Impedance Test**	**LV Impedance Test**
Pacing Lead Configuration	Bipolar	Bipolar	**Same LV configuration as the Pacing Test** **For MRI and MRI +1 Month visits:** The same LV Pacing Configuration must be used for impedance testing
Sensing Tests	**RA Sensing Test**	**RV Sensing Test**	**LV Sensing Test**
Sensing Configuration	Bipolar	Bipolar	Per HCP **For MRI and MRI+1 Month visits:** The same LV Sensing Configuration must be used for sensing testing
Note: Mode, Lower Rate Limit, Amplitude, Paced AV delay and LV Pacing Lead Configuration shall be set per physician or HCP discretion.			

12.5.1.1 Manual Right Atrial Threshold Test

If the subject does not have an active implanted RA lead, then skip to the next section.

Otherwise, perform a manual RA threshold test following these steps, unless the testing is inhibited by a patient condition (example: subject is in atrial fibrillation):

1. In the Atrial Threshold Test screen set the Test Type to Amplitude
2. Mode, Lower Rate Limit, Amplitude and Paced AV delay shall be set per physician or HCP discretion
3. Pulse Width shall be set to 0.5 ms
4. Cycles per Step shall be set to a minimum of 3
5. Start the annotated real-time ECG from the PRM, then start the manual RA threshold test
    a. A count of 2 non-capture beats at a given voltage level is required to declare loss of capture (LOC)
    b. If the subject experiences discomfort during the threshold test due to extracardiac stimulation, then stop the test and perform the manual threshold test per physician discretion.
6. When LOC is determined, stop the threshold test. Stop the PRM real-time ECG a minimum of 2 seconds after LOC is determined.
7. Label the PRM ECG with the subject ID#, date, "[Visit name; e.g. Implant, Pre-Discharge, MRI Visit, MRI + 1Month Visit, etc.] Manual RA threshold test", attempt # (if applicable).
8. The threshold for the manual RA threshold test is defined as one voltage level above the level where the 2 non-captured beats are observed. Record the threshold in the EDC system.
9. If the threshold saved on the PRM does not match the threshold, as defined in step 8, then update the RA Pace Threshold in the programmer.

12.5.1.2 Manual Right Ventricular Threshold Test

Perform a manual RV threshold test following these steps:

1. In the Right Ventricular Threshold Test screen set the Test Type to Amplitude
2. Mode, Lower Rate Limit, Amplitude and Paced AV delay shall be set per physician or HCP discretion
3. Pulse Width shall be set to 0.5 ms
4. Cycles per Step shall be set to a minimum of 3
5. Start the annotated real-time ECG from the PRM, then start the manual RV threshold test

   a. A count of 2 non-capture beats at a given voltage level is required to declare loss of capture (LOC)
   b. If the subject experiences discomfort during the threshold test due to extracardiac stimulation, then stop the test and perform the manual threshold test per physician discretion.
6. When LOC is determined, stop the threshold test. Stop the PRM real-time ECG a minimum of 2 seconds after the LOC is determined.
7. Label the PRM ECG with the subject ID#, date, "[Visit name; e.g. Implant, Pre-Discharge, MRI Visit, MRI + 1Month Visit, etc.] Manual RV threshold test", attempt # (if applicable).
8. The threshold for the manual RV threshold test is defined as one voltage level above the level where the 2 non-captured beats are observed. Record the threshold in the EDC system.
9. If the threshold saved on the PRM does not match the threshold, as defined in step 8, then update the RV Pace Threshold in the programmer.

12.5.1.3 Manual Left Ventricular Threshold Test

If the subject does not have an active implanted LV lead, then skip to the next section.

If multiple manual LV threshold tests are performed, then record the manual LV threshold test that matches the final programmed LV lead configuration following these steps:

1. In the Left Ventricular Threshold Test screen set the Test Type to Amplitude
2. Mode, Lower Rate Limit, Amplitude and Paced AV delay shall be set per physician or HCP discretion
3. Set the pulse width at 0.5 ms
4. Cycles per Step shall be set to a minimum of 3
5. Start the annotated real-time ECG from the PRM, then start the manual LV threshold test
   a. A count of 2 non-capture beats at a given voltage level is required to declare loss of capture (LOC)
   b. If the subject experiences discomfort during the threshold test due to extracardiac stimulation, then stop the test and perform the manual threshold test per physician discretion.
6. When LOC is determined, stop the threshold test. Stop the PRM real-time ECG a minimum of 2 seconds after the LOC is determined.

7. Label the PRM ECG with the subject ID#, date, "[Visit name; e.g. Implant, Pre-Discharge, MRI Visit, MRI+1month Visit, etc.] Manual LV threshold test", attempt # (if applicable).
8. The threshold for the manual LV threshold test is defined as one voltage level above the level where the 2 non-captured beats are observed. Record the threshold in the EDC system.
9. If the threshold saved on the PRM does not match the threshold, as defined in step 8, then update the LV Pace Threshold in the programmer.

12.5.2 Completing the Implant Visit

1. Program the device according to physician discretion
2. Print the 'Quick Notes' Report

12.5.3 Implant Source Data Requirements

Source data requirements at implant are described in Table 12-4.

Table 12-4: Implant Source Documentation Requirements

Source Documentation Requirement	Disposition
Device model/serial number	Retain at center
Lead model/serial numbers for all implanted leads	
Device Evaluation (pace thresholds, sense amplitudes, impedances, RV shock impedance)	
PRM ECG strips from manual threshold tests documenting LOC for all implanted leads	
Printout of 'Quick Notes' Report	
Adverse Events	

12.6 Pre-Discharge

For Phase I de novo subjects, the Pre-discharge Visit will occur either on the same day as the ImageReady System implant procedure, a minimum of 3 hours after pocket closure, or up to 72 hours after the implant procedure.

12.6.1 Device Evaluation

All implanted leads will be evaluated through the implanted PG using the test parameters listed in Table 12-3:

- Manual pacing threshold tests, as defined in sections 12.5.1.1, 12.5.1.2 and 12.5.1.3.
- Sensing amplitude

- Impedance
- Shock impedance (RV lead only)

Record the measurements in the EDC system.

12.6.2 Completing the Pre-Discharge Visit

1. Program the device according to physician discretion
2. Print the 'Quick Notes' Report
3. Schedule the MRI follow-up visit

12.6.3 Pre-Discharge Source Data Requirements

Source data requirements at Pre-discharge Visit are described in Table 12-5:

Table 12-5: Pre-Discharge Source Documentation Requirements

Source Documentation Requirement	Disposition
Device Evaluation (pace threshold, sense amplitude, impedance, RV shock impedance)	Retain at center
PRM ECG strips from manual threshold tests documenting LOC for all implanted leads	
Printout of 'Quick Notes' Report	
Adverse Events	

12.7 MRI Visit (Phase I only)

The MRI follow-up visit consists of data collection and MR scan.

For Phase I de novo subjects, the visit will occur 6 to 9 weeks (42-63 days) after implant or surgical revision of the ImageReady System implant*.

For Phase I existing implant subjects, the visit will occur **within 6 weeks** (42 days) from enrollment AND at least 6 weeks after implant or surgical intervention* of the ImageReady System. For example:

- If the subject was enrolled with an ImageReady System that was implanted >6 weeks before enrollment, the MRI visit must occur within 6 weeks (42 days).
- If the subject was enrolled with the an ImageReady System that was implanted 2 weeks (14 days) before enrollment, the MRI visit must occur between 4 – 6 weeks (28 to 42 days) after enrollment.

***Note:** If a subject has had a surgical revision to their ImageReady System (i.e., a lead revision/ reposition), and the MRI Visit is unable to be scheduled within the time window, the MRI Visit and the MRI + 1 Month Visit are not required. Enter the reason for MRI Visit and MRI + 1 Month visit not being done into EDC.

Note: For subjects enrolled under prior protocol versions and who have not been through their MRI visit, the MRI visit will occur within 6 weeks (42 days) from re-consenting and after reconfirmation that they do not meet the exclusion criterion #5

12.7.1 Device Evaluation Prior to Commencement of MR Scan

1. All implanted leads will be evaluated through the implanted PG **for THREE separate consecutive sets of measurements** using the test parameters listed in Table 12-3:
   - Manual pacing threshold tests, as defined in sections 12.5.1.1, 12.5.1.2 and 12.5.1.3.
   - Sensing amplitude
   - Impedance
   - Shock impedance (RV lead only)
2. Test for phrenic nerve stimulation (PNS) and measure the PNS threshold if detected in the programmed LV lead configuration
3. Perform an assessment of Beeper function as defined in section 12.7.1.1.
4. Print the 'Quick Notes' Report

Record the measurements in the EDC system.

12.7.1.1 Assessment of Beeper function

To test if the Beeper is audible,

1. Program Magnet Response to Inhibit Therapy
2. Place the magnet over the PG for a minimum of 5 seconds but not for more than 20 seconds in a quiet environment.
   - If the Tachy mode is programmed to 'Monitor + Therapy': A short beep may be heard once every second, as long as the magnet is placed over the PG.
   - If the Tachy mode is programmed to 'Monitor only' or 'OFF': A continuous beep may be heard as long as the magnet is placed over the PG.

   Note: The Magnet Sensor will detect Guidant/Boston Scientific CRM magnets (donut, horseshoe or wrist) within 3 cm. The Magnet Sensor will detect a 60 G < field ≤300 G, when applied perpendicularly to the surface of the PG, either face.
3. The subject and the HCP will be asked to indicate whether the Beeper is audible to them.
4. If not audible, by either the subject or the HCP, a second attempt at assessing Beeper function will be performed. The Beeper should be assessed in the alternate Tachy mode (as listed in step 2) if tolerated by the subject.
5. Record if the Beeper was audible by the subject and the HCP in the EDC..

12.7.2 Subject Evaluation Prior to Commencement of MR Scan

12.7.2.1 Confirmation of MRI Conditions of Use

Subjects must meet the MRI Conditions of Use, comprised of Cardiology and Radiology Conditions of Use, as listed in the *BSC MRI Technical Guide* and Section 6 of this protocol.

Documentation of both the Cardiology and Radiology MRI Conditions of Use assessment must be included.

Note: Subjects must satisfy the MRI Conditions of Use prior to receiving the study-required MR scan; otherwise a protocol deviation shall be assessed.

12.7.2.2 Subject History of Unexplained Syncope

Prior to the MR Scan, subjects should be questioned or a current medical history review should occur to determine if there is any history of unexplained syncope (loss of consciousness). If confirmed, the subject should not proceed with the study-required MR scan and be withdrawn from the study.

12.7.2.3 Heart Rhythm Monitoring prior to MRI protection mode programming

It is **required** that the heart rhythm be monitored by the site Principal Investigator or a sub-investigator for all subjects prior to initiation of the MRI Protection Mode and the MR Scan.

- Monitoring is to be performed in VVI 40 programming
- Monitor the heart rhythm using the programmer EGRAMs for at least 5 minutes. Heart rate and any abnormal rhythms, including incidence of ectopy shall be documented.
    - In particular, look for signs of progressive AV nodal block over time, permanent or intermittent complete AV block, or trifascicular block (alternating bundle branch block or PR > 200 ms with LBBB or other bifascicular block) or a paced event (one single paced beat) during this time period. **Any** occurrence of these events will disqualify subjects from undergoing the MRI.
        - Such subjects should be withdrawn from the study.
    - Required ECG documentation
        - 12 lead ECG and a 10s rhythm strip to be printed at any time during the 5 minutes of the monitoring (either from the ECG machine or the BSC PRM)
        - Any abnormal rhythms / ectopy shall be documented with a printed ECG or rhythm strip if possible.

12.7.3 MR Scans

The MR scan must be performed within the guidelines of this protocol and the *BSC MRI Technical Guide*. When differences exist, the ENABLE MRI Study protocol extends the *BSC MRI Technical Guide.*

MRIs must be performed in 1.5 Tesla, closed bore scanners with body coil excitation. Subjects will complete MR scans per the MR scan sequences protocol in Section 28 of this protocol.

Note: Incidental findings are defined as a "finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study[10]". The MR scans required by the ENABLE MRI Study are not intended for diagnostic purposes. Therefore, they are not intended or required to be read by trained radiologists. If the site's MR technician performing the scan determines any incidental findings, or if a site's procedures dictate that MR scans must be read, any incidental findings must be reported to the site's primary investigator by the person who reads the scan.

Additionally, it is important to note that the Image Artifact core lab (see Section 14.3) will not be required or requested to report incidental findings to BSC or the investigator, and BSC will not be reviewing any images received for diagnostic or incidental finding purposes.

