Medical Device Clinical Trial Protocol

Reference Number：C2082

Protocol Title：Observation of ImageReady™ MR Conditional Defibrillation System in China (MR ICD)

Investigational Device：ImageReady™ MR Conditional Defibrillation System

Device Model：Pulse Generator D150 et. al.
Defibrillation Lead 0692 et. al.
LV Lead 4671 et. al.

Class of device：

Class 3 medical device requiring clinical trials Yes☐ No☒
Same class device within China Yes☐ No☒

Protocol version and date： Rev/AC，2018, Mar 1

Clinical trial sites： Zhongshan Hospital Fudan University et. al.

Pricipal Investigator： Su Yangang

Sponsor： BSC International Medical Trading (Shanghai) Co., Ltd, ("BSC China")

Agent：not applicable

Observation of ImageReady™ MR Conditional Defibrillation System in China

(MR ICD)

CLINICAL PROTOCOL

Study Reference Number：C2082

Sponsored By

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Study Site List	See “MR ICD site list and contact information”

Original Release: May 11, 2017

Current Version: Mar 1, 2018

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AA	**May 11, 2017**	**90702637 Rev./Ver. AH**	**N/A**	**N/A**	**Initial release**
AB	**Jul 24, 2017**	**90702637 Rev./Ver. AH**	**Whole document**	**Delete requirement for magnet and LV lead delivery system, and related description and assessment.**	**Regulatory requirement.**
AB	**Jul 24, 2017**	**90702637 Rev./Ver. AH**	**Whole document**	**Delete non-Gore coating leads.**	**Regulatory requirement.**
AB	**Jul 24, 2017**	**90702637 Rev./Ver.**	**Whole document**	**Delete the assessment of Beeper function.**	**Regulatory and trial**

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
		AH			**management requests.**
AB	**Jul 24, 2017**	**90702637 Rev./Ver. AH**	**Table 12-3**	**Parameters for RV shock impedance tests added.**	**Protocol refinement**
AC	**Mar 1, 2018**	**90702637 Rev./Ver. AI**	**Contact Information**	**author information deleted**	**Based on protocol template**
AC	**Mar 1, 2018**	**90702637 Rev./Ver. AI**	**5.1, 6.1, 10.3, 12, 20.3**	**Descriptions regarding no pacing function during MRI protection mode deleted, and description on asynchronization pacing added.** **Item 4 and 5 from exclusion criteria dropped.** **Requirement for 12 lead ECG and 10s ECG episode cancelled.** **Sections for subject evaluation before MRI and MRI visit updated.**	**The function of pacing under MRI protection mode was added for the device.**
AC	**Mar 1, 2018**	**90702637 Rev./Ver. AI**	**12.7.1.1**	**Lift the requirement for magnet origin.**	**Based on magnet availability in hospitals**
AC	**Mar 1, 2018**	**90702637 Rev./Ver. AI**	**12.1, 12.4**	**Add: A pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential**	**Trial management request**

2. Protocol Synopsis

<table>
<tr><th colspan="2">Observation of ImageReady™ MR Conditional Defibrillation System in China (MR ICD)</th></tr>
<tr><td>Study Objectives</td><td>To observe the safety and effectiveness of ImageReady™ MR conditional defibrillation system in a Chinese population.</td></tr>
<tr><td>Test Device</td><td>ImageReady™ MR Conditional Defibrillation System</td></tr>
<tr><td>Device Type</td><td>Pulse Generator
<table>
<tr><td>DYNAGEN ICD</td><td>D150, D152</td></tr>
<tr><td>DYNAGEN CRT-D</td><td>G158</td></tr>
<tr><td>INOGEN ICD</td><td>D140, D142</td></tr>
<tr><td>INOGEN CRT-D</td><td>G148</td></tr>
</table>
Defibrillation Lead (active fixation)
<table>
<tr><td>RELIANCE 4-FRONT (single coil, Gorecoating)</td><td>0692, 0693, 0657</td></tr>
<tr><td>RELIANCE 4-FRONT (dual coil, Gore coating)</td><td>0695, 0696, 0658</td></tr>
</table>
LV Lead
<table>
<tr><td>ACUITY X4 (straight)</td><td>4671, 4672</td></tr>
<tr><td>ACUITY X4 (spiral)</td><td>4674, 4675, 4677, 4678</td></tr>
</table>
DYNAGEN series pulse generators will be used in this study, including 10 ICDs (with at least 2 single chamber and 2 dual chamber ICDs) and 10 CRT-Ds.
Lead selection will be mainly decided according to clinical requirement.</td></tr>
<tr><td>Study Design</td><td>Multi-center, prospective, single –arm study</td></tr>
<tr><td>Planned Number of Subjects</td><td>20</td></tr>
<tr><td>Planned</td><td>approximately 5 investigational sites from China</td></tr>
</table>

Observation of ImageReady™ MR Conditional Defibrillation System in China (MR ICD)	
Number of Investigational Sites	
Primary Safety Endpoint	MR scan-related Complication-free rate between the MR Scan and the MRI + 1 Month Visit
Primary Effectiveness Endpoints	1. Abnormal increase in RV shocking impedance from the pre-MR scan to the 1 Month post-MR scan 2. Increase in RV pacing threshold from the pre-MR scan to the 1 Month post-MR scan 3. Decrease in RV sensed amplitude from the pre-MR scan to the 1 Month post-MR scan 4. Increase in LV pacing threshold from the pre-MR scan to the 1 Month post-MR scan 5. Decrease in LV sensed amplitude from the pre-MR scan to the 1 Month post- MR scan
Ancillary Assessments	1. Assessment of RV and LV impedances 2. Assessment of RA lead measurements 3. Assessment of VT/VF episodes post-MR-scan 4. Assessment of programming the MRI Protection Mode 5. Assessment of Image Artifacts for non-medically necessary MR scans.
Follow-up Schedule	Phase I is completed when all the subjects finish MRI + 1 Month Visit, which starts Phase II till 1 year post implantation. − 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)

Observation of ImageReady™ MR Conditional Defibrillation System in China (MR ICD)	
	– MRI + 1 Month Visit (30 ± 7 days post-MRI Visit) – Every Three-month follow-ups post MR scan (±14 days, recommended) – One Year Visit (365±45 days post-implant)
Study Duration	Phase I is expected to last about 9 months after first subject enrollment, by when all the subjects will have finished MRI +1 Month Visit. Phase II continues to all the subjects complete one year follow-up post-implant, and the whole study is expected to last about 20 months after first subject enrollment.
Key Inclusion Criteria	1. Subject is indicated to Class I/II indications per guidelines/consensus released by Chinese Society of Cardiac Pacing and Electrophysiology 2. Subject must have the ImageReady System as their initial (de novo) defibrillation system implant 3. Subject will receive an ICD or CRT-D pulse generator in the left or right pectoral region ICD 4. Subject is able and willing to undergo an MR scan 5. 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 6. Subject is age 18 or above
Key Exclusion Criteria	1. Subject has other active or abandoned implanted cardiac rhythm devices, components or accessories present such as pulse generators, leads, lead adaptors or extenders 2. 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 3. Subject needs or will need a medically necessary MR scan, before completing the 1-month post-MR follow-up visit 4. 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

Observation of ImageReady™ MR Conditional Defibrillation System in China (MR ICD)	
	5. Subjects currently requiring dialysis 6. Subject has a mechanical heart valve 7. Subject has a known or suspected sensitivity to dexamethasone acetate (DXA) 8. Subject is currently on the active heart transplant list 9. Subject has documented life expectancy of less than 12 months 10. Subject is enrolled in any other concurrent study that might interfere with this study 11. Women of childbearing potential who are or might be pregnant at the time of this study
Statistical Methods	
Primary Statistical Hypothesis	This study is a single-arm, small sample clinical study without any hypothesis testing. It can be considered reasonable if up to 2 failed cases of primary safety endpoint event occur. It can be considered reasonable if up to 2 failed cases of endpoint event occur in each of the five primary effectiveness endpoints.
Statistical Test Method	Descriptive statistics will be conducted for the endpoint events.
Sample Size Parameters	This study is a single-arm, small sample clinical study without any hypothesis testing. Twenty subjects (10 with ICD and 10 with CRT-D) will be enrolled. It is assumed that the attrition should not be more than 2 cases in each group, so that at least 8 subjects shall be included in the final analysis for each group.

3. Table of Contents

3.1. Figure

3.2. Table

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 (ICD) have been contraindicated in MRI scanners. The potential adverse effects of MRI on defibrillation system include loss of capture due to lead tip heating and cardiac arrhythmias induced by unexpected pacing.

A number of studies have reported on the relative safety of scanning patients with non-MR conditional cardiac pacemakers or implantable cardioverter-defibrillators. Nazarian et. al.[1] reported on 438 patients (54% with pacemakers and 46% with ICDs) undergoing 555 scans (18% involving thorax). In 3 patients, the device reverted to a transient back-up programming mode without long-term effects. The observed changes in sensing, impedance and pacing threshold did not require device revision or reprogramming. Recently, the result of MagnaSafe registry was published.[2] Patients in the registry were referred for clinically indicated nonthoracic (75% with brain or spinal cord) MRI at a field strength of 1.5 T (1000 pacemaker and 500 ICD scans). No deaths, lead failures, losses of capture, or ventricular arrhythmias occurred during MRI. One ICD generator could not be interrogated after MRI; the device had not been appropriately programmed per protocol before the MRI. The ratio of pacing threshold increase≥0.5V, P-wave amplitude decrease ≥50% and R-wave amplitude decrease ≥50% immediately after scan in ICD group was 0.8%, 0.3%, and 0.2%, respectively; and the long-term ratio was 0.3%, 0, 0.

Presently some ICD manufactures are developing and producing MR conditional defibrillation systems. DYNAGEN and INOGEN, the new generation of defibrillation system series from Boston Scientific (BSC) were designed to be MR conditional. DYNAGEN and INOGEN defibrillation system series products (pulse generators and leads) have already been approved in China without MR conditional label. BSC China intends to expand the indication with additional MR conditional label, and name the defibrillation system as ImageReady™ MR conditional defibrillation system.

