Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	China CIED 3.0T MRI Performance Study
Clinical Investigation Plan Identifier	MDT23009
Study Product Name	Market released single/dual chamber pacemaker, single/dual chamber ICD, and CRT-D devices compatible with 3.0T MRI scan, Medtronic market released LV leads, and any market released RA and RV leads compatible with 3.0T MRI scan
Class III medical devices requiring clinical trial approval	Yes
Sponsor	[redacted]
Document Version	2.0
Version Date	06-Feb-2024
Lead Principal Investigator(s)	[redacted]
Coordinating Investigaor	[redacted]

1.Investigator Agreement and Signature Page

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Sponsor	Medtronic (Shanghai) Management Co., Ltd.
Clinical Investigation Plan Identifier	MDT23009
Version Number/Date	Version 2.0/06-Feb-2024

I agree that:

1. I will conduct this clinical trial in strict compliance with the Declaration of Helsinki, current laws and regulations of China, and the requirements of the Clinical Investigation Plan;
2. I will record all required data accurately on the Case Report Form (CRF) and assist to complete the final report of the clinical investigation;
3. The investigational medical device will be used only for this clinical investigation and the receipt and use of the investigational medical device will be recorded completely and accurately and the records will be retained during the process of the clinical investigation;
4. The monitors and auditors authorized or designated by the Sponsor and the regulatory authorities are allowed to conduct monitoring, audit and inspection for the clinical investigation;
5. The clinical investigation should be conducted in strict compliance with contract/articles of agreement signed by all parties.

I have already read the clinical study protocol, including the above statement and I fully agree all the above requirements.

Principal Investigator: Signature Date:

Medical device clinical trial institution: Stamp: Date:

Sponsor: Medtronic (Shanghai) Management Co., Ltd. Stamp: Date:

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2.Glossary

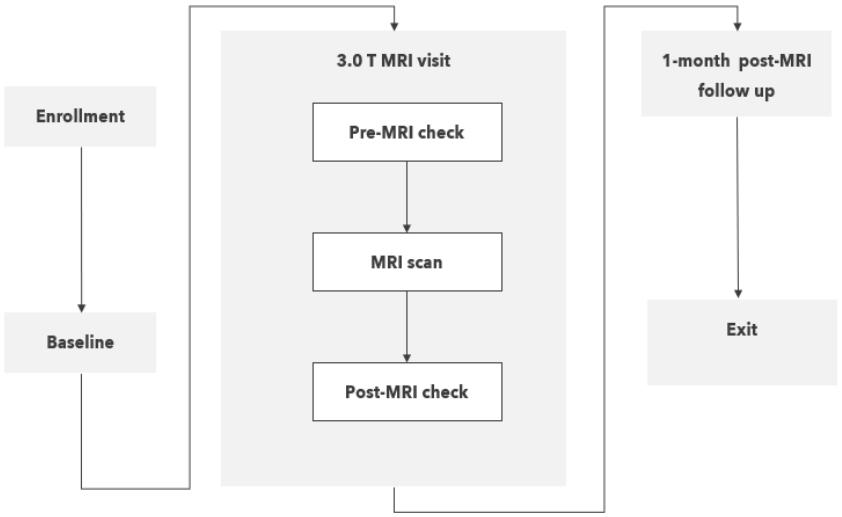
Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
CA	Competent Authority
CFR	Code of Federal Regulation
CIP	Clinical Investigation Plan
CRO	Clinical Research Organization
CRT-D	Cardiac Resynchronization Therapy Defibrillator
CRF	Case Report Form
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DoH	Declaration of Helsinki
DTL	Delegated Task List
eCRF	Electronic Case Report Form
EC/IRB/HREB/Ethics Board	Ethics Committee
FD	Financial Disclosure
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
IB	Investigator Brochure
IC	Informed Consent
ICD	Implantable Cardiac Defibrillator

Term	Definition
ICH	International Conference of Harmonization
IDE	Investigational Device Exemption
IFU	Instructions For Use
IPG	Implantable Pulse Generator
LV	Left ventricular
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
PHI	Protected Health Information
PCT	pacing capture threshold
PMDA	Pharmaceuticals and Medical Devices Agency
RA	Right Atrium
RED	Radio Equipment Directive
RPI	Report of Prior Investigations
RV	Right ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SID	Subject Identification
SOC	Standard of care
UAE	Unavoidable Adverse Event

3.Synopsis

Title	China CIED 3.0T MRI Performance Study
Clinical Study Type	prospective, multi-site , single-arm, interventional post-market study
Product Name	China market released 3.0T Magnetic resonance (MR) conditional CIED systems encompassing implantable pulse generators (IPGs), implantable cardioverter defibrillators (ICDs), and Cardiac Resynchronization Therapy Defibrillator (CRTD) devices and implantable pacing and defibrillation leads.
Sponsor	Mainland China Medtronic (Shanghai) Management Co., Ltd. 2106A, 21st Floor, No. 28. Maji Road, China (Shanghai) Pilot Free Trade Zone, 200131, Shanghai, P.R. China +86 215 866 9877
Indication under investigation	Indication for CIED implant is completed in accordance with current clinical practice guidelines. CIED systems featuring the SureScan Technology are labeled as MR conditional.
Investigation Purpose	The purpose of this study is to confirm safety and effectiveness of the SureScan CIED System in the clinical MRI environment when subjects receive 3.0T MRI scans without positioning restrictions (MRI scans may occur anywhere on the body).
Product Status	Market released
Primary Objective(s) and/or Endpoint(s)	To demonstrate the safety of SureScan system CIED in clinical 3.0T MRI environment within 1 month post-MRI scan. Endpoint Definition **The occurrence of any of the following within 30 days after the 3.0T MRI visit will be considered an MRI-related event for IPG:** ○ Medical advisor-assessed MRI-related complication within 30 days post-MRI ○ Medical advisor-assessed right ventricular MRI-related loss of capture within 30 days post-MRI **The occurrence of any of the following within 30 days after the 3.0T MRI visit will be considered an MRI-related event for ICD/CRTD:** ○ Medical advisor-assessed MRI-related complication within 30 days post-MRI ○ Sustained tachyarrhythmia originating during SureScan programming, requiring immediate treatment (defined as ATP, device shock, or external shock) as assessed by a medical advisor. ○ Medical advisor-assessed right ventricular MRI-related loss of capture within 30 days post-MRI
Secondary Objective(s) and/or Endpoint(s)	To characterize changes in atrial and ventricular pacing capture thresholds (APCT and VPCT) from pre-MRI to 1-month post-MRI scan

	Endpoint Definition PCTs to be evaluated include: ○ Atrial pacing capture threshold (if applicable) ○ Ventricular pacing capture threshold (both right and left ventricular lead if applicable)
[redacted]	
Study Design	The China CIED 3.0T MRI performance study is a prospective, multi-site , single-arm, interventional post-market study. Subjects who were implanted with an SureScan system CIED (including device and lead) over 6 weeks at the time of signing ICF will be enrolled. All subjects will have required follow-up visits at baseline, MRI scan and 1-month post-MRI. The MRI scan will occur in subjects implanted over 6 weeks.
Sample Size	64 patients
Inclusion/Exclusion Criteria	Inclusion Criteria • Subjects who were implanted with an SureScan system CIED (including device and lead)over 6 weeks at the time of signing ICF. • Subjects who are able and willing to undergo elective MRI scanning without sedation. • Subjects who were implanted an SureScan system CIED in the pectoral region. • Subjects who are geographically stable and available for follow-up at the study site for the length of the study. • Subjects who are at least 18 years of age (or older, if required by local law). Exclusion Criteria • Subjects who require a legally authorized representative to obtain informed consent. • Subjects with abandoned or capped leads. • Subjects who require an indicated MRI scan, other than those specifically described in the China CIED 3.0T MRI performance study, before the 1-month post-MRI follow-up. • Subjects with a non-MRI compatible device (such as neurostimulators) or material implant (e.g., non-MRI compatible sternal wires, neurostimulators, biostimulators, metals or alloys). • Subjects with medical conditions that preclude the testing required by the CIP or limit study participation. • Subjects who are enrolled or intend to participate in another clinical trial (of an investigational drug or device, new indication for an approved drug or device, or requirement of additional testing beyond