Site investigators must make it clear through the patient informed consent process that the MR scans required by the ENABLE MRI Study are for research only. They are not intended for diagnostic purposes, and will not necessarily be viewed by trained professionals.

12.7.3.1 Programming MRI Protection Mode

Prior to undergoing an MR scan, the ImageReady System must be programmed to the MRI Protection Mode using the PRM. The PRM is to be kept ON and in MRI Zone I or II as close to the MRI room as possible.

WARNING: The PRM is MR Unsafe and must remain outside the MRI site Zone III (and higher) as defined by the American College of Radiology Guidance Document for Safe MR Practices[11]. Under no circumstances should the PRM be brought into the MRI scanner room, (Zone IV), or the control room (Zone III). Programming the PG to MRI Protection Mode should be done as close to the planned start of the MR scan as possible.

1. Start monitoring the subject as outlined in section 12.7.3.3
2. Program the MRI Protection Time-out (nominal setting: 6 hours; programmable values are OFF, 3, 6, 9, 12 hours)

[10] Wolf SM LF, Nelson CA, Kahn JP, Cho MK, Clayton EW, et al. Managing incidental findings in human subjects research: Analysis and recommendations. *J Law Med Ethics*. 2008;36:219
[11] Kanal E, et al., American Journal of Roentgenology 188:1447-74, 2007.

3. Program the PG to the MRI Protection Mode
4. Print the MRI Protection Settings Report. This report documents the MRI Protection Mode settings and details.
    a. If the Time-out feature is used, the report includes the exact time and date when MRI Protection Mode will expire. If the Time-out feature is used, the MRI technologist/radiologist must verify that adequate time remains to complete the scan and to exit the MR scanner room.

Please refer to the *BSC MRI Technical Guide* for more information regarding PG MRI Protection Mode programming and other associated MRI warnings, cautions, and potential adverse events.

12.7.3.2 Heart Rhythm Monitoring after MRI protection mode programming

It is **required** that the heart rhythm be monitored by the site Principal Investigator or a sub-investigator for all subjects after programming MRI protection mode ON and prior to initiation of the MR Scan.

- Monitor the heart rhythm for at least 5 minutes using the monitoring equipment screen. Heart rate and any abnormal rhythms, including incidence of ectopy shall be documented.
    - In particular, look for signs of progressive AV nodal block over time, permanent or intermittent complete AV block, or trifascicular block (alternating bundle branch block or PR > 200 ms with LBBB or other bifascicular block) or a sinus pause > 2s during this time period. **Any** occurrence of these events will disqualify subjects from undergoing the MRI.
        - For such subjects, MRI protection mode must be turned OFF. These subjects should be withdrawn from the study.

12.7.3.3 Monitoring of Subjects during the MRI Protection Mode

Subjects must be continuously monitored by the site Principal Investigator or a sub-investigator for the entire duration in which the PG is in MRI Protection Mode. All subject monitoring must be documented (visual and auditory cues are acceptable when the subject is being connected to the equipment defined below).

For the entire duration that the PG is in MRI Protection Mode, the following will be performed:

1. Investigational centers must utilize continuous monitoring of all of the following
    a. ECG (minimum of a 3-lead ECG is required)
    b. Pulse oximetry with waveform monitoring (non-impedance based Finger plethysmography)
    c. Blood pressure

NOTE: Both the ECG and pulse oximeter alarms should be turned to the ON position on the monitoring machine for the entire duration of the MR scan.

2. Ensure that an external defibrillator and medical personnel trained in external defibrillation and cardiopulmonary resuscitation (CPR) are present
3. Subjects must be continuously monitored by the site Principal Investigator or a sub-investigator trained in monitoring hemodynamic stability using ECG, pulse oximetry and blood pressure, along with maintaining normal voice and visual contact.
4. In addition, **for the entire duration of the MR scan**, the following will be performed:
    a. The heart rate, blood pressure and oxygen saturation levels will be documented in 5 ± 2 minutes intervals.
    b. ECG and pulse oximeter alarms must be ON
    c. It is recommended that a rhythm strip is printed at each interval.
    d. If there are any abnormal rhythms, a rhythm strip to document the abnormal rhythm should be printed if possible.

12.7.3.4 MR Scan Sequences Protocol

Refer to Table 28-1 in Section 28 for the MR Scan Sequences Protocol.

The following data is required to be collected:

1. Medications used for sedation in the MR scanner, if applicable
2. MR Scanner manufacturer and model
3. Time of MR scan initiation
4. Time duration for each sequence within the RF intensive and Gradient intensive scans
5. Total duration of RF intensive scan sequences
6. Total duration of Gradient intensive scan sequences
7. Time of MR scan completion

12.7.3.5 Exiting the MRI Protection Mode

Upon completion of the MR scan, program the PG out of the MRI Protection Mode by interrogating the device using the wand (RF telemetry is disabled in MRI Protection Mode). It is recommended to program the PG out of MRI Protection Mode as close to the end of MR scan as possible.

- Document the Time of exiting MRI Protection Mode.

Note: The PRM is MR Unsafe and must remain outside the MRI site Zone III (and higher). Under no circumstances should the PRM be brought into the MRI scanner room, the control room, or the MRI site Zone III or IV areas.

Upon exiting the MRI Protection Mode, all parameters are restored to pre-MRI Protection Mode values with two exceptions:

- Restoration of function of the Minute Ventilation[12] (MV) sensor is delayed. If MV was programmed to ON or Passive at the time of entry into MRI Protection Mode, upon exit from the mode, an automatic six hour calibration of the sensor will begin. MV-driven rate response is not available during this calibration period. If MV-driven rate response is desired sooner, a manual calibration can be performed.
- The Beeper will remain OFF upon exiting MRI Protection Mode.

12.7.4 Device Evaluation after the MR Scan

1. All implanted leads will be evaluated within two hours upon exit from the MRI Protection Mode through the implanted PG **for THREE separate consecutive sets of measurements** using the test parameters listed in Table 12-3:
   - Manual pacing threshold tests, as defined in sections 12.5.1.1, 12.5.1.2 and 12.5.1.3. Sensing amplitude
   - Impedance
   - Shock impedance (RV lead only)
2. Test for phrenic nerve stimulation (PNS) and measure the PNS threshold if detected in the programmed LV lead configuration
3. Perform an assessment of Beeper function as defined in section 12.7.1.1. After performing the assessment of the Beeper, if the Beeper is audible, the user may choose to manually re-enable the Beeper.

Record the measurements in the EDC system.

12.7.5 Completing the MRI Visit

1. The PG data must be reviewed to document whether any episodes of polymorphic or monomorphic VT or VF that required ATP or shock therapy are present, following the MR scan.
   a. If polymorphic or monomorphic VT or VF episodes are present:
      i. Print the 'Arrhythmia Logbook' and 'Selected Episodes Report' (counters and EGMs) using the PRM
      ii. A copy of the Selected Episode Report(s) with counters and EGMs is expected to be submitted to Boston Scientific **within 5 business days** using the upload tool in the EDC system

[12] Only available internationally outside the US

iii. If a physical copy of the Selected Episode Report(s) is to be submitted (instead of an electronic upload), the copy is expected to be submitted to the ECG Core Lab **within 5 business days**

2. Program the device according to physician discretion, and indicate if any permanent device programming was changed
3. Print the 'Quick Notes' Report
4. Perform a Save All:
   a. Save device data to a USB using the programmer "Save All" feature
   b. Label the USB with the subject ID#, Date, and "MRI"
   c. Retain the original USB at the center, and a copy is expected to be submitted to Boston Scientific **within 5 business days** using the upload tool in the EDC system
      i. If a physical copy of the USB is to be submitted (instead of an electronic upload) use a PC to make the copy and label it the same way as the original. **Do not make a copy by using the programmer a second time as this will create a new USB with slightly different information**
5. Schedule the MRI+1 month follow-up visit.

12.7.6 MRI Visit Source Data Requirements

Source data requirements at the MRI Visit are described in Table 12-6:

Table 12-6: MRI Visit Source Documentation Requirements

Source Documentation Requirement	Disposition
Pre-MR scan: • Assessment of patient history of unexplained syncope • Device Evaluation (pace threshold, sense amplitude, impedance, RV shock impedance, LV Phrenic Stimulation threshold) • PRM ECG strips from manual threshold tests documenting LOC for all implanted leads • Assessment of Beeper function • Printout of 'Quick Notes' Report • Cardiology and Radiology MRI Conditions of Use are satisfied • 12 leads ECG & 10s rhythm strip (either from the ECG machine or the BSC PRM)	Retain at center
While PG is programmed to MRI Protection Mode: • MRI Protection Settings Report • Heart rate, blood pressure, Oxygen saturation levels, and Voice Contact in 5 ± 2 minute intervals	Retain at center

Source Documentation Requirement	Disposition
• Rhythm strip every 5 ± 2 minutes (recommended) • Rhythm strips for abnormal rhythms, as applicable (recommended) • Medications used for sedation in the MR scanner, if applicable • MR Scanner manufacturer and model • Time of MR scan initiation • Time duration for each sequence within the RF intensive and Gradient intensive scans • Total duration of RF intensive scan sequences • Total duration of Gradient intensive scan sequences • Time of MR scan completion	
When PG is programmed out of MRI Protection Mode: • Time of exiting MRI Protection Mode	Retain at center
Post-MR scan: • Device Evaluation (pace threshold, sense amplitude, impedance, RV shock impedance, LV Phrenic Stimulation threshold) • PRM ECG strips from manual threshold tests documenting LOC for all implanted leads • Assessment of Beeper function • Document if polymorphic or monomorphic VT/VF episodes requiring therapy, are present • Documentation of spontaneous VT/VF episode(s) by PRM strips, as applicable: o 'Selected Episodes Report' (counters and EGMs required) o 'Arrhythmia Logbook' • Printout of 'Quick Notes' Report	Retain at center
Adverse Events	Retain at center
MR scanner DICOM dump/ report file including items such as scan sequence settings and durations as well as calculated scan metrics such as whole body average SAR. **The DICOM file must contain both images and scan sequence data.**	Retain the original at the center and submit a copy to Boston Scientific
Save All	Retain the original at the center and submit a copy to Boston Scientific

12.8 MRI + 1 Month Visit (Phase I only)

The MRI + 1 Month Visit must be performed as a clinic visit and will occur at 30 ± 7 days after the MRI Visit.

12.8.1 Device Evaluation

1. All implanted leads will be evaluated through the implanted PG **for THREE separate consecutive sets of measurements** using the test parameters listed in Table 12-3:
   - Manual pacing threshold tests, as defined in sections 12.5.1.1, 12.5.1.2 and 12.5.1.3.
   - Sensing amplitude
   - Impedance
   - Shock impedance (RV lead only)
2. Test for phrenic nerve stimulation (PNS) and measure the PNS threshold if detected in the programmed LV lead configuration

Record the measurements in the EDC system.

12.8.2 VF Induction

Subjects who successfully complete the study required MRI scan and either qualify for the "for-cause" VF induction or consented to be part of the VF induction Sub-study will undergo a VF Induction.

"For cause" VF induction is required if the below criteria are met at the MRI + 1 Month Visit:

- A reduction in the RV lead R-wave amplitude of > 50% post-MRI, as measured at the MRI + 1 Month Visit compared to the pre MRI value collected during the MRI Visit, with a RV lead R wave that is greater than or equal to 5 mV post-MRI as measured during the MRI + 1 Month Visit

"For cause" VF inductions are ideally performed at the MRI + 1 Month Visit, but may be performed up to 14 calendar days after the MRI + 1 Month Visit.