BSC is conducting a global multi-center study, ENABLE MRI (NCT02652481), on MR conditional systems including DYNAGEN and INOGEN. The study will enroll 500 subjects, 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. MR ICD protocol is based on ENABLE MRI study.

China Food and Drug Administration (CFDA) requires certain clinical trial in China to support the approval of ImageReady™ MR conditional defibrillation system.

5. Device Decription

The ImageReady MR Conditional Defibrillation System included in the MR ICD Clinical Study, here to forward referred to as the ImageReady System, consists of DYNAGEN and INOGEN series pulse generators, RELIANCE 4-FRONT series defibrillation leads, ACUITY X4 series left ventricle (LV) leads, and INGEVITY series pacing leads for right atrium (RA). See Table 5-1.

Table 5-1 ImageReady MR Conditional Defibrillation System Components

Component	Name	Model	Features
Pulse Generators	DYNAGEN	D150	Single chamber ICD, DF4
		D152	Dual chamber ICD, DF4
		G158	CRT-D, DF4, IS4
	INOGEN	D140	Single chamber ICD, DF4
		D142	Dual chamber ICD, DF4
		G148	CRT-D, DF4, IS4
Defibrillation Leads	RELIANCE 4-FRONT active fixation, single coil, Gore coating	0692	59cm
		0693	64cm
		0657	70cm
	RELIANCE 4-FRONT active fixation, dual coil, Gore coating	0695	59cm
		0696	64cm
		0658	70cm
LV leads	ACUITY X4 straight	4671	86cm
		4672	95cm
	ACUITY X4 spiral S	4674	86cm
		4675	95cm

	ACUITY X4 spiral L	4677	86cm
		4678	95cm
RA leads	INGEVITY passive fixation, J type	7735	45cm
		7736	52cm
	INGEVITY active fixation, straight	7740	45cm
		7741	52cm
		7742	59cm
	INGEVITY passive fixation, straight	7731	52cm
		7732	59cm

DYNAGEN and INOGEN pulse generators, belonging to the new generation products of Galaxy, include single chamber ICD, dual chamber ICD and CRT-D, all capable of proiding defibrillation therapy. DYNAGEN and INOGEN pulse generators have the same hardware, while DYANGEN is more advance product with additional software functions such as ApneaScan,Wireless ECG and RhythmMatch.

The pulse generators and leads listed in MR ICD study protocol have been approved by CFDA with non-MR conditional label. INGEVITY MRI series leads have been approved by CFDA with MR conditional label.

The design of the DYNAGEN and INOGEN pulse generators has minimized the use of ferromagnetic materials which can interact with the fields generated in a typical MRI scan; the circuits have been designed to tolerate voltages that may be induced during scans; and the lead wire has been designed for use with the ImageReady pulse generators specifically to reduce absorption of energy from MRI fields, thus minimizing heating.

DYNAGEN will be used as the only pulse generator in MR ICD study, while lead selection will be decided mainly by investigators based on subjects' anatomy and clinical practice.

BSC intends to label the ImageReady MR Conditional Defibrillation System models "MR Conditional" as defined by the American Society for Testing and Materials (ASTM) [3], when used as a system and in accordance with labeled Conditions of Use.

5.1. MRI Protection Mode

Prior to an MRI scan, the pulse generator (PG) must be programmed to the MRI Protection Mode using the Programmer / Recorder / Monitor (PRM).

Pacing mode options include asynchronous pacing (DOO, AOO, VOO) or no pacing (Off).

Asynchronous pacing should only be used if the subjects is pacing-independent. If MRI Protection Brady Mode is programmed to Off, the subject will not receive therapy until MRI Protection Mode is exited. Off should only be used if the subject is judged to be clinically capable of receiving no pacing during the time the pulse generator is in MRI Protection Mode, including during the scan.

Considerations prior to choosing asynchronous pacing include:

- Determine whether the patient is pacing-dependent.
- Determine which chamber(s) need to be paced.
- Consider the possibility of arrhythmia induction with asynchronous pacing.
- Subjects with the following conditions may have increased risk of developing transient pacing-dependence:
    1. At risk for intermittent AV block (for example, those with progressive AV block, or a history of unexplained syncope)
    2. At risk for trifascicular block (alternating bundle branch block or PR interval > 200 ms with LBBB or other bifascicular block)

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

- Bradycardia sensing
- 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

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

Refer to the *BSC ImageReady MR Conditional Defibrillation System MRI Technical Guide*, here to forward referred to as the *BSC MRI Technical Guide*, for additional information

regarding MRI Protection Mode.

5.2. 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.

5.3. Beeper Feature

The Beeper in the PGs provides: (1) an audible patient warning when potential therapy failure is detected between scheduled PG checks with an HCP, and (2) audible feedback to HCP regarding the state of the PG such as, current tachycardia mode and when charging for shock therapy. The Beeper may no longer be audible following an MRI scan. Loss of Beeper volume cannot be recovered.

It is strongly recommended that an in-clinic follow-up schedule of every three months after an MRI scan to monitor device performance.

6. Conditions of Use

The following MRI Conditions of Use must be satisfied as listed here and in the *BSC MRI Technical Guide*. Where differences exist between the *BSC MRI Technical Guide* and the EN MR ICD study protocol, the protocol extends the *BSC MRI Technical Guide.*

6.1. Cardiology

1. Patient is implanted with an ImageReady MR Conditional Defibrillation System
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. The patient must be continuously monitored by electrocardiography (ECG) during MR scan. Ensure backup therapy is available (external rescue).
5. Patient is judged to be clinically capable of tolerating no Tachycardia protection.
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
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 electrocardiography (ECG) for the entire duration MR scan. 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 observe 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 in a Chinese population.

8. Endpoints

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

1. Abnormal increase in RV shocking impedance from the pre-MR scan to the 1 Month post-MR scan
2. Increase in RV pacing threshold (at 0.5ms) from the pre-MR scan to the 1 Month post-MR scan
3. Decrease in RV sensed amplitude from the pre-MR scan to the 1 Month post-MR scan
4. Increase in LV pacing threshold (at 0.5ms) from the pre-MR scan to the 1 Month post-MR scan
5. Decrease in LV sensed amplitude from the pre-MR scan to the 1 Month post- MR scan

8.3. Ancillary Assessments

1. Assessment of RV and LV impedances
2. Assessment of RA lead measurements
3. Assessment of VT/VF episodes post-MR-scan
4. Assessment of programming the MRI Protection Mode
5. Assessment of Image Artifacts for non-medically necessary MR scans.

The MR ICD study referenced FDA IDE trial ENABLE MRI. The major difference is that ENABLE MRI will collect 25 episodes of VT/VF events post MR scan, while the small sample size MR ICD study would use shocking impedance measurement to evaluate the

integrity of the shocking circuit. The MR ICD study will also assess any VT/VF event post MR scan.

9. Design

The MR ICD study is a multi-center, prospective, single –arm study in China. Phase I is completed when all the subjects finish MRI + 1 Month Visit, and the data will be summarized to support product CFDA registration. All subjects will be followed-up till 1 year post implantation.

9.1. Scale and Duration

The MR ICD study will enroll 20 subjects at approximately 5 investigator centers in China, including 10 ICDs (with at least 2 single chamber ICDs and 2 dual chamber ICDs) and 10 CRT-D. The PGs will be DYNAGEN series and there is no further requirement for leads (see Table 5-1).

Data will be collected from subjects upon enrollment into the study, at implant, and at pre-discharge. Subjects will have an MR scan at 6-9 weeks post-implant, or at least 6 weeks after any required surgical interventions to the ImageReady System (labeled as MRI Visit). Subsequently, there will be a clinic follow up at MRI + 1 Month Visit, and recommended clinic follow up every 3 months post MR scan. Subjects will also be followed at 1 year post-implant, see Figure 9-1.

The MR ICD study is composed of two phases. Phase I is completed when all the subjects finish MRI + 1 Month Visit, which starts Phase II till 1 year post implantation. Phase I is expected to last about 9 months after first subject enrollment, and the whole study is expected to last about 20 months after first subject enrollment.

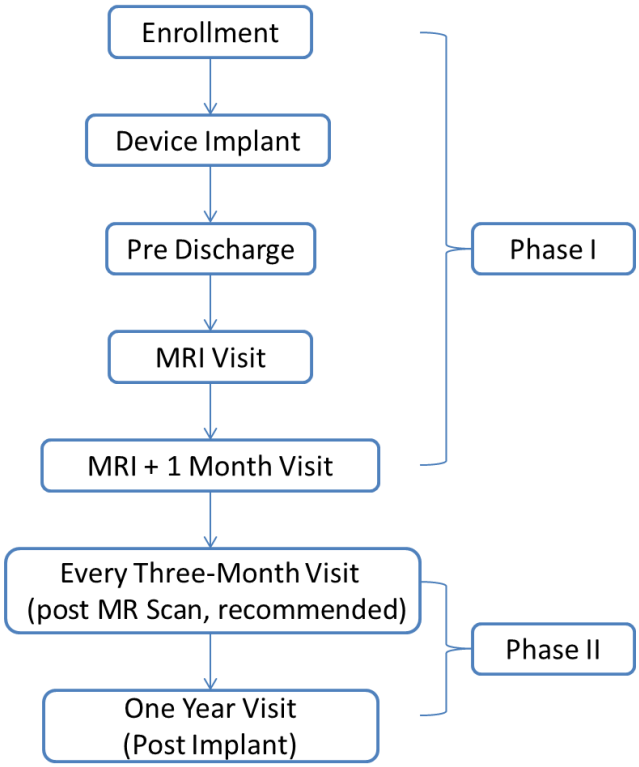

Figure 9-1 MR ICD study Design

9.2. Justification for the Study Design

BSC is conducting a global multi-center study, ENABLE MRI (NCT02652481), on MR conditional systems including DYNAGEN and INOGEN. The study will enroll 500 subjects, 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. CFDA requires certain clinical trial in China to support the approval of ImageReady™ MR conditional defibrillation system.