	standard clinical practice) during the SureScan study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic study manager. • Female patient who is pregnant, or of childbearing potential and not on a reliable form of birth control. Women of childbearing potential are required to have a negative pregnancy test within seven (7) days prior to MRI scan.
Study Procedures and Assessments	
Safety Assessments	The occurrence of any of the following within 30 days after the 3.0T MRI visit will be considered an MRI-related event for IPG: ○ Medical advisor-assessed MRI-related complication (as defined in the table 7) within 1-month post-MRI ○ Medical advisor-assessed right ventricular MRI-related loss of capture within 1-month post-MRI The occurrence of any of the following within 1 month after the 3.0T MRI visit will be considered an MRI-related event for ICD/CRTD: ○ Medical advisor-assessed MRI-related complication (as defined in the table 7) within 1-month post-MRI ○ Sustained tachyarrhythmia originating during SureScan programming, requiring immediate treatment (defined as ATP, device shock, or external shock) as assessed by medical advisor. ○ Medical advisor-assessed right ventricular MRI-related loss of capture within 1-month post-MRI
Statistics	Descriptive statistics will be used to summarize baseline demographics. The primary objective will be evaluated using a one-proportion binomial exact test along with a one-sided 97.5% lower (Clopper-Pearson) confidence bound. The Change in PCT is the PCT measured at one month post-MRI

	subtracts that measured prior to a 3.0T MRI scan. Descriptive statistics such as mean and standard deviation will be provided for changes in APCT and VPCTs, respectively. Descriptive statistics such as mean and standard deviation will be provided for the absolute change in sensing amplitude between pre- and post-MRI.

4. Introduction

4.1 Background

MRI has grown into one of the most widely used non-invasive imaging modalities. Various medical disciplines rely on the diagnostic capabilities of MRI because of its unique ability to discriminate soft tissues. In 2011, an estimated 32.0 million scan procedures were performed in the U.S. alone, up 4% from the previous year[1]. It is estimated that 50% to 75% of patients with a cardiac implantable electronic device (CIED) will need an MRI scan after the implantation over their lifetime[2]. Since the release of the first MR conditional system, clinical studies report satisfactory results concerning safety and effectiveness of these systems in terms of device performance and patient safety. However, recent evolution of MRI system from the 1.5 Tesla(T) to the 3.0T technology, with stronger magnetic fields and gradients, has imposed the need to verify that existing implantable device are safe under more compelling criteria.

Medtronic has spent the last 15 years assessing the multiple interactions between cardiac devices and MRI machines via numeric modeling, bench testing, and animal studies. Modeling enables the evaluation of implanted system performance associated with differing patient anatomies, lead lengths, lead paths, scanner manufacturers, scan types, and patient positions within the scanner. Utilizing this model, market-released leads can be evaluated for potential MR conditional use.

Today in China, the majority of implanted CIED is applicable to the certification of 1.5 T MRI environmental. Lately multiple mode of CIEDs and leads were approved for 3.0T MRI scan in China market. Although the pre-clinical testing and clinical data have demonstrated the safety and efficacy of select CIEDs in a magnetic resonance (MR) environment when used according to labeling requirements, the safety and effectiveness data of 3.0T MRI scanning is limited in local market.

4.2 Purpose

This study is a prospective, non-randomized, multi-site study conducted in mainland China. The study is considered an interventional trial in China. The purpose of the China CIED 3.0T MRI Performance Study

1. 2012 MR Benchmark Report, IMV Medical Information Division, Inc.

2. Kalin R and Stanton MS. Current Clinical Issues for MRI Scanning of Pacemaker and Defibrillator Patients. Pacing and Clinical Electrophysiology 2005 Apr: 28(4): 326-8.

is to confirm safety of SureScan CIEDs in the clinical 3.0T MRI environment when subjects receive MRI scans.

5. Objectives and/or Endpoints

5.1 Objectives

5.1.1Primary Objective

To demonstrate the safety of SureScan system CIED in clinical 3.0T MRI environment within 1 month post-MRI scan.

Endpoint Definition

The occurrence of any of the following within 30 days after the 3.0T MRI visit will be considered an MRI-related event for IPG:

- Medical advisor-assessed MRI-related complication (as defined in the table 7) within 30 days post-MRI
- Medical advisor-assessed right ventricular MRI-related loss of capture within 30 days post-MRI

The occurrence of any of the following within 30 days after the 3.0T MRI visit will be considered an MRI-related event for ICD/CRTD：

- Medical advisor-assessed MRI-related complication (as defined in the table 7) within 30 days post-MRI
- Sustained tachyarrhythmia originating during SureScan programming, requiring immediate treatment (defined as ATP, device shock, or external shock) as assessed by medical advisor.
- Medical advisor-assessed right ventricular MRI-related loss of capture within 30 days post-MRI

Rationale

This endpoint was chosen to encompass adverse events related to the 3.0T MRI scan. MRI-related event rate will be summarized and analyzed to evaluate the safety of SureScan CIED in 3.0T MRI environment.

5.1.2 Secondary Objective

To characterize changes in atrial and ventricular pacing capture thresholds (APCT and VPCT) from pre-MRI to one month post-MRI scan

Endpoint Definition

The effectiveness of the Surescan MRI CIED device will be measured by the following parameters

- Atrial pacing capture threshold (if applicable)
- Ventricular pacing capture threshold (both right and left ventricular lead if applicable)

These parameters will be measured pre-MRI scan, immediately post MRI scan and 1-month post MRI scan.

Rationale

While PCT and sensing amplitude changes will contribute to the effectiveness objective, the increased PCT will affect the pacing effectiveness and the lifetime of device.

[redacted]

6. Study Design

The China CIED 3.0T MRI Performance study is a prospective, non-blinded, multi-site, interventional post-market study. The study is expected to be conducted at mainland China. Participating devices are expected to include single/dual chamber transvenous IPG, single/dual chamber ICD and CRTD.

The number of enrolled subjects in the study is 64 considering the attrition. To ensure a reasonable distribution of experience and minimize site bias in study results, the maximum number of subjects enrolled at each site will be capped at 30% of total subjects enrolled. All subjects will have required follow-up visits at baseline, MRI visit, 1-month post-MRI. The MRI scans will occur at the MRI visit. The MRI scan region will be determined by investigator according to the subject's clinical condition.

Ethics Committee approval of the study CIP and informed consent must be obtained prior to the site enrolling patients. Subject medical history will be verified to ensure patients meet all the inclusion and none of the exclusion criteria.

6.1 Duration

The expected study duration is approximately 9 months, representing 7 months of enrollment and 2 months of subject follow-ups. The duration of individual subject participation will vary based on timing of site activation and their enrollment.

6.2 Rationale

The main purpose of this study is to demonstrate safety of Surescan CIED in 3.0T MRI environment. The performance goals for the primary safety objective are chosen based on the known performance of Medtronic SureScan Post-Approval Study and the objectives are designed to show that the Surescan CIED will perform comparably with regard to safety and efficacy in 3.0T MRI environment.

7. Product Description

7.1 General

Cardiac Implantable Electronic Device (CIED) systems encompass implantable pulse generators (IPGs), implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices and implantable pacing and defibrillation leads. CIEDs provide automated treatment of atrial and ventricular arrhythmias when the heart may be beating too fast or too slow.

CIED systems featuring the SureScan Technology are labeled as MR conditional. For purposes of evaluating the relationship of 3.0T MRI exposure to MRI-related complication, all MR conditional labeled Medtronic SureScan devices are considered interchangeable and contribute equally to the primary objective.