Subjects will be assessed for clinical stability prior to performing the VF induction testing (both those subjects who qualify for the "for-cause induction and those who are part of the VF induction Sub-study), per physician discretion. The following criteria should be considered prior to performing VF Induction testing:

1. Unstable heart failure requiring hospitalization in the last 30 calendar days
2. Unable to tolerate sedation (e.g. IV sedation, general anesthesia)
3. Planned cardiac revascularization procedure

4. Evidence of lead fracture or lead dislodgment
5. Evidence of PG malfunction (i.e. error code)
6. Right Ventricular Lead R wave is less than 5 mV

Subjects determined to be clinically stable will undergo VF Induction testing according to the following procedure:

1. Subjects will undergo IV sedation or general anesthesia, according to local standard of care for VF induction testing.
2. Program the following settings:
   - 1-Zone, VF
   - Rate = 180 bpm or less. Lower than 180 bpm may be appropriate based on patient's previous history, per physician's discretion
   - Sensitivity: 0.6 mV or less (more sensitive – 0.15 to 0.6 mV)
3. Perform the VF induction test through the implanted ICD/CRT-D through the *EP Tests* screen
4. Select the VF Induction method at the discretion of the physician (e.g. 50 Hz Manual Burst, Shock on T, V Fib, etc.)
   a. Begin printing a real-time ECG and electrograms with markers prior to starting the induction
   b. Initiate the VF induction testing
   c. If an arrhythmia is induced and the device has not started charging after 16 seconds, then the physician may choose to apply therapy through alternative methods; e.g. Stat Shock or external defibrillation
   d. Upon rhythm termination, stop the ECG and electrograms
5. If the first induction attempt induces monomorphic or polymorphic VT; or the VF spontaneously terminates prior to charging
   a. Treat as needed
   b. Attempt second VF induction using a different induction method or induction parameters (e.g. Shock on T with different Shock Coupling, Fib High longer duration etc.) A maximum of two VF induction attempts is allowed per subject. A VF Induction attempt is defined as an attempt to induce VF that results in an episode entry in the Arrhythmia Logbook, i.e. NSVT, VF/VT that spontaneously terminates.
6. Upload into the EDC all induced episodes **within 5 business days**

a. If a physical copy of induced episode(s) is to be submitted (instead of an electronic upload), the copy is expected to be submitted to the ECG Core Lab **within 5 business days**

When the VF Induction testing is complete, program the device, per physician discretion.

When 25 VF episodes in 25 subjects post MRI scan are confirmed (combination of spontaneous VF episodes, "for-cause" and VF Induction Sub-study VF episodes) by the ECG Core Lab, sites will be notified by BSC to stop all VF induction testing. This includes "for-cause" inductions, and VF Induction Sub-study inductions that were planned but not yet completed.

12.8.3 Completing the MRI + 1 Month Visit

1. The PG data must be reviewed to document whether any new episodes of polymorphic or monomorphic VT or VF that required ATP or shock therapy are present, following the MRI visit.
   a. If polymorphic or monomorphic VT or VF episodes are present:
      i. Print the 'Arrhythmia Logbook' and 'Selected Episodes Report' (counters and EGMs) using the PRM
      ii. A copy of the Selected Episode Report(s) with counters and EGMs is expected to be submitted to Boston Scientific **within 5 business days** using the upload tool in the EDC system
      iii. If a physical copy of the Selected Episode Report(s) is to be submitted (instead of an electronic upload), the copy is expected to be submitted to the ECG Core Lab **within 5 business days**
2. Program the device according to physician discretion, and indicate if any permanent device programming was changed
3. Print the 'Quick Notes' Report
4. Perform a Save All:
   a. Save device data to a USB using the programmer "Save All" feature
   b. Label the USB with the subject ID#, Date, and "MRI + 1 month"
   c. Retain the original USB at the center, a copy is expected to be submitted to Boston Scientific **within 5 business days** using the upload tool in the EDC system
      i. If a physical copy of the USB is to be submitted (instead of an electronic upload) use a PC to make the copy and label it the same way as the

original. **Do not make a copy by using the programmer a second time as this will create a new USB with slightly different information.**

5. Schedule the Annual follow-up visit.

12.8.4 MRI + 1 Month Visit Source Data Requirements

Source data requirements at MRI+1 month Visit are described in Table 12-7:

Table 12-7: MRI + 1 Month Source Documentation Requirements

Source Documentation Requirement	Disposition
Device Evaluation (pace threshold, sense amplitude, impedance, RV shock impedance, LV Phrenic Stimulation threshold)	Retain at center
PRM ECG strips from manual threshold tests documenting LOC for all implanted leads	
VF Induction real-time ECG and electrogram strips, if VF induction occurred	
Printout of 'Quick Notes' Report and 'Devices Settings Report' showing the VF induction settings, if VF induction occurred	
Documentation of spontaneous VT/VF episode(s) by PRM strips, as applicable: • 'Selected Episodes Report' (counters and EGMs required) • 'Arrhythmia Logbook'	
Printout of Final 'Quick Notes' Report	
Adverse Events	
Save All	Retain the original at the center and submit a copy to Boston Scientific

12.9 Every Three-month Follow ups through Three Years (Recommended)

For Phase I and Phase II patients with a MR scan (study required MR scan or medically necessary MR scan):

- If the patient is followed on LATITUDE NXT, monitoring of device performance is strongly recommended at least every 3 months
- If the patient is not followed on LATITUDE NXT, **an in-clinic follow-up schedule of every three months is strongly recommended to monitor device performance**

Timing for each follow up is:

- First 3-month Follow-up: 90±30 days from MRI visit

- Second 3-month Follow-up: 180±30 days from MRI visit
- Third 3-month Follow-up: 270±30 days, and so on

12.9.1 Device Evaluation

1. The standard of care evaluation for device performance is recommended. Record the available measurements in the EDC system.
    - Pacing thresholds (if LATITUDE NXT is used, collect thresholds if available)
    - Sensing amplitude
    - Impedance
    - Shock impedance (RV lead only)
2. If any new episodes of polymorphic or monomorphic VT or VF that required ATP or shock therapy are present since the prior study visit:
    i. Print the 'Arrhythmia Logbook' and 'Selected Episodes Report' (counters and EGMs)
    ii. A copy of the Selected Episode Report(s) with counters and EGMs is expected to be submitted to Boston Scientific **within 5 business days** using the upload tool in the EDC system
    iii. If a physical copy of the Selected Episode Report(s) is expected to be submitted (instead of an electronic upload), the copy must be submitted to the ECG Core Lab **within 5 business days**
3. Program the device according to physician discretion, if applicable
4. Print the 'Quick Notes' Report

12.9.2 Every Three-month Visit Source Data Requirements

Source data requirements at Every Three-month visits are described in Table 12-8.

Table 12-8: Every Three Month Source Documentation Requirements

Source Documentation Requirement	Disposition
Document if polymorphic or monomorphic VT/VF episodes requiring therapy, are present Documentation of VT/VF episode(s) by PRM strips, as applicable: • 'Selected Episodes Report' (counters and EGMs required) • 'Arrhythmia Logbook'	Retain at center
Printout of 'Quick Notes' Report	
Adverse Events	

12.10 Annual Follow ups through Three Years

For de novo: Annual follow-ups must be performed as an in-clinic visit, starting at one year post implant and continuing until 3 years post implant.

For existing implants: Annual follow-ups must be performed as a clinic visit, starting at one year post enrollment and continuing until 3 years post enrollment.

Timing for each follow up is:

- 1 Year Follow-up: 365±90 days
- 2 Year Follow-up: 730±90 days
- 3 Year Follow-up: 1095±90 days

12.10.1 Standard Device Evaluation

All implanted leads will be evaluated through the implanted PG for:

- Manual pacing threshold tests (testing parameters per physician discretion)
- Sensing amplitude
- Impedance
- Shock impedance (RV lead only)

Record the measurements in the EDC system.

12.10.2 Completing the Annual Visit

1. For all annual visits after an MR scan, the PG data must be reviewed to document whether any new episodes of polymorphic or monomorphic VT or VF that required ATP or shock therapy are present since the prior study visit.
    a. If polymorphic or monomorphic VT or VF episodes are present:
        i. Print the 'Arrhythmia Logbook' and 'Selected Episodes Report' (counters and EGMs) using the PRM
        ii. A copy of the Selected Episode Report(s) with counters and EGMs is expected to be submitted to Boston Scientific **within 5 business days** using the upload tool in the EDC system
        iii. If a physical copy of the Selected Episode Report(s) is to be submitted (instead of an electronic upload), the copy is expected to be submitted to the ECG Core Lab **within 5 business days**

2. Program the device according to physician discretion
3. Print the 'Quick Notes' Report
4. Perform a Save All:
    a. Save device data to a USB using the programmer "Save All" feature
    b. Label the USB with the subject ID#, Date, and "Annual"
    c. Retain the original USB at the center, and a copy is expected to be submitted to Boston Scientific **within 5 business days** using the upload tool in the EDC system
        i. If a physical copy of the USB is to be submitted (instead of an electronic upload) use a PC to make the copy and label it the same way as the original. **Do not make a copy by using the programmer a second time as this will create a new USB with slightly different information.**
5. Schedule the next annual follow-up visit.

12.10.3 Annual Visit Source Data Requirements

Source data requirements at annual visits are described in Table 12-9.

Table 12-9: Annual Source Documentation Requirements

Source Documentation Requirement	Disposition
Device Evaluation (pace threshold, sense amplitude, impedance, RV shock impedance)	Retain at center
PRM ECG strips from manual threshold tests documenting LOC for all implanted leads	
Document if polymorphic or monomorphic VT/VF episodes requiring therapy, are present Documentation of VT/VF episode(s) by PRM strips, as applicable: • 'Selected Episodes Report' (counters and EGMs required) • 'Arrhythmia Logbook'	
Printout of 'Quick Notes' Report	
Adverse Events	
Save All	Retain the original at the center and submit a copy to Boston Scientific

12.11 Additional Visits

An Additional Follow-up Visit will be reported when an office/clinic visit identifies a reportable event and the device is interrogated (see Section 22.1). If possible, a device evaluation and lead measurements should be performed and the results recorded in the EDC system.

12.11.1 Required Data Collection

1. Complete the Additional Follow-up form
2. Collect any adverse event information
3. Print the 'Quick Notes' Report

12.11.2 Recommended Data Collection

1. It is recommended to conduct a device evaluation:
   - Manual pacing threshold tests
   - Sensing amplitude
   - Impedance
   - Shock impedance (RV lead only)
2. For all additional visits after an MR scan, the PG data should be reviewed to document whether any new episodes of polymorphic or monomorphic VT or VF that required ATP or shock therapy are present since the prior study visit.
   a. If polymorphic or monomorphic VT or VF episodes are present:
      i. Print the 'Arrhythmia Logbook' and 'Selected Episodes Report' (counters and EGMs) using the PRM
      ii. A copy of the Selected Episode Report(s) with counters and EGMs is expected to be submitted to Boston Scientific **within 5 business days** using the upload tool in the EDC system
      iii. If a physical copy of the Selected Episode Report(s) is to be submitted (instead of an electronic upload), the copy is expected to be submitted to the ECG Core Lab **within 5 business days**
3. Perform a Save All:
   a. Save device data to a USB using the programmer "Save All" feature
   b. Label the USB with the subject ID#, Date, and "Additional Follow-up"
   c. Retain the original USB at the center, and a copy is expected to be submitted to Boston Scientific within **5 business days** using the upload tool in the EDC system
      i. If a physical copy of the USB is to be submitted (instead of an electronic upload) use a PC to make the copy and label it the same way as the original. **Do not make a copy by using the programmer a second time as this will create a new USB with slightly different information.**

Record the measurements in the EDC system for any tests performed.

12.11.3 Additional Follow-up Visit Source Data Requirements

Source data Requirements at Additional Follow-up Visit are described in Table 12-10.

Table 12-10: Additional Follow-up Source Documentation Requirements

Source Documentation Requirements	Disposition
Device Evaluation (pace threshold, sense amplitude, impedance, RV shock impedance), as applicable	Retain at center
PRM ECG strips from manual threshold tests documenting LOC for all implanted leads	
Document if polymorphic or monomorphic VT/VF episodes requiring therapy, are present *Documentation of VT/VF episode(s) by PRM strips, as applicable:* • *'Selected Episodes Report' (counters and EGMs required)* • *'Arrhythmia Logbook'*	
Printout of 'Quick Notes' Report	
Adverse Events	
Save All, as applicable	Retain the original at the center and submit a copy to Boston Scientific

Text in table that is italicized is recommended

12.12 Medically Necessary MRI Visits

During the study, if a subject needs a medically necessary MR scan, BSC recommends the subject be directed to have the scan at the Study site.

Note: In case the medically necessary MR scan is performed at a non-investigational site, all efforts must be made to collect the data and adhere to the MRI Conditions of Use.

Study flow is identical to the MRI visit as described in section 12.7. Some data collection is optional for Medically Necessary MRI visit as shown in italic in Table 12-11.

For medically necessary MRI scans, all activities performed by the site Principal Investigator or a sub-investigator at the MRI visit (i.e. heart rhythm monitoring, hemodynamic monitoring) can be performed by a trained and qualified Health Care Professional (HCP).