The MR ICD study referenced ENABLE MRI. The major difference is that ENABLE MRI will collect 25 episodes of VT/VF events post MR scan, while the small sample size MR ICD study would use shocking impedance measurement to evaluate the integrity of the shocking circuit. The MR ICD study will also assess any VT/VF event post MR scan.

The MR ICD study is composed of two phases. Phase I is completed when all the subjects finish MRI + 1 Month Visit, and the data will be summarized to support product CFDA registration. All subjects will be followed-up till 1 year post implantation.

10. Subject Selection

10.1. Study Population and Eligibility

Subjects enrolled in the MR ICD 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.

10.2. Inclusion Criteria

Subjects who meet all of the following criteria may be given consideration for inclusion in this clinical investigation, provided no exclusion criteria are met (see 10.3).

1. Subject is indicated to Class I/II indications per guidelines/consensus released by Chinese Society of Cardiac Pacing and Electrophysiology[4, 5]
2. Subject must have the ImageReady System as their initial (de novo) defibrillation system implant
3. Subject will receive an ICD or CRT-D pulse generator in the left or right pectoral region ICD
4. Subject is able and willing to undergo an MR scan
5. 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
6. Subject is age 18 or above

10.3. Exclusion Criteria

Subjects who meet any one of the following criteria will be excluded from the MR ICD study.

1. Subject has other active or abandoned implanted cardiac rhythm devices, components or accessories present such as pulse generators, leads, lead adaptors or extenders

2. 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
3. Subject needs or will need a medically necessary MR scan, before completing the 1-month post-MR follow-up visit
4. 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
5. Subjects currently requiring dialysis
6. Subject has a mechanical heart valve
7. Subject has a known or suspected sensitivity to dexamethasone acetate (DXA)
8. Subject is currently on the active heart transplant list
9. Subject has documented life expectancy of less than 12 months
10. Subject is enrolled in any other concurrent study that might interfere with this study
11. Women of childbearing potential who are or might be pregnant at the time of this study

11. Subject Accountability

11.1. Enrollment

Subjects will be considered enrolled into the MR ICD study at the time of informed consent form execution. All subject enrollments will be counted against the enrollment ceiling for the study.

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. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study. Reasons for withdrawal include, but are not limited to: subject not receiving a protocol required defibrillation system, physician discretion, subject choice to retire consent, loss to

follow-up, or death. While study withdrawal is discouraged, subjects may withdraw from the MRI ICD 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 must be completed. 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 MR ICD study will be placed into one of four classifications, as defined below.

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) for intent subjects should be maintained in the Center's files.

Attempt - Attempt refers to a subject who has had the lead(s) and/or PG introduced into the body, but is not successfully implanted with any portion of the ImageReady System during the implant procedure. 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, then withdrawn from the study.

Partial Implant - Partial Implant refers to a subject who is implanted with a component of the ImageReady System (lead or pulse generation) during the implant procedure, but does not end up with a complete ImageReady System. They shall not receive the protocol required MR Scan according to the *BSC MRI Technical Guide*. 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.

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.

11.4. Enrollment Controls

According to the study protocol, 10 ICD subjects (at least 2 single chamber ICDs and 2 dual chamber ICDs) and 10 CRT-D subjects will be enrolled. It should be ensured that at least 8 ICD subjects (at least 1 single chamber ICD and 1 dual chamber ICD) and 8 CRT-D subjects undergo protocol required MR scan and complete all the sequences. It should be ensured that both single coil and dual coil defibrillation leads are implanted. It should be ensured that both straight and spiral LV leads are implanted. Subject enrollment might be expanded to meet the above requirement to support product registration.

Generally, one individual center may not enroll more than 10 subjects. Investigational sites will be notified when the enrollment goal is close to being reached and once enrollment is complete.

11.5. End-of-Study Action Plan

Phase I is completed when all the subjects finish MRI + 1 Month Visit, and the data will be summarized to support product CFDA registration. All subjects will be followed-up till 1 year post implantation in Phase II. After that, subjects will receive routine clinical practice at each center.

12. Study Methods

12.1. Data Collection

The data collection schedule for the MR ICD study is shown in Table 12-1.

12.2. Study Candidate Screening

For the MR ICD Study, physician investigators are responsible for screening all potential patients and selecting those who are appropriate for study inclusion. The patients selected for participation should be from the investigator’s general patient population.

12.3. Informed Consent

Patients who appear to meet all of the inclusion criteria and none of the exclusion criteria and agree to participate in the MR ICD study must give written informed consent approved by

the EC prior to study participation and use of any investigational product or testing/ data collection. Patients who sign informed consent for the MR ICD study will be considered enrolled in the study at the point of executing an ICF.

12.4. Enrollment Visit

The data to be collected during enrollment into the MR ICD study comprise of subject demographic data including age, ethnicity and gender, medical history including arrhythmia history, cardiac disease history, and current cardiovascular medications, a physical assessment of the subject including height, weight, heart rate and blood pressure.
If the subject has metal objects in body, radiologist approval to undergo MRI scan should be documented. A pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential.

12.4.1. Enrollment Source Data Requirements

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

Table 12-1 Data Collection Schedule

Procedure /Assessment	Enrollment	Implant	Pre-Discharge	MRI Visit	MRI+ 1Month Visit	MRI+ Every Three-Month Visits	Implant+ 1Year Visit	Additional Visits	Medically necessary MRI
Timeframe	≤ 30 days prior to Implant	Implant Day 0	3-72 hours from Implant	6-9 weeks from Implant[a]	30 ± 7 days from MRI Visit	90 ± 14 days from MRI Visit[b]	365±45 days from implant		
Informed consent	X								
Demographics	X								
Medical history	X								
Physical assessment	X								
Pregnancy test	X								
Device implant		X							
MR Scan				X					X
Device evaluation		X	X	X pre&post	X	X	X	O	O
Beeper evaluation				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
Adverse events	X	X	X	X	X	X	X	X	X

[a] must occur at least 6 weeks after surgical revision of the ImageReady System
[b] The first Every 3-month visit will occur 90 ± 14 days after MRI visit. Subsequent Every 3-month follow-up visits will be scheduled every three months (90 days ± 14 Days) from the previous scheduled study follow-up.
[c] A pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential.

Table 12-2 Enrollment Source Documentation Requirements

Source Documentation Requirement	Disposition
Informed consent form and process	Retain at center
Demographic, Medical history and Physical assessment	
Completed Radiologists Technical Source Form (applicable for subjects with metallic implants only)	
Adverse events	

12.5. Implant

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.

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.

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.

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
Shock Impedance Tests		RV Shock Impedance Tests	
		Per HCP **For MRI and MRI+1 Month visits:** The same RV Shock Impedance Configuration must be used for impedance 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
   1) A count of 2 non-capture beats at a given voltage level is required to declare loss of capture (LOC)
   2) 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, and "Manual RA threshold test".
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
   1) A count of 2 non-capture beats at a given voltage level is required to declare loss of capture (LOC)

2) 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, and "Manual RV threshold test".
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. 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 LV threshold test
   1) A count of 2 non-capture beats at a given voltage level is required to declare loss of capture (LOC)
   2) 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, and “Manual LV threshold test”.
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

12.6.1. Device Evaluation

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.

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

The MRI Visit will occur 6 to 9 weeks (42-63 days) after implant or surgical revision ((i.e., a lead revision/ reposition) of the ImageReady System implant.

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 evaluation 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. Evaluation 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 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 evaluating 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.

12.7.2.2. 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 subinvestigator for all subjects prior to initiation of the MRI Protection Mode and the MR Scan. Heart rate and any abnormal rhythms, including incidence of ectopy shall be documented. 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 29 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[6]". 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.

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 and an appropriate pacing mode is set 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 Practices11. 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
2. Program the MRI Protection Time-out (nominal setting: 6 hours; programmable values are OFF, 3, 6, 9, 12 hours)
3. Program the PG to the MRI Protection Mode, set up appropriate pacing parameters
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. 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 of the MR scan. **For the entire duration of the MR scan, the following will be performed:**

1. Continuous ECG monitoring of the subjects
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 using ECG, along with maintaining voice and visual contact.
4. In addition, **for the entire duration of the MR scan**, the following will be performed:
    a. The heart rate will be documented in 5 ± 2 minutes intervals.
    b. ECG 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

12.7.3.3. MR Scan Sequences Protocol

Refer to Table 29-1 in Section 29 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

12.7.3.4. Exiting the MRI Protection Mode

Upon completion of the MR scan, program the PG out of the 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 (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 evaluation of Beeper function as defined in section 12.7.1.1.

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
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 using the upload tool in the EDC system. 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.
6. Assessment of the quality of the MR image. Radiologist from the investigate site will score the image quality from 1 to 5 based on comparison with site usual scans, with 1 completely unreadable and 5 similar to usual scans.

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: • 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 • Evaluation of Beeper function • Printout of ‘Quick Notes’ Report • Cardiology and Radiology MRI Conditions of Use are satisfiedAbnormal rhythms / ectopy (if possible) •	Retain at center
MR scan: • MRI Protection Settings Report • Heart rate in 5 ± 2 minute intervals • Medications used for sedation in the MR scanner, if applicable • MR Scanner manufacturer and model • Time of MR scan initiation	Retain at center

• 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 • Evaluation 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 • Assessment of MR scan image quality	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

The MRI + 1Month 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
3. Record the measurements in the EDC system.

12.8.2. Completing the MRI + 1 Month 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 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
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, and a copy is expected to be submitted to Boston Scientific using the upload tool in the EDC system. 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 Year follow-up visit.

12.8.3. 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	
Printout of ‘Quick Notes’ Report	
Documentation of spontaneous VT/VF episode(s) by PRM strips, as applicable: • ‘Selected Episodes Report’ (counters and EGMs required) • ‘Arrhythmia Logbook’	
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)

An in-clinic follow-up schedule of every three months is strongly recommended to monitor device performance. The first Every 3-month visit will occur 90 ± 14 days after MRI visit. Subsequent Every 3-month follow-up visits will be scheduled every three months (90 days ± 14 Days) from the previous scheduled study follow-up.