7.1.1 System/Product Component

MR Conditional IPGs

System configurations include a combination of a SureScan IPG, a pacing lead in the right atrium and ventricle (for dual chamber systems) or right ventricle only (single chamber IPG). All system components need to be Medtronic SureScan MR conditional products. Refer to Table 1 for details of current Medtronic MR conditional IPG system components approved for 1.5 and 3.0T MR conditional labeling in mainland China.

Table 1: Medtronic MR Conditional IPG Components

Component	Model Number
[redacted]	
Pacing Leads	
[redacted]	

Component	Model Number
[redacted]	

MR Conditional ICDs

System configurations include a combination of a SureScan ICD, a pacing lead in the right atrium and ventricle (for dual chamber systems) or right ventricle only (single chamber ICD). All system components need to be Medtronic SureScan MR conditional products. Refer to Table 2 for details of current MR conditional ICD system components approved for 1.5 and 3.0T MR conditional labeling.

Table 2: Medtronic MR Conditional ICD Components

Component	Model Number
[redacted]	
Pacing Leads	
[redacted]	
Defibrillator Leads	

Component	Model Number
[redacted]	

MR Conditional CRTD

System configurations include a combination of a SureScan CRT-D devices, a pacing lead in the right atrium or 6725 pin plug, a defibrillator lead in the right ventricle, and a left ventricular lead.All system components need to be Medtronic SureScan MR conditional products. Refer to Table 3 for details of current MR conditional CRT-D system components approved for 1.5 and 3.0T MR conditional labeling.

Table 3: Medtronic MR Conditional CRTD Components

Component	Model Number
[redacted]	
Pacing Leads	
[redacted]	
Defibrillator Leads	
[redacted]	
Left Heart Leads:	
[redacted]	

8. Study Site Requirements

8.1 Investigator/Investigation Site Selection

All investigators managing the subjects implanted Surescan CIED must be qualified practitioners and experienced in the diagnosis and treatment of subjects with implanted Surescan CIED. All physicians must be experienced and/or trained in the handling of Surescan CIED.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- have a senior professional title
- be filed at the PMPA (Provincial Medical Product Administration) Filing System
- Be experienced in the field of application and training in the use of Surescan CIED
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results
- Be able to demonstrate that the proposed investigational study site:
- Has the required number of eligible subjects needed within the recruitment period
- Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation

Study site personnel training will be completed and documented prior to participation in this study.

8.2 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the clinical investigation plan, on relevant standards and regulations, informed consent, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- EC approval (and voting list, as required by local law) of the current version of the CIP and IC.
- RA approval or notification (as required per local law)
- Fully executed CTA
- CV of investigators and key members of the investigation study site team (as required). The signature on the CV must be dated within 3 years prior to the date of activation of the study site.
- Documentation of delegated tasks
- Documentation of study training.

Additional requirements imposed by local regulations, the EC and RA shall be followed, if appropriate.

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study related activities.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

8.3 Role of the Sponsor Representatives

In addition to performing monitoring and auditing activities, sponsor representatives may provide support at the study site as required for the study under supervision of the Principal Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at MRI visits under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at study sites

In addition, for this study, sponsor representatives may be authorized by the principal investigator to perform the following significant trial related duties:

- Support study investigators in performing the study MRI scan

Any data collection completed by Medtronic personnel will be clearly identified as such.

9.Selection of Subjects

9.1 Study Population

Subjects who were implanted an SureScan system CIED over 6 weeks at the time of signing ICF.

9.2 Subject Enrollment

When a subject and the principal investigator or authorized designee, as required, have personally signed and dated the IC, the subject is considered a subject enrolled in the study. The date the subject signed the IC must be documented in the subject's medical records.

Subjects will be screened to ensure they meet all the inclusion and none of the exclusion criteria prior to signing ICF.

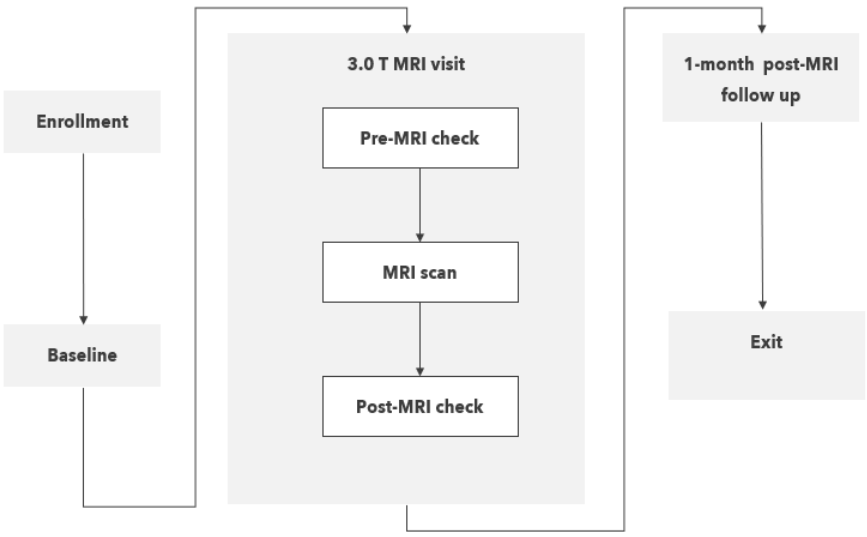
9.3 Inclusion Criteria

- Subjects who were implanted an SureScan system CIED (including device and lead)over 6 weeks at the time of signing ICF.
- Subjects who were implanted an SureScan system CIED in the pectoral region.
- Subjects who are able and willing to undergo elective MRI scanning without sedation.
- Subjects who are geographically stable and available for follow-up at the study site for the length of the study.
- Subjects who are at least 18 years of age (or older, if required by local law).

9.4 Exclusion Criteria

- Subjects who require a legally authorized representative to obtain informed consent.
- Subjects with abandoned or capped leads.
- Subjects who require an indicated MRI scan, other than those specifically described in the China CIED 3T MRI performance study, before the one-month post-MRI follow-up.
- Subjects with a non-MRI compatible device (such as neurostimulators) or material implant (e.g., non-MRI compatible sternal wires, neurostimulators, biostimulators, metals or alloys).
- Subjects with medical conditions that preclude the testing required by the CIP or limit study participation.
- Subjects who are enrolled or intend to participate in another clinical trial (of an investigational drug or device, new indication for an approved drug or device, or requirement of additional testing beyond standard clinical practice) during the SureScan study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic study manager.
- Female patient who is pregnant, or of childbearing potential and not on a reliable form of birth control. Women of childbearing potential are required to have a negative pregnancy test within seven (7) days prior toMRI scan.

10. Study Procedures



10.1 Schedule of Events

Clinical data will be collected at the study visits detailed in Table 4. Data will be collected via eCRFs, analyzer/programmer printouts, and interrogation files. Subject visits will occur at enrollment, baseline,

MRI visit, 1 month post MRI visit. Trained Medtronic personnel may assist study personnel during implant and study visits on site or remotely.

10.2 Data Collection

Data collection requirements are summarized in Table 4 below.

Table 4: Data collection and study procedure requirements at subject visits

Study Procedure	Enrollment	Baseline	MRI visit	1 month post MRI	Unscheduled Visit	Study Exit
IC	×					
Inclusion/exclusion assessment	×					
Physical Exam, Demographics, Cardiovascular Medical History，device information		×				
Pre MRI check			×			
Device interrogation			×*	×	×	
MRI scan			×			
Post MRI check			×			
Medication	As they occur **					
AEs	As they occur					
DDs	As they occur					
Study deviations	As they occur					

* Device interrogation performed twice at MRI visit(pre MRI scan and post MRI scan)

** Only collect AE related medication in this study

10.3 Scheduled Follow-up Visit Windows

After receiving notice of successful implantation/device application, Medtronic will provide the target dates and windows for each visit to the study site if applicable. Should a subject miss a visit or the visit fall outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation report. Follow-up visit windows are listed in Table 5 and are based on days post MRI scan.