As for the MRI visit, it is recommended to have a programmer powered ON in Zone II near the MRI room in case the patient develops the urgent need for pacing.

12.12.1 Medically Necessary MRI Visit Source Data Requirements

Source data Requirements for medically necessary MR scans are described in Table 12-11:

Table 12-11: Medically Necessary MRI Visit Source Documentation Requirements

Source Documentation Requirement	Disposition
Pre-MR scan: • Body Part scanned • Assessment of patient history of unexplained syncope • *Device Evaluation (pace threshold, sense amplitude, impedance, RV shock impedance, LV Phrenic Stimulation threshold)* • *PRM ECG strips from manual threshold tests documenting LOC for all implanted leads* • Assessment of Beeper function • Printout of 'Quick Notes' Report • Cardiology and Radiology MRI Conditions of Use are satisfied • 12 leads ECG & 10s rhythm strip (either from the ECG machine or the BSC PRM)	Retain at center
While PG is programmed to MRI Protection Mode: • MRI Protection Settings Report • Time of MR scan initiation • *Time of MR scan completion* • *Heart rate, blood pressure, Oxygen saturation levels, and Voice Contact in 5 ± 2 minute intervals* • *Medications used for sedation in the MR scanner, if applicable* • *MR Scanner manufacturer and model*	Retain at center
When PG is programmed out of MRI Protection Mode: • Time of exiting MRI Protection Mode	Retain at center

Post-MR scan:
• *Device Evaluation (pace threshold, sense amplitude, impedance, RV shock impedance, LV Phrenic Stimulation threshold)*
• *PRM ECG strips from manual threshold tests documenting LOC for all implanted leads*
• Assessment of Beeper function
• *Document if polymorphic or monomorphic VT/VF episodes requiring therapy, are present*
• *Documentation of spontaneous VT/VF episode(s) by PRM strips, as applicable:*
  ○ *'Selected Episodes Report' (counters and EGMs required)*
  ○ *'Arrhythmia Logbook'*
• Printout of 'Quick Notes' Report
	Retain at center

Adverse Events	Retain at center

MR scanner DICOM dump/ report file including items such as scan sequence settings and durations as well as calculated scan metrics such as whole body average SAR. ***The DICOM file must contain both images and scan sequence data.***	Retain the original at the center and submit a copy to Boston Scientific
Save All	Retain the original at the center and submit a copy to Boston Scientific

Text in table that is italicized is recommended

12.13 Study Completion

Subjects will be followed until completion of the 3-year annual follow-up visit. In the US, if a subject receives an investigational lead(s) that is not approved by the FDA before the 3-year annual follow-up, then the subject will be followed until the investigation lead(s) is approved, explanted, or until study closure. Upon completion of participation in the study, subjects will be followed per normal standard of care.

13. Statistical Considerations

13.1 Endpoints (Phase I only)

All Phase I subjects who consent to be part of the VF Sub-study or require a "for-cause" VF induction will contribute to the ancillary analysis of VT/VF assessment.

13.1.1 Primary Safety Endpoint: MR Scan-Related ImageReady System Complication Free Rate

The primary safety endpoint will be assessed for all subjects who undergo any portion of the study-required MR scan sequences. Safety will be confirmed by evaluating the **MR scan-related ImageReady System** Complication-free rate (CFR) between the MR Scan and the MRI Visit + 1 Month. For the purpose of this endpoint, a MR scan-related ImageReady System complication will be defined as those complications that are related to the MR scan and ImageReady System. All complications that the site reports as related to the MR scan and ImageReady System will be adjudicated by an external committee for relation to the MR scan. Complications that are determined to be associated with the MR scan will be considered MR scan-related complications and count against this endpoint.

13.1.1.1 Hypotheses

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

H_0: The MR Scan-related CFR rate between MR Scan and MRI Visit + 1 Month ≤ 90%

H_A: The MR Scan-related CFR rate between MR Scan and MRI Visit + 1 Month > 90%.

13.1.1.2 Sample Size

[redacted]

13.1.1.3 Statistical Methods

Endpoint analysis will be performed on all subjects that undergo an MR scan (study sequence is initiated), including subjects that have an incomplete scan. However, if a medically necessary scan occurs between implant and the MRI + 1 Month Visit, data for that subject will not be included in this endpoint.

[redacted]

The Kaplan-Meier methodology was chosen for this endpoint to utilize all available data for each subject. Subjects, who did not undergo an MR scan, i.e., the study sequence was not initiated, will be considered to have missing data. To assess the robustness of this analysis method and the potential impact missing data could have had on the analysis results, a tipping point analysis will be conducted that will include enrolled subjects. The tipping point analysis will assign each subject with missing data as either having or not having a MR Scan-related complication. All possible combinations of these patients' data will be evaluated along with the actual observed data to find the point, if any, at which the endpoint is failed.

13.1.2 Primary RV Effectiveness Endpoint 1: Pre-MR Scan vs. 1 Month Post-MR Scan RV Pacing Threshold at 0.5 ms

Increases in RV pacing threshold (at 0.5 ms) pre- MR scan and 1 Month post-MR scan will be calculated for subjects. Subjects that have an increase in average pacing thresholds ≤ 0.5V (at 0.5 ms) from pre-MR Scan to MRI Visit + 1 Month follow-up will be considered a success.

13.1.2.1 Hypotheses

The following hypotheses will be used to evaluate the Primary RV Effectiveness Endpoint 1:

H_0: The RV Pacing Threshold Success Rate ≤ 87%

H_A: The RV Pacing Threshold Success Rate > 87%.

13.1.2.2 Sample Size

[redacted]

13.1.2.3 Statistical Methods

Multiple RV pacing threshold measurements taken at each of the two visits (MRI Visit and the MRI Visit + 1 Month) will be averaged to determine the average RV pacing threshold at each visit for each subject. The change in average pacing thresholds will then be calculated for each subject and compared to 0.5V to determine success or failure. Subjects that have an increase in average pacing thresholds (pre-MR Scan and at the MRI visit + 1 Month follow-up) ≤ 0.5V will be considered a success. [redacted]

All variations of RV leads and lead families will be pooled for this endpoint.

Primary RV Effectiveness Endpoint 1 will be analyzed by per-protocol analysis. The per-protocol analysis will only include subjects who received an MR Scan, and will not include subjects that meet any of the following exclusions:

- Has a medically necessary scan between implant and the MRI + 1 Month Visit
- Fails to meet labeled MRI Conditions of Use

- Experiences a lead-related complication between MRI Visit and the MRI + 1 Month Visit
- Has an incomplete scan based on the ENABLE MRI Study MR Scan Sequences

The per-protocol analysis will consider the subjects without paired RV pacing threshold measurements as having missing data, in addition to any subject that meets an exclusion listed above. To assess the impact missing data could have had on the analysis results, a tipping point analysis will be conducted. The analysis will assign each subject with missing data as either a failure or success. All possible combinations of these patients' data will be evaluated along with the actual observed data to find the point, if any, at which the endpoint has failed.

13.1.3 Primary RV Effectiveness Endpoint 2: Pre-MR scan vs. 1 Month Post-MR Scan RV Sensed Amplitude

Decreases in RV sensed amplitude pre-MR scan and 1 Month post-MR scan will be calculated for subjects. Subjects will be considered a success if the average sensed amplitude at the MRI + 1 Month Visit remains ≥ 5.0 mV and above 50% of the pre-MR scan value. Subjects who have an average pre-scan RV sensed amplitude measurement < 5.0 mV will be excluded from this analysis.

13.1.3.1 Hypotheses

The following hypotheses will be used to evaluate the Primary RV Effectiveness Endpoint 2:

H_0: The RV Sensed Amplitude Success Rate ≤ 85%

H_A: The RV Sensed Amplitude Success Rate > 85%.

13.1.3.2 Sample Size

[redacted]

[redacted]

13.1.3.3 Statistical Methods

Multiple RV sensed amplitude measurements taken at each of the two visits (MRI Visit and the MRI + 1 Month Visit) will be averaged to determine the average RV sensed amplitude at each visit for each subject. The percent of subjects meeting the success criteria will be calculated. [redacted]

All variations of RV leads and lead families will be pooled for this endpoint.

Primary RV Effectiveness Endpoint 2 will be analyzed by per-protocol analysis. The per-protocol analysis will only include subjects who received an MR Scan, and will not include subjects that meet any of the following exclusions:

- Has a medically necessary scan between implant and the MRI + 1 Month Visit
- Fails to meet labeled MRI Conditions of Use
- Experiences a lead-related complication between MRI Visit and the MRI + 1 Month Visit
- Has an incomplete scan based on the ENABLE MRI Study MR Scan Sequences
- Average RV sensed amplitude <5mV pre-MR scan

The per-protocol analysis will consider the subjects without paired RV sensed amplitude measurements as having missing data, in addition to any subject that meets an exclusion listed above. To assess the impact missing data could have had on the analysis results, a tipping point analysis will be conducted. The analysis will assign each subject with missing data as either a failure or success. All possible combinations of these patients' data will be evaluated along with the actual observed data to find the point, if any, at which the endpoint is failed.

13.1.4 Primary LV Effectiveness Endpoint 1: Pre MR Scan- vs. 1 Month Post-MR Scan LV Pacing Threshold at 0.5 ms

Increases in average LV pacing threshold (at 0.5 ms) pre- MR scan and 1 Month post-MR scan will be calculated for subjects. Subjects that have an increase in pacing thresholds measurements ≤ 1.0V (at 0.5 ms) from pre-MR Scan at MRI Visit to MRI + 1 Month Visit will be considered a success.

13.1.4.1 Hypotheses

The following hypotheses will be used to evaluate the Primary LV Effectiveness Endpoint 1:

H_0: The LV Pacing Threshold Success Rate $\leq 87\%$

H_A: The LV Pacing Threshold Success Rate > 87%.

13.1.4.2 Sample Size

[redacted]

13.1.4.3 Statistical Methods

Multiple LV pacing threshold measurements taken at each of the two visits (MRI Visit and the MRI + 1 Month Visit) will be averaged to determine the average LV pacing threshold at each visit for each subject. The change in average pacing thresholds will then be calculated for each subject and compared to 1.0V to determine success or failure, and the percent of subjects meeting the success criteria will be calculated. [redacted]

Primary LV Effectiveness Endpoint 1 will be analyzed by per-protocol analysis. The per-protocol analysis will only include subjects who received an MR Scan, and will not include subjects that meet any of the following exclusions:

- Has a medically necessary scan between implant and the MRI + 1 Month Visit
- Fails to meet labeled MRI Conditions of Use
- Experiences a lead-related complication between MRI Visit and the MRI + 1 Month Visit
- Has an incomplete scan based on the ENABLE MRI Study MR Scan Sequences

The per-protocol analysis will consider the subjects without paired LV pacing threshold measurements as having missing data, in addition to any subject that meets an exclusion

listed above. To assess the impact missing data could have on the analysis results, a tipping point analysis will be conducted. The analysis will assign each subject with missing data as either a failure or success. All possible combinations of these patients' data will be evaluated along with the actual observed data to find the point, if any, at which the endpoint has failed.

13.1.5 Primary LV Effectiveness Endpoint 2: Pre-MR scan vs. 1 Month Post-MR Scan LV Sensed Amplitude

Decreases in average LV sensed amplitude pre-MR scan and 1 Month post-MR scan will be calculated for subjects. Subjects will be considered a success if the average sensed amplitude at the MRI + 1 Month Visit remains ≥ 5.0 mV and above 50% of the average pre-MR Scan value. Subjects who have an average pre-scan LV sensed amplitude measurement < 5.0 mV will be excluded from this analysis.

13.1.5.1 Hypotheses

The following hypotheses will be used to evaluate the Primary LV Effectiveness Endpoint 2:

H_0: The LV Sensed Amplitude Success Rate ≤ 85%

H_A: The LV Sensed Amplitude Success Rate > 85%.

13.1.5.2 Sample Size

[redacted]

13.1.5.3 Statistical Methods

Multiple LV sensed amplitude measurements taken at each of the two visits (MRI Visit and the MRI + 1 Month Visit) will be averaged to determine the average LV sensed amplitude at each visit for each subject. The percent of subjects meeting the success criteria will be calculated. [redacted]

[redacted]

Primary LV Effectiveness Endpoint 2 will be analyzed by per-protocol analysis. The per-protocol analysis will only include subjects who received an MR Scan, and will not include subjects that meet any of the following exclusions:

- Has a medically necessary scan between implant and the MRI + 1 Month Visit
- Fails to meet labeled MRI Conditions of Use
- Experiences a lead-related complication between MRI Visit and the MRI + 1 Month Visit
- Has an incomplete scan based on the ENABLE MRI Study MR Scan Sequences
- Average LV sensed amplitude <5mV pre-MR scan

The per-protocol analysis will consider the subjects without paired LV sensed amplitude measurements as having missing data, in addition to any subject that meets an exclusion listed above. To assess the impact missing data could have had on the analysis results, a tipping point analysis will be conducted. The analysis will assign each subject with missing data as either a failure or success. All possible combinations of these patients' data will be evaluated along with the actual observed data to find the point, if any, at which the endpoint is failed.