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
   - 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
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
Documentation of spontaneous 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. Implant + 1Year Visit

The Implant + 1Year Visit must be performed as a clinic visit and will occur at 365 ± 45 days

after implant.

Device Evaluation

1. The standard of care evaluation for device performance is recommended. Record the available measurements in the EDC system.
   - Pacing thresholds
   - 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
3. Program the device according to physician discretion, if applicable
4. Print the 'Quick Notes' Report
5. 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 Year"
   c) Retain the original USB at the center, and a copy is expected to be submitted to Boston Scientific using the upload tool in the EDC system. Do not make a copy by using the programmer a second time as this will create a new USB with slightly different information.

12.10.1. Implant + 1 Year Visit Source Data Requirements

Source data requirements for Implant +1 Year Visit are described in Table 12-9.

Table 12-9 Implant + 1Year Source Documentation Requirements

Source Documentation Requirement	Disposition
Device Evaluation (pace threshold, sense amplitude,	Retain at center

impedance, RV shock impedance)	
PRM ECG strips from manual threshold tests documenting LOC for all implanted leads	
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	
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. 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. 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) 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

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 using the upload tool in the EDC system. Do not make a copy by using the programmer a second time as this will create a new USB with slightly different information.

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 Requirement	Disposition
Device Evaluation (pace threshold, sense amplitude, impedance, RV shock impedance)	
PRM ECG strips from manual threshold tests documenting LOC for all implanted leads	
Documentation of spontaneous 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	
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) 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* • Evaluation of Beeper function • Printout of 'Quick Notes' Report • Cardiology and Radiology MRI Conditions of Use are satisfied	Retain at center
MR scan: • MRI Protection Settings Report • Time of MR scan initiation • *Time of MR scan completion MRI*	Retain at center

• *Heart rate in 5 ± 2 minute intervals* • *Medications used for sedation in the MR scanner, if applicable* • *MR Scanner manufacturer and model*	
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* • Evaluation 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 • *Assessment of MR scan image quality*	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 Implant + 1 Year Visit. The individual

subject will finish the study when he/she completes the Implant + 1 Year Visit.

Note: Phase I is completed when all the subjects finish MRI + 1 Month Visit, and the data will be summarized to support product CFDA registration.

13. Statistical Considerations

13.1. Primary Endpoints

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

The primary safety endpoint of the MR ICD study 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. Complication is defined as serious adverse event or permanent loss of device functions (i.e. pacing or defibrillation).

The performance goal of the primary safety endpoint for the ENABLE MRI study (MR scan related ImageReady System complication free rate) was 90%. There is no hypothesis testing in the MR ICD study, and it can be considered reasonable if up to 2 failed cases of primary safety endpoint event may occur. Descriptive statistics will be conducted for the endpoint events.

The data set for the primary safety endpoint will include all subjects who undergo the study-required MR scan sequences (scan sequences initiated, whether complete or nor). The time window for MRI + 1 Month visit is 30±7 days post MR scan, so it will capture events within at least 23 days post scan. In this small sample size study, missing data will be excluded.

13.1.2. Primary Effectiveness Endpoint 1: Pre-MR Scan vs. 1 Month Post-MR Scan RV shocking impedance

The normal RV shocking impedance measured by the system should be≤200 Ohm, with >200 Ohm considered abnormal. The primary effectiveness endpoint 1 is defined as that the average RV shocking impedance is >200 Ohm 1 month post scan, while it is ≤ 200 Ohm before scan.

There is no hypothesis testing in the MR ICD study, and it can be considered reasonable if up to 2 failed cases of primary effectiveness endpoint 1 occur.

The data set for the primary effectiveness endpoint 1 will only include subjects who undergo the study-required MR scan and complete all the sequences, 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

The time window for MRI + 1 Month visit is 30±7 days post MR scan, so it will capture events within at least 23 days post scan. In this small sample size study, missing data will be excluded.

13.1.3. Primary Effectiveness Endpoint 2: Pre-MR Scan vs. 1 Month Post-MR Scan RV Pacing Threshold at 0.5 ms

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, otherwise, it is a primary effectiveness endpoint 2 event.

The performance goal of this endpoint for the ENABLE MRI study was 87%. There is no hypothesis testing in the MR ICD study, and it can be considered reasonable if up to 2 failed cases of primary effectiveness endpoint 2 occur.

The data set for the primary effectiveness endpoint 2 will only include subjects who undergo the study-required MR scan and complete all the sequences, 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

The time window for MRI + 1 Month visit is 30±7 days post MR scan, so it will capture events within at least 23 days post scan. In this small sample size study, missing data will be excluded.

13.1.4. Primary RV Effectiveness Endpoint 3: Pre-MR scan vs. 1 Month Post-MR Scan RV Sensed Amplitude

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, otherwise, it is a primary effectiveness endpoint 3 event.

The performance goal of this endpoint for the ENABLE MRI study was 85%. There is no hypothesis testing in the MR ICD study, and it can be considered reasonable if up to 2 failed cases of primary effectiveness endpoint 3 occur.

The data set for the primary effectiveness endpoint 3 will only include subjects who undergo the study-required MR scan and complete all the sequences, 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
- Average RV sensed amplitude <5mV pre-MR scan

The time window for MRI + 1 Month visit is 30±7 days post MR scan, so it will capture events within at least 23 days post scan. In this small sample size study, missing data will be excluded.

13.1.5. Primary Effectiveness Endpoint 4: Pre MR Scan- vs. 1 Month Post-MR Scan LV Pacing Threshold at 0.5 ms

Subjects that have an increase in average pacing thresholds ≤1.0V (at 0.5 ms) from pre-MR Scan to MRI Visit + 1 Month follow-up will be considered a success, otherwise, it is a primary effectiveness endpoint 4 event.

The performance goal of this endpoint for the ENABLE MRI study was 87%. There is no hypothesis testing in the MR ICD study, and it can be considered reasonable if up to 2 failed cases of primary effectiveness endpoint 4 occur.

The data set for the primary effectiveness endpoint 4 will only include subjects who undergo the study-required MR scan and complete all the sequences, 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

The time window for MRI + 1 Month visit is 30±7 days post MR scan, so it will capture events within at least 23 days post scan. In this small sample size study, missing data will be excluded.

13.1.6. Primary Effectiveness Endpoint 5: Pre-MR scan vs. 1 Month Post-MR Scan LV Sensed Amplitude

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, otherwise, it is a primary effectiveness endpoint 5 event.

The performance goal of this endpoint for the ENABLE MRI study was 85%. There is no hypothesis testing in the MR ICD study, and it can be considered reasonable if up to 2 failed cases of primary effectiveness endpoint 5 occur.

The data set for the primary effectiveness endpoint 5 will only include subjects who undergo the study-required MR scan and complete all the sequences, 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
- Average LV sensed amplitude <5mV pre-MR scan

The time window for MRI + 1 Month visit is 30±7 days post MR scan, so it will capture events within at least 23 days post scan. In this small sample size study, missing data will be excluded.

13.2. Ancillary Assessments

The ancillary endpoints are not formal endpoints.

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.

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.

13.2.3. Assessment of VT/VF post MR scan

The detection time (first elapsed time), therapy given and conversion result, shocking impedance (if applicable) for post MR scan VT/VF episodes will be presented in the study report.

13.2.4. Assessment of Programming the MRI Protection Mode

The following information will be summarized 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

13.2.5. Assessment of Image Artifacts for non-medically necessary MR scans

MR image quality scores will be presented in the study report.

13.3. Sample Size

The MR ICD study is a small sample size study without any formal hypothesis testing. Twenty subjects (10 with ICD and 10 with CRT-D) will be enrolled. It is assumed that the attrition should not be more than 2 cases in each group, so that at least 8 ICD subjects (at least 1 single chamber and 1 dual chamber ICD) and 8 CRT-D subjects shall undergo required MR scan and complete all the sequences. Sample size might be expanded to meet this assumption.

13.4. General Statistical Methods

13.4.1. Control 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. An independent Clinical Events Committee (CEC) will determine the MR Scan-related ImageReady System complications. The study will be conducted in approximately 5 sites and one single site may not enroll more than 10 subjects generally.

13.4.2. Data Analyses

The MR ICD study is a multi-center, prospective, single –arm study. There is no formal hypothesis testing. Descriptive statistics will be conducted for the endpoint events. Please refer to section13.1for endpoint assessment.

13.4.3. Data Set, Subgroups and Missing Data

The data set for the safety endpoint will include all subjects who undergo the study-required MR scan sequences (scan sequences initiated, whether complete or nor). The data set for the effectiveness endpoint will only include subjects who undergo the study-required MR scan and complete all the sequences, 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 MRI

Subjects whose average RV sensed amplitude <5mV pre-MR scan will also be excluded for primary effectiveness endpoint 3 assessment, and subjects whose average LV sensed amplitude <5mV pre-MR scan will also be excluded for primary effectiveness endpoint 5 assessment.

There is no formal subgroup analysis in the MR ICD study, however, descriptions may be grouped on study site, subject sex, device type (single chamber ICD, dual chamber ICD and CRT-D), etc.

The primary endpoints for the MR ICD study are comparisons between MRI Visit and the MRI + 1 Month Visit, absence of either comparator will be missing data for that endpoint. Missing data will be excluded for endpoint assessment in this small sample size MR ICD study.

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

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

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

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

14.2. Data Retention

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines and China relative regulations. Documents must be retained for 10 years after complete of the clinical study, or longer according to the individual site's requirement. BSC must retain relative clinical study documents till discontinuation of clinical use of the products.
BSC should inform the Principal Investigators and investigation sites the time period required to maintain these documents. The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

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 of the

revised clinical investigational plan by Ethics Committee 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 EC of any major deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

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

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

Deviations will be classified by BSC according to the following definitions:

- Type A - Deviation to protect the life or physical well-being of a patient in an unforeseen emergency.
- Type B - Deviation based on medical judgment.
- Type C - Deviation due to misunderstanding of protocol requirements.
- Type D - Deviation due to a situation that is beyond control.
- Type E - Deviation due to an oversight, error or protocol non-compliance.