Table 5: Scheduled follow-up visit window

Study Follow-up **Visit**	Window**(Calculated days post-MRI visit)**		
	Window Start (days post-MRI)	Target (days post- MRI)	Window End (days post-MRI)
MRI visit*	-	-	-
1 month post MRI	30	30	56

*highly recommend completing the MRI scan within 30 days after baseline visit

10.4 Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular study after information has been given and explained to the subject on all aspects of the study that are relevant to the subject's decision to participate. This process includes obtaining an IC form as required by law that has been approved by the study site's EC and signed and dated by the subject. A subject may only consent after information has been given and explained to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, the IC site must be approved by the EC. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved by the EC. Any adaptation of the sample IC must be reviewed and approved by Medtronic and the EC reviewing the application prior to enrolling subjects.

The investigator must notify the subject of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, consent may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize study sites to submit subject information to the study sponsor. The IC process must be conducted by the principal investigator or an authorized designee, and the IC Form in a language he/she is able to read and understand. The process of IC must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other study site personnel. The IC process shall not waive or appear to waive subject's legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the IC form, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the study, the IC must be signed and personally dated by the subject and investigator or authorized designee, as required by the IC, and ensured by the principal investigator or his/her authorized designee.

A copy of the IC signed and dated as required by law, must be provided to the subject and his/her authorized designee.

If the IC is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial witness) IC will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the IC. The IC should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated consent to participate in the study.

The original of the signed IC must be filed in the hospital/clinical chart and/or with the subject's study documents.

The IC must be available for monitoring and auditing. Any Medtronic Field personnel who support the MRI procedure must be able to review the subject's signed and dated IC and verify its completeness prior to proceeding with the implant/download. In the event the Medtronic Field personnel identify IC as being incomplete, the MRI procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

10.5 Enrollment

A subject is considered enrolled when the consent process has been finalized. The date the subject signed the IC must be documented in the subject's medical records. Confirmation of Inclusion/Exclusion Criteria of subject will be performed by investigator at enrollment visit. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. Once consent is obtained, report adverse events, device deficiency, study deviations and subject exits as they occur.

10.6 Baseline

The baseline visit can be a stand-alone visit or can be performed on the same day as the MRI visit.

The following information is required to be collected at the baseline visit:

- Physical Exam: a basic physical exam will be performed, including height and weight
- Demographics
- Relevant cardiovascular medical history
- Device /lead information
- Adverse Event assessment
- Device Deficiency assessment

10.7 MRI visit

The following information is required to be collected at the MRI visit:

- Pre MRI check*(appendix A)
- Pacing Threshold Testing Pre-MRI
- Sensing Testing Pre-MRI
- Impedance Testing Pre-MRI
- Final device Interrogation Pre-MRI
- Pre-MRI System Checks
- Device Programming Pre-MRI
- MRI Scan Procedure **
- Device Programming Post-MRI
- Pacing Threshold Testing Post-MRI
- Sensing Testing Post-MRI
- Impedance Testing Post-MRI
- Final device Interrogation Post-MRI
- Adverse Event assessment
- Device Deficiency assessment

*The subject unmet the pre MRI checklist will exit the study

**A cardiac resuscitation-trained individual must be present during the MRI scan.

10.8 Scheduled Follow-up Visits

Scheduled visits will occur at 1 month post MRI at study site.

The following information is required to be collected at follow-up visits:

- Pacing Threshold Testing
- Sensing Testing
- Impedance Testing
- Final device Interrogation
- Adverse Event assessment
- Device Deficiency assessment

10.9 Unscheduled Follow-up Visits

An Unscheduled follow-up visit is defined as any non-standard of care visit by the subject to the study site due to the 3.0T MRI scan before subject completed CIP-required exit visits.

The following information is required to be collected at unscheduled follow-up visits:

- Document any adverse events and/or device deficiencies on the associated eCRFs, as applicable.
- Where possible, initial (beginning of the visit) and final (end of the visit) device interrogation data should be collected

- If electrical testing is conducted , save and print the Test Report and store at site and send a copy to Medtronic if possible

10.10 Recording Data

Data entered must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data, and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, device data and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the study).

In general, eCRFs (or paper copies) may not serve as source documents. An exception may be the completion of QoL Questionnaires and clinical scales. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. The type and location of source documents should be documented.

The source documents must be made available for monitoring or auditing by Medtronic's representative or representatives of the competent authorities and other applicable regulatory agencies.

The CRF may be considered source for the following data collection elements:

- Enrollment Notification
    - Study site assigned subject reference
- Baseline
    - Administrative information
- AE eCRF
    - Date study site became aware of event
    - Relatedness of adverse event
- Medication eCRF
    - Medication related with AE
- DD eCRF
    - Date study site became aware of device deficiency
- Deviations
    - Reason for deviation

10.11Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the CIP or the CTA.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to

protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the CRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. Multiple deviations of the same type at the same visit may be reported on one case report form.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the EC as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with EC policies and/or local laws and must be reported to Medtronic as soon as possible upon the study site becoming aware of the deviation. Reporting of deviations must comply with EC policies, local laws, and/or RA requirements. Refer to Investigator Reports, Table 10for geography-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or RAs.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and study site, and in some cases, may necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide study site-specific reports to investigators summarizing information on deviations that occurred at the investigational study site on a periodic basis.

Examples of study deviations include but are not limited to:

- Failure to obtain proper IC
- Failure to collect required study data
- Inclusion/exclusion criteria not met
- Missing required device interrogation files
- Missing visit

10.12 Subject Exit, Withdrawal or Discontinuation

10.12.1 Study Exit

A study exit eCRF is required for all subjects, can be performed as remote or on site. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system and/or procedure related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care. Upon exiting from the study, no further study data will be collected or no further study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Study completed
- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion/exclusion criteria
- Subject did not provide consent
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

The following information is required to be collected at study exit:

- Reason for exit

If discontinuation is because of safety or lack of effectiveness, the subject shall be asked to be followed for collecting safety data outside the clinical investigation.

10.12.2 Study Completed

All subjects at the completion of the last enrolled subject 1 month follow-up visit will be exited from the study.

10.12.3 Lost to Follow-up

A subject is considered to be lost to follow-up if at least two attempts to contact the subject are unsuccessful. The method of attempt (e.g., one letter and one phone record, or two letters) must be documented in the subject's medical record. In addition, regulation set forth by the governing EC must be followed.

10.12.4 Subject Chooses to Exit (i.e. Revokes Consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the study site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing EC. If possible, the following data should be collected prior to subject withdrawal:

- Reason for exit

10.12.5 Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study team prior to withdrawing subjects. If an Investigator Withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Reason for subject withdrawal

10.12.6 Conditional Disengagement

After a subject is enrolled every effort should be made to keep the subject in the study. However, it is recognized that there are circumstances where limited data may be collected, or study exit will need to

occur. In these cases we will consider either modified data collection requirements where subjects may conditionally disengage in study procedures but data from the subject can still be collected because the subject has not revoked consent, or exit when study participation is completely ended.

Subjects may be conditionally disengaged from study procedures for any of the following reasons:

- Subject chooses to disengage (e.g., follow-up schedule cannot be adhered to, study burden too large, relocation to another geographic location but telephone follow-up still acceptable)
- Investigator deems conditional disengagement necessary (e.g. medically justified)

If the subject wishes to disengage from the study, or the investigator deems it necessary, the study site is required to document the reason. Prior approval from the study team is required and a Limited Data Collection CRF needs to be completed. Data collection requirements no longer apply, but study sites are encouraged to collect as much data as possible on the regular CRFs.

11.Risks and Benefits

11.1 Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance.