13.2 Ancillary Assessments

The ancillary endpoints are not formal endpoints and are not statistically powered.

13.2.1 Assessment of RV and LV Impedances

The changes in RV and LV impedances pre-MR scan versus 1 Month post-MR scan (MRI Visit and MRI + 1 Month Visit) will be presented in the study report. There are no success criteria for impedances, so a failure rate will not be presented.

13.2.2 Assessment of RA lead measurements

The changes in RA lead measurements including pacing thresholds, sensed amplitudes and impedances, between pre- and 1 Month post-MR scan measurements will be presented in the study report. Also a summary by lead family, INGEVITY MRI and FINELINE II, will be presented. There are no success criteria for RA lead measurements, so a failure rate will not be presented.

13.2.3 Assessment on MR Scan Effect on Lead Measurements

If a subject fails any of the effectiveness endpoints, it may indicate a potential MR scan effect on the corresponding lead for that endpoint. However if the same subject fails both the pacing threshold and sensed amplitude effectiveness endpoints, this would represent stronger evidence of MR Scan effect on the corresponding lead. Summaries of the subjects failing

both the pacing threshold and sensed amplitude effectiveness endpoints for each chamber will be included in the study report.

13.2.4 Assessment of VT/VF

In Phase I, VT and VF episodes from the following three sources will be collected and analyzed:

- Spontaneous VT/VF episodes that required therapy
- VT/VF episodes from "for-cause" VF induction
- VF Induction Sub-study VT and VF episodes

The VT/VF episodes will be evaluated by an ECG Core Lab. The performance objective is to demonstrate the continued ability of the ImageReady MR Conditional Defibrillation System to sense and detect VF post-MR scan (Phase I). Any instances of a detection delay of $\geq$5 seconds above the detection time expected, based on the VF rate and programming, will be further evaluated and the analysis will be provided.

In addition, Boston Scientific plans to collect available spontaneous VT/VF episodes post MR scan from Phase I and II subjects over a 3-year follow-up period. The VT/VF episodes will be evaluated by an ECG core lab. A summary of the results from the ECG core lab will be included in the study report.

13.2.5 Assessment of Effect of Medically Necessary MR Scans

Boston Scientific proposes to collect available data on medically necessary MR scans (MNS) from Phase I and II subjects over a 3-year follow-up period. A summary of changes in lead measurements pre- to post- MNS and any MNS related complications will be presented.

To assess the additive effect of multiple MR scans, the same summaries will be done for subjects with multiple MR scans.

13.2.6 Assessment of Beeper Function

As the beeper function may be affected by the MR Scanner static magnet field, beeper functionality will be summarized using descriptive statistics, for pre- and post-scan, for both the study required MR scans and MNS scans.

13.2.7 Assessment of Programming the MRI Protection Mode

In order to understand the use of the MRI Protection Mode, the following time durations will be summarized using descriptive statistics for both study-related MR scans and medically necessary MR scans:

- Duration of the PG in the MRI Protection Mode
- Time from the start of the MRI Protection Mode to the start of the MR scan
- Time from the end of the MR scan to exiting the MRI Protection Mode

13.2.8 Assessment of Image Artifacts for non-medically necessary MR scans

The image artifact core laboratory will evaluate the MR scan image artifacts in a subset of the non-medically necessary MR scan images from Phase I of the study. The results from the core lab analysis will be summarized in the study report.

13.3 Sample Size Summary

The study will enroll a total of 500 subjects.

The estimated sample size for Phase I is based on the following assumptions:

The sample size for the whole study was chosen at up to 500 subjects in order to observe 30 spontaneous VT/VF episodes post MRI scan.

13.4 General Statistical Methods

13.4.1 Control of Systematic Error/Bias

Selection of patients will be made from the Investigator's usual patient load. All patients meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study. To control for inter-observer variability among sites, an independent Clinical Events Committee (CEC) will determine the MR Scan-related ImageReady System complications to be used in the analysis of the Primary Safety Endpoint.

13.4.2 Control of Type I Error

Each primary effectiveness endpoints can be tested at the significance level of 5% and the primary safety endpoint can be tested at the significance level of 2.5% while still maintaining the overall type I error level at no greater than 5%. This follows the methodology of the Intersection-Union Test (IUT).

13.4.3 Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to implant or attempt more than 100 subjects (20% of the maximum number of subjects).

13.5 Data Analyses

The following data analyses are planned for the ENABLE MRI Clinical Study:

13.5.1 Interim Analyses

No formal interim analyses are planned for the purpose of stopping the study early for declaring effectiveness or for futility. The interim analysis being conducted on 20 subjects is to support regulatory requirements and submissions. Analysis of each endpoint will be performed when all applicable data for that endpoint has been collected.

13.5.2 Pooling Analyses

13.5.2.1 Assessment of Pooling Across Device Type

The single chamber ICDs and the CRT-Ds are expected to perform similarly regarding any effect of MRI on RV pacing threshold or RV sensed amplitude as well MR Scan-related complications. Any effects of MRI on tissue surrounding each respective electrode design are expected to be proportionally similar. Therefore, device (PG and lead) type will be pooled for the analyses of all endpoints. Additionally, analysis will be performed for each of the primary safety and effectiveness endpoints 1 and 2 to verify poolability. To assess the impact of device type on each endpoint, a likelihood ratio test from a regression model will be conducted. The regression model may include additional baseline covariates to attempt to adjust for any imbalances between the device type groups, and will examine the effect of device type. The following baseline covariates may be considered for inclusion: age, gender, height, weight and geography. The likelihood ratio test will compare the log likelihoods between a model containing device type as a covariate and a model not containing device type as a covariate. The test will be performed at an α equal to 15%. Endpoint results will be presented for each device type regardless of the poolability analysis results.

13.5.2.2 Assessment of Pooling Across Geographies and Investigational Centers

In addition to testing the poolability of data by device type, the poolability of data by geography and investigational center will be tested. These analyses will be performed to determine whether there are differences between the US and international geographies, and from center-to-center.

A minimum of 50% of Phase I patients will be from the US. Center-to-center heterogeneity will be assessed for each endpoint by performing random effects logistic regression analyses. Centers enrolling 5 subjects or fewer will be combined within region (US versus OUS) into pooled sites of 6 or more subjects for the purpose of this pooling analysis.

Investigational center will be added into the model as a random effect. Centers will be deemed to be heterogeneous if the variance of the random center effect is found to significantly differ from zero. A significance level of 15% will be used for each test.

13.5.2.3 Assessment of Pooling Across protocol versions

The inclusion/exclusion criteria have been updated with version AE. The poolability of data of subjects enrolled under version AE or later will be compared to subjects enrolled under all prior versions of the protocol.

To assess the impact of the protocol version on each endpoint, a likelihood ratio test from a regression model will be conducted. The regression model may include additional baseline covariates to attempt to adjust for any imbalances between the device type groups, and will examine the effect of protocol version. The following baseline covariates may be considered for inclusion: age, gender, height, weight and geography. The likelihood ratio test will compare the log likelihoods between a model containing protocol version as a covariate and a model not containing protocol version as a covariate. The test will be performed at an α equal to 15%. Endpoint results will be presented for each protocol version regardless of the poolability analysis results.

13.5.3 Subgroup Analyses

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

- Device Type (Single Chamber ICD vs. CRT-D) – note that this analysis will not be done for Primary Effectiveness Endpoint 3 or 4,
- Sex (Female vs. Male),
- Geography (International vs. United States),
- Age (< 65 years vs. ≥ 65 years).

The subgroup variable will be added to a logistic regression model. For effectiveness endpoints, treatment and an interaction term of subgroup and treatment will be added as well. A test for significance at the 15% level will be performed. For each subgroup variable in which a significant difference exists, the results for each subgroup will be presented separately. BSC does not plan to seek labeling for these subgroups based on these analyses.

13.5.4 Multivariate Analyses

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

13.5.5 Changes to Planned Analyses

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

14. Data Management

14.1 Data Collection, Processing, and Review

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

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

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

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

14.2 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 ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other 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.

14.3 Image Artifact Core Laboratory

An independent Image Artifact core laboratory will evaluate MR scan image artifact in the torso region in a subset of the MR scan images collected during Phase I of the study. The core lab Radiologist will review a subset of the images from complete scans, based on the Scan Sequences Protocol in Section 28.

14.4 ECG Core Laboratory

An independent core laboratory will evaluate VT/VF episodes collected post-MR scan, during Phase I and Phase II of the study. An electrophysiologist (EP) will review the episodes to assess sensing and detection of the episodes by the PG.

15. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., Institutional Review Board (IRB) / Ethics Committee (EC_/ US Food and Drug Administration (FDA) / Competent Authority (CA) of the revised clinical investigational plan must be obtained prior to implementation.

16. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/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 business days after the emergency occurred, or per prevailing local requirements, if sooner than 5 business days.

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

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

17. Device Accountability

This section applies to sites in the US, as the only geography with investigational devices.

Investigational devices in this study may include the:

- ACUITY X4 leads, and associated accessory items if those items are distributed separately
    - May include de-novo or existing implant

- RELIANCE 4-FRONT, and associated accessory items if those items are distributed separately
    - May include existing implant only

17.1 Device Accountability for Existing Implants of Investigational Leads

Subjects with existing implant of investigational lead(s) from another BSC-sponsored IDE study (NAVIGATE X4 Study, NCT02071173, G130222) are allowed to enroll into the ENABLE MRI Study. Device accountability is managed by the NAVIGATE X4 Study.

17.2 Device Accountability for De-Novo Implants of Investigational Leads

If investigational devices are distributed for this study, they shall be securely maintained, controlled, and used only in this clinical study. Current Boston Scientific processes will be used to track investigational device allocations during the study.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.

The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include the following

- Date of receipt
- Identification of each investigational device (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device was returned/explanted from subject, if applicable
- Date of return of unused, expired, or malfunctioning investigational devices, if applicable.

Written procedures may be required by national regulations.

Upon completion of enrollments, or as directed by Boston Scientific, all unused investigational products must be returned to Boston Scientific.

18. Compliance

18.1 Statement of Compliance

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

18.2 Investigator Responsibilities

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

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

- Prior to beginning the study, sign the Clinical Study Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the 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 protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency as described in this protocol.

- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.

- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

18.2.1 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.

18.3 Institutional Review Board/ Ethics Committee

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

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

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

18.4 Sponsor Responsibilities

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

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

18.4.1 Role of Boston Scientific Representatives

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

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

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Performing lead diagnostic testing using a Pacing System Analyzer or programmer to obtain pacing and sensing thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from Pacing System Analyzers, programmers, and other equipment

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

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

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP

- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

18.5 Insurance

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

19. Monitoring

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

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

20. Potential Risks and Benefits

20.1 Risks Associated with a CRT-D

Patients participating in this study who will receive a CRT-D system will be consented prior to the implant procedure and are subject to the same risks shared by all patients that receive a CRT-D system.