Also, a major PD is a protocol deviation that directly or potentially disrupts the study progress (i.e., the study design, study data and results can be compromised), OR a protocol deviation that compromises the safety and welfare of study participants. A minor PD is a protocol deviation that does not disrupt study progress (i.e., the study design, study data and

results will not be compromised), AND does not compromise the safety and welfare of study participants.

17. Device Accountability

The investigational devices shall be securely maintained, controlled, and used only in this clinical study. The current BSC processes will be used to track subjects and device allocations during the study.

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

Records shall be kept by the investigation sites to document the physical location and conditions of storage of all investigational devices.

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 (unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Manufacture date of investigational device
- Batch number of investigational device
- Date on which the investigational device was returned, if applicable
- Date of return of unused, expired, or malfunctioning investigational devices, if applicable.

18. Compliance

18.1. Statement of Compliance

This study will be conducted in accordance with ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practice, the relevant parts of the ICH Guidelines for Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and China laws and regulations. The study shall not begin until the required approval/favorable opinion from the EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

18.2. Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ISO 14155:2011, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

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

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page (if applicable) 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 site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency. Provide analysis report, which includes the causality assessed by both investigator and BSC and decision on study continuance, to EC per local and/or country requirements.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential USADE or UADE.
- Report to the EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential USADE or UADE, if required by the national regulations or this protocol or by the EC, and supply BSC with any additional requested information related to the safety reporting of a particular event. Provide all required source documents related to a death event to BSC and the EC per local requirements.
- 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 clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the EC when performing auditing activities.

- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of 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 Principal 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. Ethics Committee

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

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

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

- Entering technical data on technical source form as long as the responsible investigator verifies and signs the completed worksheet
- Print out programming reports directly from the clinician programmer and provide original to clinical site as source documentation
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

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

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

Boston Scientific personnel will not do the following.

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

China BSC will provide insurance coverage for subjects in the study. If any study related health injury occurs and a site is held responsible for its compensation, where required, BSC will assume the responsibility, except in the case that damages are incurred due to deviation of the protocol, intentional or serious negligence at the site.

19. Monitoring

Monitoring will be performed during the study, according to the study Monitoring Plan, to assess continued compliance with the current, approved protocol/amendment(s) and applicable regulations. In addition, the monitor verifies that informed consent is obtained from all enrolled study subjects, 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. Pre-defined thresholds for protocol deviation and compliance once met or exceeded, can also trigger increased monitoring frequency and/or the implementation of corrective action plans at clinical sites. For the MR China Study, source documents include, at a minimum but not limited to, the ICF; patient medical records, including nursing records and catheterization laboratory records; diagnostic imaging records; laboratory results; reports of SAEs; and device accountability logs. Data documented in the eCRF relevant to device deficiencies, relationship of AE to study device(s), index procedure, and antiplatelet medication; and anticipatedness assessment of ADEs, may be considered source data for the study.

The Investigator/institution guarantees direct access to original source documents (electronic or paper) by BSC personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review. Photocopies of original source documents related to SAEs (from either the study site or a non-study institution, if applicable) must also be made available for submission to BSC.

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

20. Potential Risks and Benefits

20.1. Anticipated Adverse Events

Subjects participating in this study are subject to the same risks shared by all patients undergoing implantation of a defibrillation system. Table 20-1 list the potential adverse events for pulse generator and/ or lead system implants.

Table 20-1 Potential Adverse Events for Pulse Generator and/ or Lead System Implants

Potential Adverse Events for Implantation of a Pulse Generator and/ or Lead System	
Adverse reaction to procedure (e.g., bradycardia, general, respiratory, hypotension)	Lead dislocation
Air embolism	Lead fracture
Allergic reaction	Lead insulation breakage or abrasion
Allergic reaction to the contrast media	Lead perforation
Arterial damage with subsequent stenosis	Lead tip deformation and / or breakage
Bleeding	Local tissue reaction
Bradycardia	Loss of capture
Breakage/failure of the implant instruments	Low amplitude VF signals
Cardiac tamponade	Malignancy or skin burn due to fluoroscopic radiation
Chronic nerve damage	Myocardial Infarction
Component failure	Myocardial necrosis
Conductor coil fracture	Myocardial trauma (e.g., irritability, injury, tissue damage, valve damage)
Coronary venous spasm	Myopotential sensing
Death	Oversensing / undersensing
Electrolyte imbalance/ dehydration	Pacemaker-mediated tachycardia (PMT)
Elevated thresholds	Pericardial rub, effusion
Erosion	Pneumothorax
Excessive fibrotic tissue growth	Post-shock rhythm disturbances
Extracardiac stimulation (muscle/ nerve stimulation)	Prolonged exposure to fluoroscopic radiation
Fluid accumulation	Pulse generator and/or lead migration
Foreign body rejection phenomena	Renal failure from contrast media used to visualize coronary veins
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 (shocks, ATP or pacing)	Vasovagal response
Incisional pain	Venous occlusion
Insulating myocardium during defibrillation internal or external paddles	Venous trauma (e.g., perforation, dissection, erosion)
Incomplete lead connection with pulse generator	Worsening heart failure
Infection including endocarditis	

Subjects may develop psychological intolerance to a pulse generator system and may experience the following: dependency, depression, fear of premature battery depletion, fear that shocking capability may be lost, imagined shocking/fear of shocking while conscious, and fear of device malfunction.

20.2. Risks Associated with Study Devices

Risks Associated with Study Devices are listed in Table 20-1. There are no additional risks associated with the study devices compared with other commercial products in the market.

20.3. Risks Associated with Participation in the Clinical Study

Subjects in the MR ICD Study will have the added risk of an 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 Tech Guide*:

- Arrhythmia induction
- Bradycardia
- Patient death
- Patient discomfort due to slight movement or heating of the device
- 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.

- Syncope
- Worsening heart failure

MRI scanning of patients when the Conditions of Use are NOT 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
- 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.

20.3.1. Beeper

The Beeper may no longer be audible following an MRI scan.

The beeper provides: (1) an audible patient warning when potential therapy failure is detected between scheduled PG checks with a device-following physician, and (2) audible

feedback to clinical personnel regarding the state of the PG such as, current tachycardia mode and when charging for shock therapy. An inaudible beeper results in an increase of the associated risk. **An in-clinic follow-up schedule of every three months is strongly recommended to monitor device performance.** Refer to the *BSC MRI Technical Guide* for more information on the Beeper.

Situations that will no longer trigger audible Beeper tones once the device is programmed into MRI Protection Mode:

Programmable Beeper options	• Beep During Capacitor Charge • Beep When Lead Impedance Out-of-Range • Beep when Explant is Indicated
Non-Programmable Beeper options	• Application of the patient magnet over the pulse generator in certain situations (e.g. confirming Tachycardia Mode) • Battery capacity depleted (End of Life (EOL)) • Battery fault alert • High voltage fault alert • Reversion of the PG to Safety Core Operation • PG Reset

20.4. Risk Minimization Actions

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

20.5. 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.

20.6. Risk to Benefit Rationale

There are no unacceptable residual risks/intolerable risks and all applicable risks have been addressed through the provision of appropriate Directions for Use (DFU). Evaluation of the risks and benefits that are expected to be associated with use of the ImageReady System demonstrate that when used under the conditions intended, the benefits associated with use of the System should outweigh the risks.

21. Safety Reporting

21.1. Reportable Events by investigational site to Boston Scientific

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

- All Serious Adverse Events
- All Investigational Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

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

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

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

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE (see Table 21-1 for AE definitions).

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

21.2. Definitions and Classification

Adverse event definitions are provided in Table 21-1. Administrative edits were made on the definition of serious adverse event from ISO 14155and MEDDEV 2.7/3.

Table 21-1 Safety Definitions

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

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

Complication is defined as serious adverse event or permanent loss of device functions (i.e. pacing or defibrillation).

21.3. Relationship to Study Devices

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in Table 21-2:

Table 21-2 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.
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

Classification	Description
	- 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 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.

21.4. Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 21-3.

Table 21-3 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 24 hours of first becoming aware of the event • Reporting required through the end of the study
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event • Reporting required through the end of the study
	Provide all relevant source	• When documentation is

Event Classification	Communication Method	Communication Timeline
	documentation of the reported event	available
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event • Reporting required through the end of the study
	Provide all relevant source documentation of the reported event	• When documentation is available
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 AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event • Reporting required through the end of the study
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• Within 10 business days after becoming aware of the information • Reporting required through the end of the study

21.5. 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 in Device Management Plan. 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.

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

Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event, and should be reported according to Table 21-3.

21.6. Reporting to Regulatory Authorities / ECs / Investigators

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

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

BSC shall notify all participating study centers if SAEs/SADEs occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

According to China local reporting requirements, Boston Scientific Corporation will report all SAEs and device deficiencies that could lead to SAEs to the local regulatory authorities within 5 business days of BSC first becoming aware of the event, and notify all participating investigators/sites and ECs in a timely manner.

BSC, Investigator, or Site must notify the EC of UADEs, USADEs, SADEs, SAEs, Device Deficiencies and/or other CEC events as applicable according to local reporting requirements. A copy of the Investigator's reports and other relevant reports (if applicable) to the EC must be provided to BSC in accordance with local requirements.

21.7. Subject Death reporting

A subject death during the study should be reported to Boston Scientific as soon as possible and, in any event, within 24 hours of site notification. The site's EC must be notified of any deaths in accordance with that site's EC policies and procedures.
Notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death. A death narrative in the local language is acceptable, if accompanied by a translation in English. The details listed below should be addressed in the death narrative, in order for BSC to understand the circumstance surrounding the death:

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

Also submit the following documentation, if the patient 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 patient 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 IPG should be interrogated. Investigational leads and related Boston Scientific RM system components (e.g., IPGs) should be removed intact and returned promptly to Boston Scientific RM for analysis. The Clinical Events Committee (CEC) must review information regarding subject deaths.