Possible additional risks that can occur during and after an MRI include, but are not limited to, the following (these potential risks associated with the MRI are the same as those for any patient without an SureScan CIED system who undergoes an MRI):

- Feelings of claustrophobia
- Temporary hearing loss due to the loud noise
- Stiffness due to lack of movement
- Mild lightheadedness
- Sweating due to the heat from the MRI machine
- Warm body sensation after the exam is performed

Possible additional risks that can occur during an MRI procedure with an Surescan CIED system include, but are not limited to:

- Lead electrode heating and tissue damage resulting loss of sensing or capture or both
- Spontaneous tachyarrhythmia occurring during the scan that is not detected and treated because tachyarrhythmia detection is suspended while MRI SureScan is programmed to On
- Potential for VT/VF induction when the patient is programmed to an asynchronous pacing mode during MRI SureScan
- Device heating resulting in tissue damage in the implant pocket or patient discomfort or both
- MRI-induced stimulation on leads resulting in continuous capture, VT/VF, hemodynamic collapse, or all three

- Damage to the device or leads causing the system to fail to detect or treat irregular heartbeats, or causing the system to treat the patient's condition incorrectly
- Damage to the functionality or mechanical integrity of the device resulting in the inability of the device to communicate with the programmer
- Movement or vibration of the device or leads resulting in dislodgement
- If the subject is a female and becomes pregnant or is pregnant, there may be unforeseen risk to the female or to the embryo or fetus

11.2 Risk Minimization

The potential risks associated with the 3.0T MRI scan in patient implanted SureScan CIED system were identified and have been successfully mitigated. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the CIP. In addition, investigators will be actively involved in the follow-up of the subjects undergoing 3.0T MRI scan.

Risks will be minimized by careful assessment of each subject prior to, during, and after 3.0T MRI scan. Prior to MRI scan, it is recommended subjects undergo a complete physical evaluation.

Medtronic has further minimized the possibility of risks by: performing required laboratory and pre-clinical testing prior to the China CIED 3.0T MRI performance study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

After MRI scan, subjects in the China CIED 3.0T MRI performance study will be followed at regular intervals to monitor the condition of the SureScan CIED system. At each protocol required follow-up, the investigator must interrogate the Surescan CIED system to verify appropriate function and to evaluate pacing and sensing characteristics and to assess any adverse events.

Additionally, Capture Management must be programmed to Adaptive following the MRI. Capture Management evaluates and adjusts the pacing threshold automatically. This mitigates the need for programming high pacing outputs following the MRI.

11.3 Potential Benefits

The potential benefits of having the 3.0T MRI scan include receiving a diagnosis of scan region . The information gained from this study could result in the improved management of Surescan CIED system. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or IFU.

11.4 Risk-Benefit Rationale

In the Medtronic 3.0T MRI PAS study, no adverse events were as related to the 3.0T MRI scan and no deaths or events were as related to a 3.0T MRI scan. A systematic process is in place to continuously collect, analyze, and assess data relevant to the safety performance of the Surescan CIED system during the study.In summary, the anticipated risks of the 3.0T MRI scan in subject implanted Surescan CIED system are consistent with the risks of routine clinical conditions 3.0T MRI scan .The potential benefits of the 3.0T MRI scan in subject implanted Surescan CIED system are also consistent with the benefits of routine clinical condition.

12. Adverse Events and Device Deficiencies

12.1 Adverse Events

AE definitions are provided in Table 7. All AEs will be collected throughout the study duration, starting at the time of signing the IC.

Reporting of these events to Medtronic will occur on an AE Form. Each event must be reported separately. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

The completed AE CRF must be submitted to Medtronic as soon as possible.

Any medication/treatment associated with the treatment of an AE must be reported.

Subject deaths are also required to be reported. Refer to Section 12.5 for Subject Death collection and reporting requirements.

In addition, further classification of the relationship will be done by the investigator according to the following parameters:

Table 6 Adverse events parameters

Not Related	Relationship to the device or procedures can be excluded when: • the event has no temporal relationship with the use of the device or procedure • the event does not follow a known response pattern to the device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of 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 event; • the event involves a body-site or an organ not expected to be affected by the device or procedure; • the 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 device used for diagnosis, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Possible	The relationship 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 where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship seems relevant and/or the event cannot reasonably explained by another cause.

Causal Relationship	The event is associated beyond reasonable doubt when:
	• the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
	• the event has a temporal relationship with device use/application or procedures;
	• the event involves a body-site or organ that
	  ○ the device or procedures are applied to;
	  ○ the device or procedures have an effect on;
	• the event follows a known response pattern to the device (if the response pattern is previously known);
	• the discontinuation of 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 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 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 event.

For summary and analysis, AEs determined as having “possible,” “probable,” or “causal relationship” will be conservatively considered to be “related.”

12.2 Device Deficiency

The DD definition is provided in Table 7. DD information will be collected throughout the study, starting at the time of signing the IC and reported to Medtronic. Note that DD that result in an AE to the subject should be captured as an AE only.

12.3 Processing Updates and Resolution

For any changes in status of a previously reported adverse event or DD (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. All AEs must be followed until the AE has been resolved, or is unresolved with no further actions planned, or the subject dies or exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study completion, all efforts should be made to continue following the subject until all unresolved system or procedure related AEs, as classified by the investigator, are resolved, or unresolved with no further actions planned whichever occurs first.

At the time of study exit, all collected adverse events that are unresolved must be reviewed and an update to the original AE must be reported. Adverse events that have not resolved at the time of the

subject's discontinuation or completion of the study should have an "outcome" of Not Recovered/Not Resolved at study end in subject source and on an eCRF.

Where the definition indicates "device", it refers to any device used in the study. This might be the device for any market released component of the system, and includes but is not restricted to: the IPG, ICD or CRT-D device, the RA, RV or LV leads, the programmer, and implant tools.

Table 7: Adverse Event and Device Deficiency Definitions

Definition	Description
General	
Adverse Event (AE)	Untoward medical occurrence during the clinical study, whether or not related to investigational medical devices. (China GCP 2022 No.28 Article 64) Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. Note 1 to entry: This definition includes events related to the investigational medical device or the comparator. Note 2 to entry: This definition includes events related to the procedures involved. Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators. (ISO 14155:2020, section 3.2)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. Note 3 to entry: This includes 'comparator' if the comparator is a medical device. (ISO 14155:2020, section 3.1)

Definition	Description
Device Deficiency (DD)	Any unreasonable risk caused by a medical device in normal use during clinical trial that may endanger human health or life safety, such as label error, quality issues, malfunction and etc. (China GCP 2022 No.28 Article 64) Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, section 3.19)
Relatedness	
System related[12]	**IPG/ICD/CRTD Device related:** An adverse event that results from the presence or performance (intended or otherwise) of the IPG/ICD/CRTD device **RA lead related:** An adverse event that results from the presence or performance (intended or otherwise) of the RA lead **RV lead related:** An adverse event that results from the presence or performance (intended or otherwise) of the RV lead **LV lead related:** An adverse event that results from the presence or performance (intended or otherwise) of the LV lead **Programmer related:** An adverse event that results from the presence or performance (intended or otherwise) of the programmer

12 The system includes all implantable components and features, associated introduction tools, operational/download software, and device programmers necessary for conducting study-related procedures as defined in the CIP.

Note that if an event occurs as a result of a system component but it is unclear which tool or component it is related to, the default will be to the last tool/component used prior to the event being observed.