The risks associated with a CRT-D system, including the implant procedure, shall be reviewed with subjects prior to enrollment. Refer to the CRT-D Physician's Technical Manual and CRT-D Reference Guide for additional information related to the CRT-D. The following risks are shared by all subjects who undergo an implant of a CRT-D device and are not unique to the ENABLE MRI Study:

Table 20-1: Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System*	
Air embolism	Lead dislodgment

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System*	
Allergic reaction	Lead fracture
Arterial damage with subsequent stenosis	Lead insulation breakage or abrasion
Bleeding	Lead perforation
Bradycardia	Lead tip deformation and / or breakage
Breakage/failure of the implant instruments	Local tissue reaction
Cardiac tamponade	Loss of capture
Chronic nerve damage	Low amplitude VF signals
Component failure	Malignancy or skin burn due to fluoroscopic radiation
Conductor coil fracture	Myocardial Infarction
Death	Myocardial necrosis
Electrolyte imbalance/ dehydration	Myocardial trauma (e.g., irritability, injury, tissue damage, valve damage)
Elevated thresholds	Myopotential sensing
Erosion	Oversensing / undersensing
Excessive fibrotic tissue growth	Pacemaker-mediated tachycardia (PMT)
Extracardiac stimulation (muscle/ nerve stimulation)	Pericardial rub, effusion
Failure to convert an induced arrhythmia	Pneumothorax
Fluid accumulation	Post-shock rhythm disturbances
Foreign body rejection phenomena	Pulse generator and/or lead migration
Formation of hematomas or seromas	Shunting current during defibrillation with internal or external paddles
Heart block	Syncope
Hemorrhage	Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
Hemothorax	Thrombus, thromboemboli
Inability to defibrillate or pace	Valve damage
Inappropriate therapy (e.g., shocks, and antitachycardia pacing [ATP] where applicable, pacing)	Vasovagal response
Incisional pain	Venous occlusion
Incomplete lead connection with pulse generator	Venous trauma (e.g., perforation, dissection, erosion)
Infection including endocarditis	Worsening heart failure
Insulating myocardium during defibrillation with internal or external paddles	

*From the CRT-D Physician's Technical Manual and Lead Manuals

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

Table 20-2 Potential Adverse Events of a Pulse Generator

List of Potential Adverse Events of a Pulse Generator	
Dependency	Fear that shocking capability may be lost
Depression	Imagined shocking/Fear of shocking while conscious
Fear of premature battery depletion	Fear of device malfunction

* From the CRT-D Physician's Technical Manual

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

Table 20-3: Potential Adverse Events for implantation of a Coronary Venous Lead

List of Potential Adverse Events for Coronary Venous Lead System*	
Allergic reaction to the contrast media	Prolonged exposure to fluoroscopic radiation
Adverse reaction to procedure (e.g., bradycardia, general, respiratory, hypotension)	Renal failure from contrast media used to visualize coronary veins
Coronary venous spasm	

*From the CRT-D Physician's Technical Manual and CV lead Physician's Lead Manual

20.2 Risks Associated with an ICD

Patients participating in this study who will receive an ICD system will be consented prior to the implant procedure and are subject to the same risks shared by all patients that receive an ICD system.

The risks associated with an ICD system, including the implant procedure, shall be reviewed with subjects prior to enrollment. Refer to the ICD physician technical manual and ICD reference guide for additional information related to the ICD. The following risks are shared by all subjects who undergo an implant of an ICD device and are not unique to the ENABLE MRI Study:

Table 20-4: Potential Adverse Events for implantation of a Pulse Generator and/ or Lead System

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System*	
Air embolism	Lead dislodgment
Allergic reaction	Lead fracture
Arterial damage with subsequent stenosis	Lead insulation breakage or abrasion
Bleeding	Lead perforation
Bradycardia	Lead tip deformation and / or breakage
Breakage/failure of the implant instruments	Local tissue reaction
Cardiac tamponade	Loss of capture
Chronic nerve damage	Low amplitude VF signals

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System*	
Component failure	Malignancy or skin burn due to fluoroscopic radiation
Conductor coil fracture	Myocardial Infarction
Death	Myocardial necrosis
Electrolyte imbalance/ dehydration	Myocardial trauma (e.g., irritability, injury, tissue damage, valve damage)
Elevated thresholds	Myopotential sensing
Erosion	Oversensing / undersensing
Excessive fibrotic tissue growth	Pacemaker-mediated tachycardia (PMT)
Extracardiac stimulation (muscle/ nerve stimulation)	Pericardial rub, effusion
Failure to convert an induced arrhythmia	Pneumothorax
Fluid accumulation	Post-shock rhythm disturbances
Foreign body rejection phenomena	Pulse generator and/or lead migration
Formation of hematomas or seromas	Shunting current during defibrillation with internal or external paddles
Heart block	Syncope
Heart failure following chronic RV apical pacing	Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation
Hemorrhage	Thrombus, thromboemboli
Hemothorax	Valve damage
Inability to defibrillate or pace	Vasovagal response
Inappropriate therapy (e.g., shocks, and antitachycardia pacing [ATP] where applicable, pacing)	Venous occlusion
Incisional pain	Venous trauma (e.g. perforation, dissection, erosion)
Incomplete lead connection with pulse generator	Worsening heart failure
Infection including endocarditis	
Insulating myocardium during defibrillation with internal or external paddles	

*From the ICD Physician's Technical Manual and Lead Manuals

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

Table 20-5 Potential Intolerance to a Pulse Generator

List of Potential Intolerance to a Pulse Generator	
Dependency	Fear that shocking capability may be lost
Depression	Imagined shocking/Fear of shocking while conscious
Fear of premature battery depletion	Fear of device malfunction

* From the ICD Physician's Technical Manual

20.3 Risks Associated with the Study Device(s)

The implantable portion of the ImageReady System includes the PG, the pace/ sense lead(s) and defibrillation lead. In the US, the ACUITY X4 LV pacing leads and the RELIANCE 4-FRONT leads may be investigational during a portion or the entire duration of the study. The basic safety and effectiveness of these leads are being studied in separate clinical studies for the US.

The non-implantable portion of the ImageReady System includes the 2868 programmer software application v3.07 or later. The MRI Protection Mode provides for simplified device programming that is available through multiple programming steps of existing features and therefore does not result in additional risk.

There are no additional risks associated with the ImageReady System, other than those included in Sections 20.1 and 20.2. There are additional risks associated with MR scanning of the ImageReady System as described in Section 20.4.

20.4 Risks associated with Participation in the Clinical Study

Phase I subjects will have the added risk of a study-required MRI scan. Phase II subjects and Phase I subjects will have the added risks and benefits associated with a MRI scan if they decide to undergo a medically necessary MR scan. Potential adverse events associated with an MR scan are minimized by assuring that the subject meets the MRI Conditions of Use.

MRI scanning of patients when the Conditions of Use are met could result in the following potential adverse events, as included in the *BSC MRI Technical Guide*:

- Arrhythmia induction
- Bradycardia
- Patient death
- Patient discomfort due to slight movement or heating of the device
- Syncope
- Worsening heart failure

MRI scanning of patients when the Conditions of Use <u>are NOT</u> met could result in the following potential adverse events, as included in the *BSC MRI Technical Guide*:

- Arrhythmia induction
- Bradycardia
- Damage to the pulse generator and/or leads
- Erratic pulse generator behavior
- Inappropriate pacing, inhibition of pacing, failure to pace
- Increased rate of lead dislodgement (within six weeks of implant or revision of system)
- Irregular or intermittent capture or pacing

- Loss of defibrillation therapy
- Pacing threshold changes
- Patient death
- Patient discomfort due to movement or heating of the device
- Physical movement of pulse generator and/or leads
- Sensing changes
- Syncope
- Side effects of pacing at a fixed high rate such as competition with intrinsic rhythms and arrhythmias. Competitive pacing may increase the rate of pacing induced arrhythmia until the device is reprogrammed.
- Worsening heart failure

**Note: It is important to note that the risks listed in this section may lead to the subject requiring a partial or full pacing system replacement.

20.4.1 Beeper

[redacted]

20.4.2 Risks Related to VF Induction Testing

Risks related to the "for cause" or VF Induction Sub-Study testing are outlined below:

List of Potential Risk Related to VF Induction Testing	
Acceleration/induction of atrial or ventricular arrhythmia	Inappropriate sensing
Adverse reaction to induction testing	Signal interference with already implanted heart rhythm management device function or standard of care equipment
Allergic/adverse reactions to medications, including anesthesia	Muscle stimulation
Chest pain (angina)	Myocardial infarction
Death	Reduced cardiac function
Discomfort/pain during or after testing	Shunting current during defibrillation with internal or external paddles
Heart Block	Stroke
Heart Failure	Syncope
Inappropriate pacing of the heart Inappropriate shock delivery	Non-elective Intubation

20.5 Possible Interactions with Concomitant Medical Treatments

The implantable lead(s) of the ImageReady System contain the steroid DXA, 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 ImageReady System.

20.6 Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject

selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

[redacted]

20.7 Anticipated Benefits

Subjects may not receive any benefit from participating in this study. However, medical science and future patients may benefit from their participation in this clinical study.

20.8 Risk to Benefit Rationale

Risk management activities, including hazard analyses and fault tree analysis, have been performed on the ImageReady System to identify and analyze known and foreseeable hazards (in both normal and fault conditions) and reasonably foreseeable sequences or combinations of events that could result from using this product and the risks associated with each hazard. Mitigations have been implemented in the design, processes, and/or labeling and instructions for use of the product to reduce the residual risk of each hazard as necessary and practicable. The hazard analysis has been reviewed and approved and the remaining risks are acceptable when weighed against the intended benefits to the patient.

21. Safety Reporting

All devices used as part of the ImageReady MR Conditional Defibrillation System will be referred to as the study device(s). All reportable events experienced by the study subject after informed consent, whether during or subsequent to the procedure, should be reported through the EDC system. However, in case of any issues where an alternative method of reporting is necessary (i.e. the EDC is not available), please report the event(s) to Boston Scientific by sending the AE Notification Form to the following email address:

enablemri.safety@bsci.com

21.1 Events Reportable by Sites to Sponsor

The Principal Investigator is responsible for determining the reportability of events. Reportable events include the following:

- All Device Related Adverse Events

- All Cardiac Events Related Adverse Events associated with an untoward medical occurrence
    - Pre-existing cardiac conditions are not considered reportable unless the condition has exacerbated
- All Study Procedure Related Adverse Events
- All MRI Scan Related Adverse Events, for both protocol required MR scans and medically necessary scans
- All Adverse Events Related to the use of the MRI Protection Mode
- All Serious Adverse Events (including death), regardless of causality
    - Planned hospitalizations for pre-existing conditions prior to enrolment are not considered a serious adverse event
    - Procedures required by the clinical investigational plan without serious deterioration in health are not considered a serious adverse event
    - For centers in Austria cancer must always be reported as a Serious Adverse Event
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in the physician manuals

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

Events reported to Boston Scientific during the study will be reviewed and reported to comply with applicable regulations (relevant parts of ISO 14155: 2011 and/or 21 CFR Part 812). Investigators will be asked to classify whether an adverse event is considered serious or non-serious, whether it is anticipated or unanticipated (meets USADE/ UADE definition) as defined in Table 21-1 below, and whether it is considered device or procedure related, as defined in section 21.4.2. Any event that is determined to be an unanticipated serious adverse device effect (USADE; ISO 14155: 2011) will also be considered an unanticipated adverse device effect (UADE; CFR Part 812), as defined in Table 21-1 below.

Death should not be recorded as an adverse event. Death should be recorded as an outcome of only one (1) serious adverse event.

21.2 Event Definitions and Classification

Event definitions are provided in Table 21 1, based on ISO 14155-2011 and MEDDEV 2.7/3 12/2010, and 21 CFR Part 812. Reportable Events for this study are defined in Section 22.1

Table 21-1: 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 clinical investigation plan). 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.
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 clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
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 Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or

Table 21-1: Event Definitions

Term	Definition
Ref: 21 CFR Part 812	degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011* *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: EC=Ethics Committee; IRB=Institutional Review Board

Refer to Section 20 for the known risks associated with the study device(s).

21.3 Unanticipated Adverse Device Effects

All devices are subject to occasional random problems or failures. These may manifest themselves in altered pacing or sensing characteristics. There are wide variations in the seriousness of the effects. Refer to the device(s) Physician's Manual for information regarding potential adverse effects.

If the unanticipated adverse device effect is serious or life-threatening, the Investigator is required to notify Boston Scientific, the IRB, and other regulatory authorities as required (e.g., Competent Authority if European center) as soon as possible, but no later than one business day after the Investigator first learns of the effect. For all other unanticipated adverse device effects, Boston Scientific and the IRB must be notified within ten business days.

Boston Scientific will conduct an evaluation of all reported adverse events. If the event is determined to be an unanticipated adverse device effect, Boston Scientific personnel shall notify the Boston Scientific Regulatory department and initiate communication to all reviewing IRBs and participating Investigators within ten business days after initial notice is received.

If Boston Scientific determines that an unanticipated adverse device effect presents an unreasonable risk to patients, the study shall be terminated. The termination shall occur no

later than five days after the termination decision is made and no later than 15 business days after Boston Scientific first received notice of the effect.

21.4 Adverse Event Classification for FDA Reporting

21.4.1 Observation/Complication

Reported events will be classified, by BSC personnel or trained authorized representatives as a clinical observation or complication; as defined in the Table 21-2.