22. Informed Consent

Subject participation in this clinical study is voluntary. If a subject is unable to make the decision to participate in this clinical investigation (e.g. seriously ill or unconscious subject, mentally ill person, mentally handicapped person), the legally authorized representative might sign the ICF. In such case, the subject shall also be informed about the clinical study within his/her ability to understand. An independent witness shall present through a supervised informed consent process and sign the ICF if a subject or legally authorized representative is unable to read or write. 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 ICH/GCP, the Declaration of Helsinki, ISO 14155, any applicable national regulations by CFDA, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by the site's EC, or central EC, if applicable.

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

The process of obtaining Informed Consent includes:

- be conducted by the Principal Investigator or designee authorized to conduct the process,

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

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

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements. Any violations of the informed consent process must be reported as deviations to the sponsor, EC and local regulatory authorities, 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 protocol, a change in Principal Investigator, administrative changes, or following annual review by the EC. The new version of the ICF must be approved by the EC. Boston Scientific approval is required if changes to the revised ICF are requested by the center's EC. The EC will determine the subject population to be re-consented.

The investigator shall inform the subject that even if he/she gives consent to participate in the study, test(s) results might prove the subject's illegibility. The subject's informed will be recorded in a screen sheet, including but not limited to the reason of screen failure.

23. Committees

23.1.Safety Monitoring Process

To promote early detection of safety issues, the BSC Safety team and its delegated CRO Safety team will provide review, process, monitor and evaluation of the safety events defined in the study-specific safety plan. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information. The BSC Medical Safety group includes physicians with expertise in relative field and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

23.2.Clinical Events Committee

A Clinical Events Committee (CEC) will be used in this study. A CEC is an independent group of individuals with pertinent expertise, including Cardiology, which reviews and adjudicates important endpoints and relevant adverse events reported by study investigators. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study sites, and adjudicate study endpoint related clinical events.. The responsibilities, qualifications, membership, and committee procedures of the CEC are outlined in the CEC charter.

For the purpose of the study primary safety endpoint, an 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.

Complication is defined as serious adverse event or permanent loss of device functions (i.e. pacing or defibrillation).

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

24.2.Criteria for Premature Termination of the Study

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

- Important information that impacts the progression of the study (e.g. safety or production performance).
- Regulatory authorities decide to terminate the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

Note: According to requirements in section21, even if the MR ICD study is terminated, subjects with study device(s) shall be followed up for AE, SAE, SADE and device deficiency, which are to be assessed and reported.

There is no hypothesis testing or interim analysis in this study. If the study is terminated prematurely, the already collected data shall be described according to section13.

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

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

24.4.Requirements for Documentation and Subject Follow-up

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

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

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

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

24.5.Criteria for Suspending/Terminating a Study Site

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

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed till end of the study. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

According to section21, all subjects with study device(s) shall be followed up for AEs, which are to be assessed and reported. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

25. Publication Policy

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

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

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.

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, and if required by applicable law.

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28. Abbreviations

Abbreviations are shown in Table 28-1.

Table 28-1 Abbreviations

Abbreviations	Term	Chinese
ADE	Adverse Device Effect	器械不良反应
AE	Adverse Event	不良事件
BSC	Boston Scientific	波士顿科学

CFDA	China Food and Drug Administration	中国食品和药品监督管理局
CFR	Complication-free rate	无并发症率
CRF	Case Report Form	电子病例报告表
EC	Ethics Committee	伦理委员会
ECG	Electrocardiogram	心电图
eCRF	Electronic Case Report Form	电子病例报告表
EDC	Electronic data capture	电子数据采集
FDA	Food and Drug Administration	食品和药品监督管理局
GCP	Good Clinical Practice	临床试验质量管理规范
ICF	Informed Consent Form	知情同意书
IDE	Investigational Device Exemptions	研究器械豁免
IPG	Implantable Pulse Generator	植入性脉冲发生器
LOC	Loss of Capture	失夺获
MRI	Magnetic Resonance Imaging	磁共振成像
ms	Milliseconds	毫秒
mV	Millivolts	毫伏
MV	Minute Ventilation	分钟通气量
RA	Right atrium/ atrial	右心房
RF	Radio-frequency	射频
RV	Right ventricle/ ventricular	右心室
SADE	Serious Adverse Device Effect	严重器械不良反应
SAE	Serious Adverse Event	严重不良事件
T	Tesla	特斯拉
UADE	Unanticipated Adverse Device Effect	非预期的器械不良反应
USADE	Unanticipated Serious Adverse Device Effect	非预期的严重器械不良反应

29. MR Scan Sequences Protocol

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

29.1.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).

29.2.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.

29.3.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 defibrillation 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.

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 29-1 Scan Sequence Protocol

Scan Sequence*	**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		
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		

* Scan sequence names may be slightly different depending on scanner manufacturer.

Statistical Analysis Plan

An Observation of ImageReady™ MR Conditional Defibrillation System in China (MR ICD)

MR ICD CHINA

Study Reference # C2082

Version AB

11FEB2020

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APPROVALS (Check/Complete one below):

☐ Approvals are captured electronically

☒ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

Lead Biostatistician – [Sunil Babu, Sr.Biostatistician]	**Date (dd-mon-yyyy)**
Clinical Project/Trial Manager – [Zhiwei Gu, Clinical Trial Manager]	**Date (dd-mon-yyyy)**
Medical Director – [Zhiyu Zeng, Medical Director]	**Date (dd-mon-yyyy)**

Revision History

Version AB Latest Version
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Document Revision Number/Date	Section	Change	Reason for Change
Version **AA**/ 28AUG2019	None	None	Original Release
Version **AB**/ 11FEB2020	• Section : 4.1 • Section 5.1.2 • Section 5.1.3 • Section 7.5 • 1.Protocol summary • Section 3.3	• Included Attempt and Partial Implant population definitions • Removed the plot based on complication free rate • Updated Ancillary measurement summary for VT/VF episodes and included listing of the Arrhythmia Logbook details • SAS code for Clopper-Pearson • Updated CFDA to National Medical Products Administration (NMPA)	• Including population definitions in accordance to protocol, ir-respective of considering the populations for analysis • Due to less time point duration the plot been excluded from analysis • Ancillary measurements, SAS code and NMPA update suggested by sponsor

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1. PROTOCOL SUMMARY

The study is conducted in accordance to the requirement of global multi-center study, ENABLE MRI (NCT02652481), on MR conditional systems including DYNAGEN and INOGEN. MR ICD (Magnetic Resonance - Implanted Cardiac Devices) protocol is based on ENABLE MRI study. National Medical Products Administration (NMPA) requires certain clinical trial in China to support the approval of ImageReady™ MR conditional defibrillation system. The ImageReady MR Conditional Defibrillation System included in the MR ICD Clinical Study, here to forward referred to as the ImageReady System, consists of DYNAGEN and INOGEN series pulse generators, RELIANCE 4-FRONT series defibrillation leads, ACUITY X4 series left ventricle (LV) leads, and INGEVITY series pacing leads for right atrium (RA).

1.1 Study design:

This is a prospective, multi-center, single-arm, pre-market study

1.2 Study objective:

The study objective is to evaluate the safety and effectiveness of ImageReady™ MR conditional defibrillation system in Chinese population, to support the regulatory approval by NMPA.

1.3 Number of sites and patients and enrollment

Subjects in this trial will not be randomized. Subjects will be considered enrolled into the MR ICD study at the time of informed consent form execution. All subject enrollments will be counted against the enrollment ceiling for the study.

This study will be conducted at up to 5 centers in China. Data will be collected at 20 patients. All participating patients will sign the informed consent form approved at the participating center per local requirements. Generally, one individual center may not enroll more than 10 subjects. Investigational sites will be notified when the enrollment goal is close to being reached and once enrollment is complete.

1.4 Description of study population

Subjects enrolled in the MR ICD 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 Inclusion and Exclusion criteria.

1.5 Description of device(s) including model numbers used in the study

The ImageReady MR Conditional Defibrillation System included in the MR ICD Clinical Study, here to forward referred to as the ImageReady System, consists of DYNAGEN and INOGEN series pulse generators, RELIANCE 4-FRONT series

defibrillation leads, ACUITY X4 series left ventricle (LV) leads, and INGEVITY series pacing leads for right atrium (RA). DYNAGEN and INOGEN pulse generators, belonging to the new generation products. DYNAGEN will be used as the only pulse generator in MR ICD study, while lead selection will be decided mainly by investigators based on subjects' anatomy and clinical practice. This study intention is to label the ImageReady MR Conditional Defibrillation System models "MR Conditional" as defined by the American Society for Testing and Materials (ASTM) 3, when used as a system and in accordance with labeled Conditions of Use.

The below table give the details of ImageReady MR Conditional Defibrillation System Components

Component	Name	Model	Features
Pulse Generators	DYNAGEN	D150	Single chamber ICD, DF4
		D152	Dual chamber ICD, DF4
		G158	CRT-D, DF4, IS4
	INOGEN	D140	Single chamber ICD, DF4
		D142	Dual chamber ICD, DF4
		G148	CRT-D, DF4, IS4
Defibrillation Leads	RELIANCE 4-FRONT active fixation, single coil, Gore coating	0692	59cm
		0693	64cm
		0657	70cm
	RELIANCE 4-FRONT active fixation, dual coil, Gore coating	0695	59cm
		0696	64cm
		0658	70cm
LV leads	ACUITY X4 straight	4671	86cm
		4672	95cm
	ACUITY X4 spiral S	4674	86cm
		4675	95cm
	ACUITY X4 spiral L	4677	86cm
		4678	95cm
RA leads	INGEVITY passive fixation, J type	7735	45cm
		7736	52cm
	INGEVITY active fixation, straight	7740	45cm
		7741	52cm
		7742	59cm
	INGEVITY passive fixation, straight	7731	52cm
		7732	59cm

1.6 Study procedure

Data will be collected from subjects upon enrollment into the study, at implant, and at pre-discharge. Subjects will have an MR scan at 6-9 weeks post-implant, or at least 6 weeks after any required surgical interventions to the ImageReady System (labeled as MRI Visit). Subsequently, there will be a clinic follow up at MRI + 1 Month Visit, and recommended clinic follow up every 3 months post MR scan. Subjects will also be followed at 1-year post-implant. The MR ICD study is composed of two phases. Phase I is completed when all the subjects finish MRI + 1 Month Visit, which starts Phase II till 1-year post implantation. The first Every 3-month visit will occur 90 ± 14 days after MRI visit. Subsequent Every 3-month follow-up visits will be scheduled every three months (90 days ± 14 Days) from the previous scheduled study follow-up. Phase I is expected to last about 9 months after first subject enrollment, and the whole study is expected to last about 20 months after first subject enrollment.