Definition	Description
	MRI SureScan feature: An adverse event that results from the presence, performance or programming of the SureScan feature **Note:** Any of the above parameter is assessed as system related will be considered as system-related
MRI procedure related	An adverse event which is caused by the interaction between the IPG/ICD/CRTD system and the MRI system that occurs during the MRI procedure and includes the time the subject is within the 5 Gauss line of the MRI system and up through the one-month post-MRI follow-up visit. AEs occurring due to the subject's MRI programming will be considered MRI procedure related. In addition, this includes treated (via ATP, device shock or external defibrillation) VT/VF events that originate while the subject is in SureScan mode.
Seriousness	
Serious Adverse Event (SAE)	Any untoward medical occurrence during the clinical study: results in death or serious deterioration in health; life-threatening diseases or injuries; causing permanent damage to the body structure or function; requires hospitalization or prolongation of hospitalization; requires medical measures to prevent from persistent or significant disability/incapacity; results in fetal distress, fetal death, or congenital anomaly/birth defect. (China GCP 2022 No.28 Article 64) Adverse event that led to any of the following: • death • a serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: ○ A life-threatening illness or injury, or ○ A permanent impairment of a body structure or a body function including chronic diseases, or ○ In-patient or prolonged hospitalization, or ○ Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

Definition	Description
	• foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment. Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE. (ISO 14155:2020, section 3.45)
Complication	An adverse event that includes the following is considered a complication: • Results in death, • Involves any termination of significant device function, or • Requires an invasive intervention Non-invasive (21 CFR 812.3(k)): when applied to a diagnostic device or procedure, means one that does not by design or intention: Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os Note: Only system or procedure related AEs will be classified for complication/observation
Observation	Any adverse event that is not a complication. Note: Only system or procedure related AEs will be classified for complication/observation
Other	
Unavoidable Adverse Event Related to the MRI Procedure	An Adverse Event inherent to a MRI procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:

Definition	Description
	<table><tr><th>Event Description</th><th>Timeframe (hours) from the MRI Procedure</th></tr><tr><td>Claustrophobia</td><td>During MRI</td></tr><tr><td>Mild diaphoresis</td><td>During and < 1 hour post-MRI</td></tr><tr><td>Hearing impairment</td><td><24 hours</td></tr><tr><td>Mild lightheadedness</td><td><30 minutes</td></tr><tr><td>Sensation of bodily warmth</td><td><1 hour</td></tr><tr><td>Body stiffness related to immobility</td><td><48 hours</td></tr></table> UAE listed in the above table need not be reported unless the adverse event worsens or is present outside the stated timeframe post-implant.
Hospitalization	A therapeutic inpatient hospitalization (excludes observation unit, emergency roomand outpatient visits) lasting greater than or equal to 24 hours, or overnight.

12.4 Reporting of Adverse Events and Device Deficiencies

12.4.1 Adverse Event and Device Deficiency Classification

All AEs and DDs will be reviewed by a Medtronic representative and classified according to the definitions provided.

Upon receipt of AE/DD at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and, when necessary, will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA for Regulatory Activities, to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Table 9 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of both parties to abide by any additional AE reporting requirements stipulated by the EC responsible for oversight of the study.

For emergency contact regarding a SAE, contact a study representative immediately (refer to the study contact list provided in the study site's study documents binder/investigator site file or refer to the Sponsor contact information provided on the title page).

AEs and Deaths will be classified according to the standard definitions as outlined below:

Table 8: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	IPG/ICD/CRTD, RA Lead, RV Lead, LV Lead, Programmer, MRI SureScan Feature, MRI procedure
	Sponsor	IPG/ICD/CRTD, RA Lead, RV Lead, LV Lead, Programmer, MRI SureScan Feature, MRI procedure
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac Death, Non-sudden Cardiac Death, Non-cardiac Death, Unknown

12.4.2 Adverse Event and Device Deficiency Reporting Requirements

Table 9: Reporting Requirements

SAEs	
Investigator shall submit to:	
Medtronic	Within 24 hours of first acknowledgement
GCP office	Within 24 hours of first acknowledgement
EC	Within 24 hours of first acknowledgement
All other reportable AEs	
Investigator shall submit to:	
Medtronic	Submit AE in a timely manner after the investigator first learns of the event.
EC	Submit to EC per local reporting requirement.
All Device Deficiencies	
Investigator shall submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the deficiency.
EC	Submit to EC per local reporting requirement.

12.5 Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of fatal) as soon as possible after the investigator first learns of the death. In case of death, there should be one AE with the outcome of fatal.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if available should be sent to the Medtronic clinical study team. If an autopsy is conducted, a copy of the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote study site, it is the investigative study site's responsibility to attempt retrieval of information about the death.

In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or MRI procedure
- Device interrogation information/reports and Save-to-Media information/reports (if available)
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

12.5.1 Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

- Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If the time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.
- Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Death Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

A Medical Advisor will review deaths and provide a final assessment of the primary cause of death and classification of death.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

12.6 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the RAs (e.g. CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
  - Life-threatening illness or injury
  - Permanent impairment of a body function or permanent damage to a body structure
  - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

13. Medical Advisor Review

At regular intervals, a medical advisor will conduct a medical review of all adverse events.

If the sponsor disagrees with the investigator's classification of the event, the sponsor assessment will be provided to the investigator. If the investigator agrees with the sponsor assessment, the CRF documenting the AE will be updated accordingly.

If the investigator does not agree with the sponsor assessment, both determinations will be provided within the final report; however, the medical advisor's assessment will be used for data analysis. The disagreement will also be included in reporting to ECs and regulatory authorities, if required.

14.Statistical Design and Methods

14.1 General Aspects of Analysis

Data analysis will be performed by Medtronic statisticians or designees.

The cohort will include all enrolled subjects who undergo the study procedures unless the subject does not complete the required testing, and there are no pre-specified subgroups for assessment. For endpoints involving only measurements collected at follow-up visits, only subjects who complete those visits will be included in the analysis of those endpoints.

A Statistical Analysis Plan (SAP) will be developed and kept under separate cover and will include a comprehensive description of the statistical methods and analyses to be included in study reports. It will also include descriptions on how missing, unused, and spurious data will be accounted. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

14.2 Primary Objective(s) Primary Objective for Safety: MRI-related Events

To demonstrate the safety of SureScan system CIED in clinical 3.0T MRI environment within 1-month post-MRI scan.

Hypothesis

The MRI-related event-free rate within 1-month post-MRI is greater than 90%.

H_0: $p \leqslant 0.90$

H_A: $p > 0.90$

Where p is the percentage of subjects free of an MRI-related event within 1-month post-MRI.

Endpoint Definition

For subjects with IPG devices, the occurrence of any of the following within 30 days after a 3.0T MRI procedure will be considered an MRI-related event:

- Medical advisor-assessed MRI-related complication within 30 days post-MRI

- Medical advisor-assessed right ventricular MRI-related loss of capture within 30 days post-MRI

For subjects with ICD or CRT-D devices, the occurrence of any of the following within 30 days after a 3.0T MRI procedure will be considered an MRI-related event:

- Medical advisor-assessed MRI-related complication within 30 days post-MRI
- Sustained tachyarrhythmia originating during SureScan programming, requiring immediate treatment (defined as ATP, device shock, or external shock), as assessed by a medical advisor.
- Medical advisor-assessed right ventricular MRI-related loss of capture within 30 days post-MRI

Performance Requirements

The null hypothesis will be rejected if the one-sided 97.5% lower confidence bound is greater than 90% or, equivalently, if the p-value is less than 0.025.

Rationale for Performance Criteria

All events that can be attributed to the MRI are expected to occur within one month. There is no evidence of lingering effects of MRI scans on devices. Therefore, assessing this objective one month post-MRI will capture all MRI-related events that result following the MRI procedure.

Previous 1.5T MRI clinical studies including EnRhythm MRI, Advisa MRI and 5076 MRI for IPG devices and Evera MRI for ICD devices have used an Objective Performance Criterion (OPC) of 90% for a similar safety objective, and all of them have met their safety objective with 0 MRI-related events observed (Table 10).

[redacted]

[redacted]

Analysis Methods

The objective will be evaluated using a one-proportion binomial exact test along with a one-sided 97.5% lower (Clopper-Pearson) confidence bound. The proportion of subjects free from MRI-related events will be calculated by dividing the number of subjects without an MRI-related event by the number of subjects at risk for an event. The denominator is all subjects implanted with a SureScan study device who underwent a 3.0T MRI scan and completed the one month post-MRI scan visit or later follow-up, or have had an MRI-related event prior to completing the one month post-MRI scan visit. The numerator will be the subjects included in the denominator who are free from MRI-related events. Subjects who are lost to follow-up or withdraw for other reasons prior to the one-month post-MRI scan follow-up will not be included in the analysis unless they have had an MRI-related event.