Table 21-2: Definition of Observation and Complication

Clinical Event	Description
Observation	Adverse event that was transient or reversible and corrected with non-invasive interventions, such as reprogramming or oral medications, or was resolved with no intervention or monitoring
Complication	An adverse event that resulted in: death, serious injury* a, correction using invasive intervention**, or permanent loss of device functions***.

* Per 21 CFR 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 adverse event 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 (This is a complication due to the IV antiarrhythmic medication used for the cardioversion.)

Invasive procedures that are purely diagnostic in nature should not be considered as a complication. Examples of procedures that are invasive, but not considered to be an intervention (observation), include:

- Blood draw for laboratory analysis
- Cardiac catheterization in which pressures are recorded, but without therapeutic interventions
- Electrophysiology study to map arrhythmias, but without therapeutic intervention
- Transesophageal echo (TEE)
- Electrical (external) Cardioversion with IV sedation (the IV sedation used is for patient comfort and not part of the treatment)

Other invasive procedures may occur that are not strictly interventional and done for medical convenience rather than medical necessity. These are not considered to be an adverse event since they are not related to an undesirable clinical outcome. Examples include:

- Foley catheter placed in anticipation of a prolonged procedure
- Intravenous fluids or medications related to a diagnostic procedure

***Permanent Loss of device Function is where a malfunction occurs in a manner which there is compromised therapy. For the purposes of this study the following definitions will be utilized:

- **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)
- **Malfunction with compromised therapy – Pulse Generator**: 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.
    - Examples include (but are not limited to): sudden loss of battery voltage; accelerated current drain such that low battery was not detected before loss of therapy sudden malfunction during defibrillation therapy resulting in aborted delivery of therapy; intermittent malfunction where therapy is compromised while in the malfunction state

21.4.2 Adverse Event Type Classification

An Investigator is required to report all reportable events (as defined in Section 21.1) for this study. All adverse events must recorded in the Adverse Event case report form in the EDC system,, including an event description, suspected cause, corrective action, and clinical outcome for the patient.

Upon receipt of adverse event information, CRFs are reviewed by BSC personnel or trained authorized personnel. During the review process, the adverse event is classified as an observation or complication and each event is coded according to the types below. Classifications and type descriptions will be included with the adverse event information in appropriate submissions to the regulatory agencies. If the opinions between the investigator and BSC differ, both opinions will be reported, as appropriate.

Table 21-3: Adverse Event Types I-V Utilized for BSC AE Classification

Type	Description
Type I	Related to an investigational device, investigational procedure, investigational therapy, or procedure related to the implant of the investigational device.
Type II	Related to the protocol or procedures specifically related to protocol testing that is not standard of care.
Type III	Related to commercially available implanted components or commercially available features of an investigational device, or the procedure of a commercially available device
Type IV	Related to a change in the patient's condition or to therapies other than delivered by the implanted system.
Type V	Comments Only

21.4.3 Adverse Event Outcome Status

Adverse Events when reported are assigned an outcome status by centers (such as Recovering/Resolving, Resolved with residual effects, etc.) depending on the nature of the event or the corrective action involved. When clinically appropriate, centers should work to close events that may not be resolvable during the term of the investigation.

21.5 Subject Death Reporting

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

Notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death and is signed and dated by the Principal Investigator or authorized sub-Investigator. A death

narrative in the local language is acceptable, and will be translated to English by BSC (signed by an authorized translator). The death narrative must include all of the following, if available:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Rhythm at the time of death, if known (include any available documentation)
- Whether the death was related to the pulse generator, lead/catheter, clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Device status and/or activity at the time of death
- 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., H & P, consults, test results, operative reports, and/or progress notes from the hospital chart)
- Death certificate (if available)
- Autopsy report (if applicable)

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

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

Whenever possible, the PG should be interrogated. Investigational leads and related Boston Scientific system components (e.g., PGs) should be removed intact and returned promptly to Boston Scientific for analysis.

The Clinical Events Committee (CEC) must review information regarding subject deaths, refer to section 23.1.

21.6 Subject Death Classification

The following definitions of each category, along with the Epstein article,[13] are to be used by the Investigator when completing the Death Information section.

I. Primary Organ Cause - The root problem that initiated the terminal event if multiple factors were involved, e.g., HF - primary, renal failure - secondary.

A. Cardiac

1. Arrhythmic

2. Pump Failure - Death occurring in a patient with severe heart failure, refractory to medical therapy, in whom death is anticipated within days to two months. Often such patients are referred for hospice care, comfort care is provided and aggressive treatment is curtailed. The terminal event could be sudden and may be arrhythmic. This does not change the non-sudden, non-arrhythmic course that preceded the terminal event.

3. Ischemic

a. Acute MI - Symptoms compatible with an acute coronary syndrome (chest pain, acute dyspnea etc.), with evidence of myocardial necrosis as defined by:

i. creatinine kinase (CK) ≥ 2x upper limit of normal (ULN) and CK MB isoenzyme percent > ULN

ii. troponin level ≥ 2 x ULN

Patients with an acute coronary syndrome and diagnostic ST-T wave changes (>2 mm ST elevation in two contiguous leads) will be included if the death occurs prior to enzyme confirmation.

b. No Acute MI - Patient has not met the enzymatic or electrocardiographic criteria for an acute myocardial infarction. The testing was done and came back negative. For example, a patient who survives an unstable angina episode long enough to provide documentation that they did NOT have an MI, e.g., cardiac enzyme confirmation.

c. MI Unknown - Myocardial infarction suspected but data to prove or disprove are not available. Used to capture the patient who is suspected of having a probable MI but dies prior to the MI being documented. For example, chest pain > 20 minutes, or chest pain with a nondiagnostic ECG (LBBB), or chest pain of unknown duration.

4. Other Cardiac

5. Unknown

B. Noncardiac

C. Unknown

II. Temporal Course

A. Sudden - death that occurred within one hour of onset of symptoms

B. Non-Sudden - death that occurred greater than one hour of onset of symptoms

C. Unknown/Presumed Sudden - This category should be used for patients who were not expected to die of other causes, and were not witnessed at the time of death. There *must* be documentation of the patient's condition within 24 hours prior to the event and there should be no acute change in the patient's condition or circumstances leading up to the event. An example would be a stable patient who dies in his sleep. Patients can have worsening heart failure prior to the event and be included in this category, as long as the severity of heart failure does not fit the definition of death due to pump failure.

D. Unknown

III. Antecedent Worsening Heart Failure - Patients with signs or symptoms of worsening heart failure within the two weeks prior to death or the event that led to death (e.g. cardiac arrest and hypoxic encephalopathy from which the patient does not recover). In order to avoid recall bias, there *must* be documentation of a clinical evaluation documenting worsening signs or symptoms or a change in medication recommended for symptoms of worsening heart failure.

A. N/A (Not Applicable)

B. Yes

C. No

D. Unknown - Insufficient information to determine state of heart failure at time of the event

IV. Death Witnessed - Someone witnessed the death event (in the same room or within earshot)

A. Yes

B. No

C. Unknown

V. Monitored - The patient rhythm at the onset of the terminal event (just prior to death) was documented. This may or may not be related to the actual cause of death. Device stored electrograms may not be used for this determination (depending on the study, i.e., heart failure).

A. Yes

1. Ventricular Tachyarrhythmia

2. Bradyarrhythmia

a. Sinus Bradyarrhythmia

b. High degree AV block with slow ventricular response

c. Asystole

3. PEA (Pulseless Electrical Activity)

4. Other (AF, SVT, sinus tachycardia, normal sinus rhythm)

5. Unknown

B. No

C. Unknown

VI. Operative Relationship

A. Pre-Operative - deaths that occur after the consent is signed, but before the procedure

B. Peri-Operative - deaths that occur ≤ 30 days post-op or prior to hospital discharge following any system related surgery including lead and pulse generator revisions.

C. Post-Operative - deaths that occur > 30 days post-implant or revision following discharge.

VII. Procedure Related - includes events during, or as a result of, events from pre-op anesthesia through leaving the OR suite, the EP lab, or an office visit.

A. Yes

B. No

C. Unknown

VIII. Investigation Related - related specifically to differences in procedure or necessary equipment used or implanted used solely for the new or investigational aspects of the study. An example would be a coronary sinus perforation from a new left ventricular pacing lead introduced via the coronary sinus.

A. Yes

B. No

C. Unknown

IX. Pulse Generator Related - includes events associated with pulse generator's ability to detect and treat an arrhythmia.

A. Yes

B. No - including events where initiating event was nonarrhythmic

C. Unknown

D. N/A

X. Lead/Catheter Related - includes events associated with the lead system's ability to detect and treat an arrhythmia.

A. Yes

B. No - including events where initiating event was nonarrhythmic

C. Unknown

21.7 Relationship to Study Device(s) or Procedure

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in Table 21-4

Table 21-4: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

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

Classification	Description
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; **In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.**

21.8 Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 21-5.

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

enablemri.safety@bsci.com

Source documentation for UADE/USADE, any SAE/SADE which resulted in subject death and BSC requested AE's can either be uploaded in the EDC system or sent via email when available, with the accompanying source document checklist to the following email address,:

enablemri.safety@bsci.com

Table 21-5: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
Serious Adverse Event including Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event and as per local/regional regulations. • Reporting required through the end of the study
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency eCRF with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event and as per local/regional regulations. • Reporting required through the end of the study
Adverse Event, Adverse Device Effect (includes device and procedure related events), all MRI related events.	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• No later than 10 business days after becoming aware of the information • Reporting required through the end of the study

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

21.9 Exceptions for Use of Investigational Feature at Non-Investigational Sites – US Only

While geographic stability is necessary at the time of enrollment, it is possible for conditions to change for the subject in which continuing follow-up at the investigational center may pose a challenge. Every attempt should be made to keep the patient care at the Investigational Center and under the care of a trained investigator.

In order to protect patient safety, use of investigational feature (MRI Protection Mode) at non-investigational sites is not allowed without prior sponsor and IRB approval. Notify sponsor as soon as possible to obtain approval, as the approval process may take time. Use of

the investigational feature at a non-investigational site is considered a protocol deviation and needs to be reported appropriately.

Use of investigational feature will be considered for the following conditions:

- Subject has sought medical attention at a non-investigational site and software use is intended to protect the health and welfare of the subject
- Health of the subject prevents reasonably safe travel to an investigational site
- Travel to investigational site presents a significant hardship on the subject (e.g. physical distance to an approved investigational site is too great, limited access to transportation to the investigational site, subject is under inpatient care, or subject is seen frequently for recurring treatment, such as dialysis or chemotherapy, at another site and the investigator agrees to allow device interrogations at that site)
- Subject refuses to return to the investigational center despite being informed of the risks associated with seeking follow-up care at a non-investigational location
- Urgent, unplanned medical attention of study subjects requiring the use of investigational software to protect patient safety supersedes such consideration

Upon use of the investigational feature at a non-investigational site, information is to be collected surrounding the circumstances of use of the investigational feature and reported to Boston Scientific **within 5 business days**.

Required documentation:

- Completion of the Investigational Software Use Form
- Completion of the Deviation Form

21.10 Boston Scientific Device Deficiencies

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

In addition, 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 should be reported. Following receipt, the investigator's assessment is reviewed by internal BSC personnel. If the opinions between the investigator and BSC differ, both opinions will be reported, as appropriate.

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

21.11 Reporting to Regulatory Authorities / IRBs / ECs / Investigators

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

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

22.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 the use of any investigational devices, study-required procedures and/or testing, or data collection.

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

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB/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 will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

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

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,

- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the 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 (e.g., FDA requirement is within 5 business days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

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

23. Committees

23.1 Clinical Events Committee

A CEC is an independent group of individuals with pertinent expertise that reviews and adjudicates all of the following, as reported by study investigators for Phase I and II subjects:

- Events related to the study-required MR scan and ImageReady System between the MRI Visit and MRI + 1 month Visit (safety endpoint)
- Events related to medically necessary scan(s) and ImageReady System
- Subject deaths

The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites. At the discretion of the sponsor, additional events may be sent to the CEC.

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

24. Suspension or Termination

24.1 Premature Termination of the Study

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

24.1.1 Criteria for Premature Termination of the Study

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

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

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

Any investigator, or IRB/ EC in the ENABLE MRI Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

24.3 Requirements for Documentation and Subject Follow-up

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

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

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

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

24.4 Criteria for Suspending/Terminating a Study Center

Boston Scientific Corporation 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 protocol 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 IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the center will continue to be followed. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

25. Publication Policy

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

- All authorship and contributorship requirements as described above must be followed.