1.7 Follow-up schedule

After First MRI visit the patient visit include:

a. MRI + 3month visit
b. MRI + 6month visit
c. MRI + 9month visit
d. Implant+ 1-Year visit
e. Medically necessary MRI
f. Any Additional visits

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. The individual subject will finish the study when he/she completes the Implant + 1 Year Visit.

1.8 Study duration

Phase I is expected to last about 9 months after first subject enrollment, by when all the subjects will have finished MRI +1 Month Visit. Phase II continues to all the subjects complete one-year follow-up post-implant, and the whole study is expected to last about 20 months after first subject enrollment. Statistical analysis reports are also generated based on Phase I and Phase II study durations. (See section 5.1)

2. INTRODUCTION

This statistical analysis plan addresses the planned analyses for the MR ICD CHINA-Clinical Trial based on the latest version of protocol dated May 1, 2018, Version AC. Specified analyses may be used for scientific presentations and/or manuscripts, and regulatory submissions.

Subjects depending on the implanted leads will be performed :

a. Manual Right Atrial Threshold Test
b. Manual Right Ventricular Threshold Test
c. Manual Left Ventricular Threshold Test

Upon the completion of Implant procedure, 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. Then MRI visits and other follow-up visits will occur.

The primary safety analysis will be based on MR Scan-related ImageReady System Complication-Free Rate between the MR Scan and the MRI + 1 Month Visit. The primary effectiveness endpoints based on Abnormal increase and decrease in RV and LV on impedance, threshold and amplitude. Ancillary components RA & IV assessments, VT/VF episodes assessments and Image Artifacts assessments will be analyzed as well. These analyses are more elaborately detailed in the below endpoint analysis.

3. ENDPOINT ANALYSIS

The primary safety endpoint analysis is based on MR Scan-Related ImageReady System Complication Free Rate.

3.1 Primary Safety Endpoint

i. Primary Safety Endpoint: *The primary safety endpoint of the MR ICD study 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. There is no hypothesis testing in the MR ICD study, and it can be considered reasonable if up to 2 failed cases of primary safety endpoint event may occur. Descriptive statistics will be conducted for the endpoint events with 95% CI. The time window for MRI + 1 Month visit is 30±7 days post MR scan, so it will*

capture events within at least 23 days post scan. Missing data will be excluded.

3.2 Primary Efficacy Endpoint

There are 5 primary effectiveness endpoints on the Abnormal increase and decrease in RV and LV components for shocking impedance, pacing threshold and sensed amplitude. There is no hypothesis testing in the MR ICD study, and it can be considered reasonable upon the failed cases of primary effectiveness endpoint occur.

i. ***Primary Effectiveness Endpoint 1****: Pre-MR Scan vs. 1 Month Post-MR Scan RV shocking impedance:*

The data set for the primary effectiveness endpoint 1 will only include subjects who undergo the study-required MR scan and complete all the sequences, 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*

The normal RV shocking impedance measured by the system should be≤200 Ohm, with >200 Ohm considered abnormal. The primary effectiveness endpoint 1 is defined as that the average RV shocking impedance is >200 Ohm 1-month post scan, while it is ≤ 200 Ohm before scan.

ii. ***Primary Effectiveness Endpoint 2****: Pre-MR Scan vs. 1 Month Post-MR Scan RV Pacing Threshold at 0.5 ms:*

The data set for the primary effectiveness endpoint 2 will only include subjects who undergo the study-required MR scan and complete all the sequences, 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*

The primary effectiveness endpoint 2 is defined as ‘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 as success', otherwise it's a failure (event).

iii. ***Primary Effectiveness Endpoint 3:*** *Pre-MR scan vs. 1 Month Post-MR Scan RV Sensed Amplitude:*

The data set for the primary effectiveness endpoint 3 will only include subjects who undergo the study-required MR scan and complete all the sequences, 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*
- *Average RV sensed amplitude <5mV pre-MR scan*

The primary effectiveness endpoint 3 is defined as '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 as success', otherwise it's a failure (event).

iv. ***Primary Effectiveness Endpoint 4:*** *Pre-MR Scan- vs. 1 Month Post-MR Scan LV Pacing Threshold at 0.5 ms:*

The data set for the primary effectiveness endpoint 4 will only include subjects who undergo the study-required MR scan and complete all the sequences, 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*

The primary effectiveness endpoint 4 is defined as 'increase in average pacing thresholds ≤1.0V (at 0.5 ms) from pre-MR Scan to MRI Visit + 1 Month follow-up will be considered a success', otherwise it's a failure (event).

v. ***Primary Effectiveness Endpoint 5:*** *Pre-MR scan vs. 1 Month Post-MR Scan LV Sensed Amplitude:*

The data set for the primary effectiveness endpoint 5 will only include subjects who undergo the study-required MR scan and complete all the

sequences, 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*
- *Average LV sensed amplitude <5mV pre-MR scan*

3.3 Ancillary Assessments

The ancillary endpoints are not formal endpoints

- Changes in RV and LV impedances pre-MR scan versus 1 Month post-MR scan (MRI Visit and MRI + 1 Month Visit) assessed for RV and LV Impedances
- Changes in RA lead measurements including pacing thresholds, sensed amplitudes and impedances, between pre- and 1 Month post-MR scan measurements assessed for RA lead measurements
- The detection time (first elapsed time), therapy given and conversion result, shocking impedance (if applicable) assessed for post MR scan VT/VF episodes. For a VT/VF episode, there might be no therapy, ATP or Shock therapy. Only shock therapy will have a shocking impedance, while shock for VT/VF might be very few in this small sample study. Data collected from Arrhythmia Logbook Report used for Assessment of VT/VF post MR scan and only VT/VF episodes from Arrhythmia log book considered for analysis. Detection time, Therapy given are summarized based on subject total episodes from visit and shocking impedance summarized based on subjects.
- The following information will be summarized 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
- MR image quality scores will be presented in study report for assessment of Image Artifacts for non-medically necessary MR scans

3.4 Hypotheses

There is no formal hypothesis planned for this study. The individual performance goal is sort of hypothesis, to decide the performance status of each endpoint.

3.5 Sample Size

The MR ICD study is a small sample size study without any formal hypothesis testing. Twenty subjects (10 with ICD and 10 with CRT-D) will be enrolled. It is assumed that the attrition should not be more than 2 cases in each group, so that at least 8 ICD subjects (at least 1 single chamber and 1 dual chamber ICD) and 8 CRT-D subjects shall undergo required MR scan and complete all the sequences. Sample size might be expanded to meet this assumption.

3.6 Statistical Methods

The procedure success rate for both primary safety and efficacy endpoints will be summarized descriptively. Categorical variables will be tabulated with frequencies, percentages and 95% confidence intervals. Continuous variables will be tabulated with mean, median, standard deviation, minimum, maximum, and 95% confidence interval of the mean.

4. GENERAL STATISTICAL METHODS

4.1 Analysis Sets

The definition of analysis datasets planned for the study detailed below:

a. ***Intent population*** *- includes all subjects who undergo the study-required MR scan sequences (scan sequences initiated, whether complete or nor). The Intent-to-Treat group will be analyzed for safety data and effectiveness specific to stent placement/removability.*

b. ***Implant population*** *- is the subset of the ITT subjects that will only include subjects who undergo the study-required MR scan and complete all the sequences, 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 MRI*

Subjects whose average RV sensed amplitude <5mV pre-MR scan will also be excluded for primary effectiveness endpoint 3 assessment and subjects whose average LV sensed amplitude <5mV pre-MR scan will also be excluded for primary effectiveness endpoint 5 assessment.

c.Attempt *- Attempt refers to a subject who has had the lead(s) and/or PG introduced into the body but is not successfully implanted with any portion of the ImageReady System during the implant procedure. 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, then withdrawn from the study.

d. ***Partial Implant*** *- Partial Implant refers to a subject who is implanted with a component of the ImageReady System (lead or pulse generation) during the implant procedure but does not end up with a complete ImageReady System. They shall not receive the protocol required MR Scan according to the BSC MRI Technical Guide. 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.*

However, the results for the populations been analyzed when the subjects status been categorized in Attempt and Partial Implant populations and based on the sponsor requirements.

4.2 Control of Systematic Error/Bias

There is no randomization schema assigned in the study. 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. An independent Clinical Events Committee (CEC) will determine the MR Scan-related ImageReady System complications. Consecutively eligible subjects should be enrolled into the study to minimize selection bias.

4.3 Number of Subjects per Investigative Site

The study will be conducted in approximately 5 sites and one single site may not enroll more than 10 subjects.

5. DATA ANALYSES

5.1 Endpoints/Measurements analysis

Statistical endpoint and other analysis report generated based on study design phases, which as detailed in study duration section. Phase I include the statistical report till 9 months study duration and Phase II statistical report for complete study including all follow-ups and additional visits information. A set of additional tables and listings will be provided based on final available data lock, compared to initial Phase I generated report. However, this analysis plan created in context to final statistical report.

5.1.1 Primary efficacy endpoint analysis:

The primary effectiveness endpoints are defined as 'a success based on the specified criteria conditions earlier', otherwise it's a failure (event) .