To assess the robustness of this analysis to missing data, a tipping point analysis will be performed based on all subjects enrolled.

Determination of Patients/Data for Analysis

All subjects implanted with a SureScan study device who have a 3.0T MRI scan after enrollment and have completed their one month post-MRI scan follow-up, or have had an MRI-related event without completion of their one-month post-MRI scan follow-up will be included in the analysis.

14.3 Secondary Objective(s) Atrial and Ventricular Pacing Capture Thresholds

To characterize changes in atrial and ventricular pacing capture thresholds (APCT and VPCT) from pre-MRI to 1-month post-MRI scan

Hypothesis

There is no hypothesis for this objective.

Endpoint Definition

PCTs to be evaluated include:

- APCT of atrial lead for subjects with an IPG device
- APCT of atrial lead and VPCT of right ventricular (RV) lead for subjects with an ICD device
- APCT of atrial lead and VPCTs of right ventricular (RV) and left ventricular (LV) leads for those with a CRT-D device.

PCTs of each subject will be measured prior to the 3.0T MRI scan and at the one month post-MRI. Change in PCT is defined as PCT measured at one month post-MRI subtracts that measured prior to a 3.0T MRI scan. Proportion of subjects with an increase less than or equal to 0.5V in APCT or VPCTs from pre-MRI to one-month post-MRI will also be used to characterize the efficacy performance of SureScan with respect to PCTs.

If the 1-month post-MRI APCT or VPCT is missing, the PCT measured immediately post-MRI will be used instead.

Performance Requirements

There are no performance requirements.

Rationale for Performance Criteria

The 0.5V threshold for the incease in a PCT from pre-MRI to one-month post-MRI is consistent with what have used in the FDA approved pre-market MRI studies such as EnRhythm MRI, Advisa MRI, and Evera MRI.

Analysis Methods

The change in PCT is the PCT measured at one month post-MRI subtracts that measured prior to a 3.0T MRI scan. Descriptive statistics such as mean and standard deviation will be provided for changes in APCT and VPCTs, respectively.

In addition, the percentage of subjects with an increase less than or equal to 0.5V from pre- to one month post-MRI in APCT and VPCTs will be determined.

Determination of Patients/Data for Analysis

To be included in the analysis, all of the following must be met:

- The subject must undergo a 3.0T MRI scan.
- The subject must have valid PCT measurements pre and post-MRI (see paragraph below for definitions).
- The (atrial, right or left ventricular) lead is not dislodged within 6 weeks prior to MRI scan.
- The (atrial, right or left ventricular) lead has not been replaced or repositioned within 6 weeks prior to MRI scan or between MRI scan and the one-month post-MRI visit.
- The VPCTs of RV at the pre-MRI must be $\leqslant$ 2.0V. This is because subjects with a higher VPCT cannot have an MRI per CIP

To be a valid PCT measurement, the pulse width must be set to 0.4ms and a printed pacing capture threshold testing strip must be available to confirm the pulse width and capture threshold reported.

The pre-MRI period value will be the pre-MRI period PCT measurement. For the post-MRI period PCT value, the PCT value on the one-month post-MRI period CRF will be used. If that does not exist or is not valid, the PCT measured immediately post-MRI will be used instead.

[redacted]

[redacted]

14.5 Sample Size Determination

Sample Size

The sample size estimation is based on the following assumptions:

- α (the type I error rate) = 0.025
- power (1 – β) = 90%
- P_0 (proportion under null hypothesis) = 0.90
- P_1 (assumed true proportion) = 0.995. Rationale for 0.995: There have been 0 MRI-related events in previous MRI studies (EnRhythm MRI, Advisa MRI and 5076 MRI for IPG devices and Evera MRI for ICD devices).

The sample size calculation is performed using the inequality tests for one proportion with a one-sided, one-sample proportion exact test in PASS (2008). Under the above assumptions, the minimum required sample size is 54 subjects to undergo a 3.0T MRI scan and be followed for at least 1 month post MRI procedure.

Attrition from enrollment to completion of an MRI scan and being following for one month post MRI ranges from 12% to 18% in historical MRI studies (Table 11). Assuming an attrition rate of 15%, a total enrollment of 64 subjects is needed in the China 3.0T MRI study. If the actual attrition rate exceeds 15%, further evaluation may be considered.

[redacted]

15. Ethics

15.1 Statement(s) of Compliance

This study will be conducted in compliance with international ethical and scientific quality standards, known as GCP. GCP includes review and approval by an independent EC before initiating a study, continuing review of an ongoing study by an EC, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The China CIED 3.0T MRI Performance Study was designed to reflect the GCP principles (referred the definition of AE,DD, ADE and SAE from ISO 14155:2020 and the definition of no invasive from 21 CFR). These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators.

The principles of the DoH have been implemented through the IC process, EC approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy.

Ultimately, all study sites in all geographies will follow and comply with:

- Principles of DoH
- China GCP 2022 (Considering investigational product are marketed, investigator's qulicaifcation of Tertiary A hospital and at least 3 clinical trial experience is not needed for low risk.)
- The CTA
- The procedures described within this CIP
- Local EC Requirements

The study will be publicly registered prior to in accordance with the 2007 FDAAA and DoH on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law/regulations)
- An independent medical EC or IRB.

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above mentioned groups prior to implementation of the revised CIP at the study site.

16. Study Administration

16.1Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the

subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the IC, Research Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

16.1.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents will be reviewed at each study site. Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess study site progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to EC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs in accordance to the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

16.2 Data Management

Data will be collected using an electronic data management system for studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained by Medtronic in accordance with applicable regulations.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to pseudonymize for instance, where the subject's name cannot be removed from the data carrier.

Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets, subject medical records, programmer printouts, and interrogation files, must be created and maintained by the investigational study site team.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

Device data from transmissions will be uploaded to secure servers. Save-to-disk data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

16.3 Direct Access to Source Data/Documents

Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly

involved in the study. RAs, such as the NMPA, may also perform inspections at participating study sites. The investigator and/or institution shall permit Medtronic, ECs and RAs direct access to source data and documents during monitoring, audits and regulatory inspections.

16.4 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique SID to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

16.5 Liability/Warranty/Insurance Information

Warranty

Warranty information is provided in the product packaging and additional copies are available upon request.

Insurance

Medtronic maintains appropriate Clinical Trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Board.

16.6 CIP Amendments

Any revisions or amendments to the CIP or IC document, along with a statement of justification for the changes, will be submitted to governing ECs, according to applicable regulations. All amendments to the CIP shall be agreed upon between Medtronic and the principal investigator(s), or the coordinating investigator. Approval by regulatory agencies and ECs (where applicable) must be obtained prior to implementing a CIP revision at the study site.

16.7 Record Retention

No study document or image will be destroyed without prior written agreement between Medtronic and the investigator. The investigator should take measures to prevent accidental or premature destruction of documents. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

16.7.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) .

All correspondence between the EC, sponsor, monitor, RA and the investigator that pertains to the investigation, including required reports.

Subject's case history records, including:

- Signed and dated IC
- Observations of AEs/ADEs/DDs
- Medical history
- Documentation of the dates and rationale for any deviation from the protocol
- List of investigation study sites
- Subject screening log & ID log (if applicable)
- All approved versions of the CIP, IC
- Signed and dated CTA.
- CV of principal investigators and key members of investigation study site team (as required by applicable regulations.
- Documentation of delegated tasks.
- EC approval documentation. Written information that the investigator or other study staff, when member of the EC, did not participate in the approval process. Approval documentation must include the ECs composition, where required per local law.
- Study training records for study site staff.
- Insurance certificates
- Final Study Report including the statistical analysis.