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

26. Reimbursement and Compensation for Subjects

26.1 Subject Reimbursement

Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

Travel and other expenses incurred by subjects for completing a non-standard of care MRI and MRI + 1 month visits in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's fee agreement.

26.2 Compensation for Subject's Health Injury

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

27. Abbreviations and Definitions

27.1 Abbreviations

Abbreviations are shown in Table 27-1.

Table 27-1: Abbreviations

Abbreviation/Acronym	Term
AE	Adverse Event
ASTM	American Society for Testing and Materials
ATP	Antitachycardia Pacing
BSC	Boston Scientific Corporation
CA	Competent Authority
CEC	Clinical Events Committee
CFR	Complication-free rate
CFR	Code of Federal Regulations
CRF	Case Report Form
CRT-D	Cardiac Resynchronization Therapy Defibrillator
DR	"Dual Chamber"
EC	Ethics Committee

Table 27-1: Abbreviations

Abbreviation/Acronym	Term
ECG	Echocardiography
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGM	Electrogram
FDA	Food and Drug Administration
FW	Firmware
HCP	Health Care Provider
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Standards Organization
MRI	Magnetic Resonance Imaging
Ms	Millseconds
PG	Pulse generator
PNS	Peripheral Nerve Stimulation
PRM	Programmer / Recorder / Monitor
PVT	Polymorphic Ventricular Tachycardia
RA	Right Atrium
RF	Radiofrequency
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAR	Specific Absorption Rate
US	United States
USB	Universal Serial Bus
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VR	Single Chamber
VT	Ventricular Tachycardia
ZWT	Zoom Wireless Transmitter

28. MR Scan Sequences Protocol

This section includes the scan sequences for use in the ENABLE MRI Study for subjects in Phase I.

28.1 Background

The MR scan sequences have been selected for their clinical relevance and their intensity as regards the RF and time-varying gradient fields the implanted system will be exposed to during the scan duration. The scan sequences selected are intended for utilization during a total of approximately 30 minutes of imaging (the total duration of time in the bore will be approximately one hour).

28.2 MR Conditional Labeling

Key aspects of the initial MR Conditional labeling being sought by Boston Scientific for the ImageReady System, which affect the types of scan sequences are:

- 1.5 T, closed-bore MRI machines only
- No anatomical scan restrictions (e.g. no isocenter scan exclusion zone)
- Scans up to Normal Operating Mode SAR limits are allowed

The scan sequences, target anatomical locations and positions of the subjects in the scan are selected in order to challenge and evaluate the safety of the ImageReady System for these key aspects of the MR Conditional labeling.

28.3 Notes Regarding the MR Scan

1. During the course of the imaging, the subject will be located in two unique positions:
    a. In order to maximize RF exposure, RF-intensive scan sequences will be run with the thoracic spine anatomical region centered within the bore. This will result in the implanted pacing system being located near the center of the scanner RF transmit coil, where the transmitted RF fields are strongest.
    b. In order to maximize gradient exposure, gradient-intensive scan sequences will be run with the lumbar spine anatomical region centered within the bore. This will result in the implanted pacing system being located near the edges of the scanner gradient coils where gradient fields are strongest.
2. External coils are not to be used, in order to prevent unnecessary complexity in moving the subject between the two locations in the bore. To maintain consistency across scans, the body coil in the MRI scanner is to be used for all scan sequences.
3. All DICOM files from the scans must be saved as part of the study data.
4. Notes for RF-intensive scan sequences
    a. A portion of the scan images obtained via the FSE sequences will be evaluated for the impact of image artifact near the implanted system on the overall clinical utility of the images. As such, a wide field of view (FOV) should be used, such as 40-48 cm depending on subject size, in order to image

across the torso and include the PG in the image. Additionally, a frequency matrix size of 512 pixels should be used.[13]

b. FSE sequences are to be T2-weighted, which are sequences that normally result in a high whole body average specific absorption rate (SAR). Utilize scan sequence parameters that would normally be used in clinical practice. All sequences in the RF-intensive section must only be run at Normal Operating Mode. Sequence parameters may be altered in order to increase whole body average SAR , such as (in addition to the settings mentioned in 4a) increasing the turbo factor or number of slices while ensuring the duration of the scan sequences is maintained, but must not exceed Normal Operating Mode SAR limits.

c. If any individual sequence in the RF-intensive sequences is not available or cannot be run, that sequence must be abandoned and the durations of one or more of the other scan sequences increased such that the overall duration of the RF-intensive scanning is maintained.

5. The suggested duration of all sequences are guidelines for the MR Technician running the scan. Variations from the suggested duration for each of the individual sequences are not to be considered as deviations from the protocol provided the overall scan durations for the RF-intensive and gradient-intensive scan regimens are adhered to (e.g. 11.5 minutes minimum and a maximum of 14 minutes for the RF-intensive scan regimen, 17 minutes minimum and a maximum of 21 minutes for the gradient -intensive scan regimen). Active scan time must not be greater than 35 minutes. Pre-scan time does not count towards the required duration.

Table 28-1: Scan Sequence Protocol

Scan Sequence[14]	**Suggested Duration per Scan Sequence**	**Anatomical Region Centered in Bore**	**Scanning Mode Requirements**
RF-Intensive (*See note 4 above)			
Sagittal Fast Spin Echo T2	3.5 - 4 minutes	Thoracic spine	Must not exceed Normal Operating Mode SAR limits
Axial Fast Spin Echo T2	3.5 - 4 minutes		
Coronal Fast Spin Echo T2	3.5 - 4 minutes		
Single Shot Turbo Spin Echo	1 - 1.5 minutes		
	Required sub-total = 11.5 - 14 minutes		
Gradient-Intensive			
Axial Diffusion EPI	2.5 - 3 minutes	Lumbar spine	
Axial Perfusion EPI	2.5 - 3 minutes		

[13] Only images from FSE sequences performed using the FOV and frequency matrix size values specified here will be evaluated for the impact of image artifact near the implanted system on the clinical utility of the images.
[14] Scan sequence names may be slightly different depending on scanner manufacturer.

Sagittal Diffusion EPI	2.5 - 3 minutes		
3D Plane Localizer	30 seconds		
Axial 3D TOF MRA	5 - 5.5 minutes		
Coronal 3D Bolus MRA	1 - 1.5 minutes		
Axial Fast Spin Echo T2 Flair	3 - 3.5 minutes		
	Required sub-total = 17 - 21 minutes		
	Maximum scan time= 35 minutes		

29. Medicare Study Criteria

The study protocol describes the method and timing of release of results on all pre-specified outcomes, including release of negative outcomes and that the release should be hastened if the study is terminated early.

Access to clinical study data provides opportunities to conduct further research that may help advance medical science and improve patient care. This helps ensure the data provided by research participants are used in the creation of knowledge and understanding. To this end, the study results on all pre-specified outcomes, including negative outcomes, will be submitted to ClinicalTrials.gov not later than one year after the study completion date, where the completion date is defined as the date that the final subject was examined or received an intervention for purposes of data collection for the primary outcome measure. Results submission could be delayed if an extension is granted to the results submission deadline; however, the release of all results on pre-specified outcomes will be hastened if the study is terminated early. See also Protocol Section 25, Publication Policy.

The study protocol must describe how Medicare beneficiaries may be affected by the device under investigation, and how the study results are or are not expected to be generalizable to the Medicare beneficiary population. Generalizability to populations eligible for Medicare due to age, disability, or other eligibility status must be explicitly described.

Subjects for the ENABLE MRI study will be selected from the investigators general patient population indicated for an Implantable Cardiac Defibrillator (ICD) or Cardiac Resynchronization Therapy-Defibrillator (CRT-D) device. Therefore it is not anticipated the device under investigation will affect Medicare beneficiaries differently than it would the Medicare eligible patients found in the investigators general patient population indicated for and receiving ICD or CRT-D implantation. With the aging of the US population, expanding indications for ICD implantation, and growing evidence favoring device-based therapy over antiarrhythmic drugs, data on the utilization and efficacy of ICDs in older patients is becoming increasingly important.[1] Therefore, the results of this study are expected to be generalizable to the Medicare eligible population primarily due to age (E.g., 65 years or older) for beneficiaries with implanted cardiac devices.

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1. Kong M.H., Al-Khatib S.M., Sanders G.D., Hasselblad V., Peterson E.D.; Use of implantable cardioverter-defibrillators for primary prevention in older patients: a systemic literature review and meta-analysis. *Cardiol J.* 2011;18:503-514.

30.Bibliography

1. Hayes DL HD, Gray JE. Effect of 1.5 tesla nuclear magnetic resonance imaging scanner on implanted permanent pacemakers. *J Am Coll Cardiol* 1987;10:782-786
2. Goldschlager N EA, Friedman P, Gang E, Krol R, Olshansky B. Environmental and drug effects on patients with pacemakers and implantable cardioverter/defibrillators. *Arch Intern Med* 2001;161:649-655
3. Martin ET CJ, Shellock FG, Pulling CC, Fair R, Jenkins K. Magnetic resonance imaging and cardiac pacemaker safety at 1.5-tesla. *J Am Coll Cardiol* 2004;43:1315-1324
4. Sommer T NC, Yang A, Ziejlemaker V, Hackenbroch M, Schmiedel A, Meyer C, et al. Strategy for safe performance of extrathoracic magnetic resonance imaging at 1.5 tesla in the presence of cardiac pacemakers in non-pacemaker-dependent patients: A prospective study with 115 examinations. *Circulation*. 2006;114:1285-1292
5. Levine GN GA, Arai AE, Bluemke DA, Glamm SD, Kanal E, et al. Safety of magnetic resonance imaging in patients with cardiovascular devices: An american heart association scientific statement from the committee on diagnostic and interventional cardiac catheterization, council on clinical cardiology, and the council on cardiovascular radiology and intervention: Endorsed by the american college of cardiology foundation, the north american society for cardiac imaging, and the society for cardiovascular magnetic resonance. *Circulation*. 2007;116:2878-2891
6. Roguin A SJ, Vahlhaus C, Lombardi M, Brugada J, Vardas P, et al. Magnetic resonance imaging in individuals with cardiovascular implantable electronic devices. *Europace*. 2008;10:336-346
7. Nazarian S RA, Zviman MM, Lardo AC, Dickfeld TL, Calkins H, Weiss RG, et al. Clinical utility and safety of a protocol for noncardiac and cardiac magnetic resonance imaging of patients with permanent pacemakers and implantable-cardioverter-defibrillators at 1.5 tesla. *Circulation* 2006;114:1277-1284
8. Mollerus M AG, Lipinski M, Lucca J. Magnetic resonance imaging of pacemakers and implantable cardioverter-defibrillators without specific absorption rate restrictions. *Europace*. 2010;12:947-951
9. Cohen JD, Costa HS, Russo RJ. Determining the risks of magnetic resonance imaging at 1.5 tesla for patients with pacemakers and implantable cardioverter defibrillators. *Am J Cardiol. 2012 Dec 1;110(11):1631-6.*
10. Nazarian S, Hansford R, Roguin A, Goldsher D, Zviman MM, et al. A prospective evaluation of a protocol for magnetic resonance imaging of patients with implanted cardiac devices. *Ann Intern Med. 2011 Oct 4;155(7):415-24.*
11. Gimbel JR, Bello D, Schmitt M, Merkely B, Schwitter J, Hayes DL, Sommer T, Schloss EJ, Chang Y, Willey S, Kanal E. Randomized trial of pacemaker and lead system for safe scanning at 1.5 tesla. Heart Rhythm. 2013;10:685-691
12. Sutton R, Kanal E, Wilkoff BL, Bello D, Luechinger R, Jenniskens I, Hull M, Sommer T. Safety of magnetic resonance imaging of subjects with a new medtronic enrhythm mri surescan pacing system: Clinical study design. Trials. 2008;9:68

13. Friedman HL, Acker N, Dalzell C, Shen WK, Asirvatham SJ, Cha YM, Hodge D, Felmlee J, Watson R, Friedman PA. Magnetic resonance imaging in subjects with recently implanted pacemakers. Pacing Clin Electrophysiol. 2013;36:1090-1095
14. Wollmann CG, Thudt K, Kaiser B, Salomonowitz E, Mayr H, Globits S. Safe performance of magnetic resonance of the heart in subjects with magnetic resonance conditional pacemaker systems: The safety issue of the estimate study. J Cardiovasc Magn Reson. 2014;16:30
15. Revo MRI™ Surescan™ pacing system clinical study summary of clinical results, 2014