All the 5- primary endpoints are based on Implant population,

- Pre-MR Scan vs. 1 Month Post-MR Scan RV shocking impedance
- Pre-MR Scan vs. 1 Month Post-MR Scan RV Pacing Threshold at 0.5 ms
- Pre-MR scan vs. 1 Month Post-MR Scan RV Sensed Amplitude
- Pre-MR Scan- vs. 1 Month Post-MR Scan LV Pacing Threshold at 0.5 ms
- Pre-MR scan vs. 1 Month Post-MR Scan LV Sensed Amplitude

are summarized descriptively with counts and percentages presenting 95% Clopper-Pearson confidence interval with two-sided exact binomial confidence bound at 95% will be presented to anticipate that the endpoint success is more than the lower bound of the confidence limits.

The time window for MRI + 1 Month visit is 30±7 days post MR scan, so it will capture events within at least 23 days post scan for all the endpoints and Missing data will not be considered in the denominator part while deriving confidence limits and performance goals.

5.1.2 Primary safety endpoint analysis:

The primary safety endpoint of the MR ICD study 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. This endpoint is analyzed based on Implant population. Counts and percentages presenting 95% Clopper-Pearson confidence interval with two-sided exact binomial confidence bound at 95%.

Complications that are determined to be associated with the MR scan will be considered MR scan-related complications and count against this endpoint. Complication is defined as serious adverse event or permanent loss of device functions (pacing/defibrillation).

All the primary efficacy endpoint and safety endpoint been summarized presenting 95% Clopper-Pearson confidence interval with two-sided exact binomial confidence made for both Intent and Implant study populations. If subject's status been categorized to either Attempt or Partial Implant, then the results been presented for both these populations as well.

5.1.3 Ancillary Assessments

We are also analyzing the ancillary assessments for pacing threshold, Pulse width, sensed amplitude and pacing impedance for RA, RV and LV components. The ancillary endpoints are not formal endpoints; however, we present results based on Ancillary Assessments requirements. A listing will be provided with all the details provided from the Arrhythmia log book.

All the categorical response of the measurements summarized using counts and percent. The continuous parameters including time variables presented with mean, standard deviation with counts and minimum and maximum values. is based on Implant population

We are also presenting the plots in connection with ancillary assessments for pacing threshold, Pulse width, sensed amplitude and pacing impedance for RA, RV and LV components.

- A mean plot generated based on the duration and pacing threshold by RA, RV and LV components by separate panel.
- A mean plot generated based on the duration and Pulse width by RA, RV and LV components by separate panel.
- A mean plot generated based on the duration and Sensed amplitude by RA, RV and LV components by separate panel.
- A mean plot generated based on the duration and Pacing impedance by RA, RV and LV components by separate panel.

5.1.4 Interim Analyses

No formal interim analyses are planned for this study. If the study is terminated prematurely, the already collected data shall be described according

5.1.5 Subgroup Analyses

No subgroup analyses are planned for this study. There is no formal subgroup analysis in the MR ICD study, however, descriptions may be grouped on study site, subject sex, device type (single chamber ICD, dual chamber ICD and CRT-D), etc.

5.1.6 Justification of Pooling

This study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analyses. Every effort will be made to promote consistency in study execution at each investigational site.

5.1.7 Multivariable Analyses

No multivariate methodology included for the primary, secondary or other endpoints

5.2 General considerations

All continuous measurements will be summarized descriptively at each visit by treatment using observed data. Endpoints that are analysed untransformed and endpoints that are not formally analysed are summarized by the arithmetic mean, standard deviation (SD), minimum and maximum value with counts (N). Mean and SDs rounded to one decimal, minimum, maximum is presented exact as per the data values.

5.3 Other Statistical considerations

All the statistical analysis for other tables other than endpoint results will be generated based on Implant population only. However, depending on the results and sponsor requirements the Implant population results will be performed.

5.3.1 Patient disposition/status

Number of subjects enrolled by investigator and site will be summarized with counts and percent based on Implant population.
A table based on Subject Disposition of Clinical Follow-up Compliance will be provided at MRI Visit +1Month visits after device implant. A table supported to present the counts based on the enrollments per site will be provided.
If any deaths happened, a supporting listing based on deaths will be provided with related to study device and study procedure, with date of death and duration of days from device implant.

5.3.2 Baseline and Demographic analysis

Baseline characteristics with Arrhythmia and Cardiac disease history, physical examinations summarized at screening or baseline visit. Continuous measurements will be summarized descriptively and categorical measurements with counts and percent.

5.3.3 Procedure Characteristics and performance

Procedure evaluation summary for Atrial Fibrillation., RA, RV & LV lead measurements and PNS threshold with New Episode of polymorphic and Image Artifacts measurement are summarized. Device Information like Pulse generator, Defibrillation Lead & LV Lead are summarized for Implant populations at Implant procedure, Pre-Discharge, MNS Pre - Post MR Scan visits, Pre MR-Scan Visit, Post MR Scan Visit & MRI Visit+1 Month procedure, MRI Visit+ 3-month, MRI Visit+ 6-month, MRI

Visit+ 9-month visits and Implant+1-year visits. However, the results will be summarized only for the above available timepoint visits.

A comprehensive listing based on MRI information by visits is presented by subject with MRI protection mode, Time of MR scan initiation and completion, exiting MRI protection and radiologist scores are presented.

- A listing based on pacing threshold LEAD (RA/RV/LV) for each subject with site
- A listing based on Sensed Amplitude LEAD (RA/RV/LV) for each subject with site
- A listing based on Pacing Impedance LEAD (RA/RV/LV) for each subject with site
- A listing based on Shocking Impedance LEAD (RA/RV/LV) for each subject with site

will be presented based on available analysis time points including Implant procedure, Pre-Discharge, MNS Pre - Post MR Scan visits, Pre MR-Scan Visit, Post MR Scan Visit & MRI Visit+1 Month procedure, MRI Visit+ 3-month, MRI Visit+ 6-month, MRI Visit+ 9-month visits and Implant+1-year visits. All the above listings are based on Implant populations.

A summary table for all medications with Generic medication name summarized for cardiovascular medication usage based on Implant population presented for Implant, pre-Discharge, MR Scan, MRI Visit+1-week, MRI Visit+1-month, MRI Visit+ 3-month, MRI Visit+ 6-month , MRI Visit+ 9-month visits and Implant+1-year visits.

5.3.4 Analysis of Adverse and Serious adverse events

Subject-level event rates will be calculated at various time points (e.g. exact days) based on all events reported by the site regardless of whether they are ultimately adjudicated. Frequency of site reported Serious adverse events and non-serious adverse events and also Frequency of site-reported Serious adverse events and Non-serious adverse events are associated with the implant procedure up to MRI Visit+1 Month are exhibited using counts and percent with total available subjects based on safety population. The events are summarized by MedDRA system organ class and MedDRA system preferred terms with events and rates.

For calculating events and rates, need to consider 'Events numbers' are total episodes of each type of event among all subjects. 'Rate of Subjects with Event' numbers are percent of subjects who experienced one or more episodes of the event. 'Events' numbers for "TOTAL" are the sum of the individual event category totals. 'Rate of Subjects with Event' numbers for "TOTAL" is the percent of subjects who experienced an adverse event.

5.3.5 Protocol Deviations

A summary table for Deviations from Investigational Protocol collated during procedure and post procedure for all the planned events as specified in protocol.

- Enrollment
- Implant
- Pre-Discharge
- Partial Implant / Attempt + 1 Month
- Medically Necessary Scan(MNS)
- MRI Visit
- MRI Visit + 1 Month
- MRI Visit + 3 Month
- MRI Visit + 6 Month
- MRI Visit + 9 Month
- 1 Year Follow-up Visit
- Additional Visit
- Adverse Events
- Cardiovascular Medications
- Device Deficiency
- End of Study

A summary table by protocol deviation are summarized with counts and percent and another summary table presented based on deviations reasons

5.3.6 Device Deficiencies

A table exhibited based on device deficiencies with out of service reasons been presented with count and percent for the available parameters with a supported listing. Also, a listing based on Device deficiency identifier with description and connected to SAE with occurrence instance been listed for Implant population.

5.4 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.

6. VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation. The validation level R1 chosen for all primary, secondary, safety and other additional endpoints.
The validation program includes checking logs and generating compare reports in comparing with main programming datasets.

7. PROGRAMMING CONSIDERATIONS

All statistical programming tasks will be performed by IQVIA™ independently.

7.1 Statistical Software

All statistical analyses will be done using The SAS System Version 9.2 software or above (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved.).

7.2 Format of Output

Results of analysis will be output programmatically to Microsoft Office® Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

7.3 Methods for Handling Missing Data

No imputation method will be performed for the missing data handling.
Missed or late visits will be recorded as Protocol Deviations.
When calculating rates of treatment-emergent adverse events, missing and partial dates will be handled as shown in the table below.

Partial Date	Action Taken
Entire adverse event onset date is missing	The procedure date will be used for the onset date.

Partial Date	Action Taken
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

7.4 Rules and Definitions

For baseline categorical variables, missing values will not be counted in rate denominators. Number of patients completing the visit will be considered in denominators.

7.5 SAS code for Clopper-Pearson

The confidence intervals for Clopper-Pearson and binomial proportion of CI are produced using PROC FREQ procedure. Below is a glimpse of sample code to extract the required values. For example, for the primary endpoint hypotheses for deriving Clopper-Pearson confidence limits, using the below dummy frequency table, coded as below:

```
data main;
   input code $4. count;
   datelines;
yes 56
no  4
;
run;
proc freq data=main order=freq;
   tables code / binomial (exact ) alpha=.05;
   tables code / binomial (cl=Wald ) alpha=.05;
   weight Count;
run;
```

The SAS code is presented for the binomial proportion for 95% Clopper-Pearson confidence intervals is specified. The use of ORDER=FREQ, in the SAS program, keep the highest frequency of success/failure as base and option binomial (EXACT) with alpha=0.05 will generate 95% Clopper-Pearson Confidence limits. We also get Wald's (Asymptotic) 95 % Confidence limits that need to present in the exhibit.