16.7.2 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- Signed Investigator Trial Agreements, FD (if applicable) and current signed and dated CV of principal investigator and key members of the investigation study site team (as required by local law), delegated task list
- All signed and dated case report forms submitted by investigator, including reports of AEs, DDs
- All approved IC templates, and other information provided to the subjects and advertisements, including translations

- Copies of all EC approval letters and relevant EC correspondence and EC voting list/roster/letter of assurance
- Names of the institutions in which the study will be conducted
- Insurance certificates
- Names/contact addresses of monitors
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the study
- Study training records for study site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during this study.

After closure of the study Medtronic will archive records and reports indefinitely.

16.8 Reporting Requirements

16.8.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an EC with respect to this study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in table 9. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 12: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB/EC	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	IRBs/ECs	This report must be submitted within 3 months of study completion or termination.

Table 13: Investigator reports applicable to China per China GCP 2022

Report	Submit to	Description/Constraints
Progress reports	EC	Principal investigators shall report the progress of clinical trials of medical devices to the Ethics Committee on time. (China GCP 2022 Article 34)
Suspension, termination	GCP office, Sponsor and EC	Investigators shall promptly report safety information in clinical trials of medical devices: (II)When the risks in clinical trials of medical devices are identified to outweigh the possible benefits and it is indeed necessary to suspend or terminate the clinical trials, principal investigators shall report to the sponsor, the regulatory department of the clinical trial institution of medical devices and the Ethics Committee. In addition to informing the subjects in time, they shall also ensure that the subjects could receive appropriate treatment and follow-up visits. (China GCP 2022 Article 32(II))
Protocol deviation	EC	Principal investigators shall report any deviation from the clinical trial protocol in time. (China GCP 2022 Article 34)
Site-specific summary	Sponsor	For multi-center studies: The site-specific summary of each sub-center shall be signed and dated by the principal investigator of the center, reviewed and signed by the clinical trial institution of medical device of the center, and then submitted to the sponsor. The site-specific summary of clinical trials in sub-centers mainly includes personnel information, information of investigational medical devices and control medical devices (if applicable), trial overview, case inclusion, implementation of clinical trial protocol, summary and descriptive analysis of trial data, quality management of clinical trials of medical devices, occurrence and treatment of adverse events and device defects, description of deviation from the protocol, etc. (China GCP 2022 Article 56)

16.8.2 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below. In addition to the reports listed below, Medtronic shall, upon request of the reviewing EC, RA or NMPA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in table 14.

Table 14: Sponsor reports for China per China GCP 2022

Report	Submit to	Description/Constraints
Closeout, premature termination or suspension of the clinical investigation	PIs, EC, GCP office, Relevant authorities	The sponsor shall report in writing to all principal investigators, regulatory departments of clinical trial institutions of medical devices and the Ethics Committee within 10 working days after the suspension, termination or completion of the clinical trial. The sponsor shall report to the drug regulatory departments of the province, autonomous region or municipality directly under the Central Government where the sponsor is located within 10 working days after the termination or completion of the clinical trial of medical devices. (China GCP 2022 Article 48) The sponsor shall evaluate and report the safety information during clinical trials of medical devices: (II)In case of any serious adverse events on the medical device under clinical trial on a large scale or any other major safety problems, the sponsor shall suspend or terminate clinical trials of medical devices and report to the regulatory department of all clinical trial institutions of medical devices, the Ethics Committees and principal investigators, to the drug regulatory departments in the province, autonomous region and municipality directly under the Central Government where the sponsor is located, and to the drug regulatory departments and health administration departments in the provinces, autonomous regions and municipalities directly under the Central Government where all clinical trial institutions of medical devices are located. (China GCP 2022 Article 44(II))

16.9 Publication and Use of Information

Publications from the China CIED 3.0T MRI Performance Study will be handled according to Standard Operating Procedures and as indicated in the CTA.

16.9.1 Publication Committee

Medtronic may form the China CIED 3.0T MRI Performance Study Publication Committee from study investigators. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to: 1) manage elements addressed in the publication plan as outlined in this appendix, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary, secondary and ancillary study results, 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet at regular intervals.

16.9.2 Management of Primary, Secondary, and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the CIP.

An ancillary publication is any publication that does not address the study objectives identified in the CIP. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this study, and clinicians not participating in this study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual study site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

16.9.3 Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND

- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the "Medtronic China CIED 3.0T MRI Performance Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

16.9.4 Transparency

Transparency of clinical study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, ECs and CAs of participating countries when required by local law
- Registering and posting the study results on a <publicly accessible database, e.g., ClinicalTrials.gov> based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual study sites study data accessible to the corresponding investigator after the completion of the study, if requested

16.10 Suspension or Early Termination

16.10.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or RA, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing EC oversight is required until the overall study closure process is complete.

16.10.2 Early Termination or Suspension

Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single study site.

16.10.2.1 Study-wide termination or suspension

Possible reasons for considering study-wide suspension or termination of the study include but are not limited to:

- AEs associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or RA (where the study is operating under RA)
- Technical issues during the manufacturing process

16.10.2.2 Investigator/study site termination or suspension

Possible reasons for investigator or study site termination or suspension include but are not limited to:

- Failure to obtain initial EC approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring observations in a timely manner, etc.)
- EC suspension of the study site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

16.10.3 Procedures for Termination or Suspension

16.10.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the RAs where required
- In the case of study termination or suspension for reasons other than a temporary EC approval lapse, the investigator will promptly inform the EC
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

16.10.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the EC
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided

- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

16.10.3.3 Ethics Committee-initiated

- termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with EC policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects, or legally-authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension

16.11 Contents included in the clinical study report

The Clinical Study Reports (CSR) shall reflect the clinical trial results comprehensively, completely and accurately, and the data of safety and effectiveness of the clinical trial report shall be consistent with the source data of the clinical trial as described in NMPA GCP 2022 and compliant with NMPA GCP 2022 Announcement Annex 2 “Template of Clinical Trial Report of Medical Devices”. Any deviations from original statistical plan and the rationale will be described in the Clinical Study Report.

Primary endpoint CSR and subsequent CSRs, along with the CIP, may support the new generation(s) of study devices being commercially available.

17.References

1. 2012 MR Benchmark Report, IMV Medical Information Division, Inc.

2. Kalin R and Stanton MS. Current Clinical Issues for MRI Scanning of Pacemaker and Defibrillator Patients. Pacing and Clinical Electrophysiology 2005 Apr: 28(4): 326-8.

18.Appendices

AppendixA: Pre MRI check list

- Check device clinic information

  Device was implanted in the pectoral region

  Leads are Medtronic MRI labeled

  Leads are electrically intact

  No implanted lead extenders, lead adaptors, or abandoned leads are present

  RV capture threshold should not exceed 2.00 V at 0.40 ms for pacemaker dependent patients

- Radiology considerations for MRI scan

  Observe the restrictions described in the product MRI technical manual

Continuous monitoring of the patient during MRI SureScan operation is required

19. Version History

Version	Summary of changes	Author(s)/Title
1.0	Not Applicable, New Document	[redacted]
2.0	• Cover page updated to Lead Principal Investigator(s) and Coordinating Investigaor information • Footer update CIP template version • Synopsis updated to inclusion criteria • Synopsis updated to exclusion criteria • Synopsis updated to safety assessments • Ancillary Objective(s) and/or Endpoint(s) delete Ventricular sensing amplitude of left ventricular lead • Section 5.1.1 updated to primary objective for right ventricular • Section 6.1 updated the duration of study • Table 2 updated the MR Conditional ICD list and defibrillator Leads list • Table 3 updated the left heart leads list • Section 8.1 updated to principal investigator qualification requirement • Section 9.3 updated to inclusion criteria • Section 9.4 updated to exclusion criteria • Section 10.2 add device interrogationtask for unscheduled visit • Section 10.3 updated to follow up window base point • Section 10.10 update the event to device deficiency and delete Device/Software/Programmer Disposition Log and • Table 7 update definition of AE, DD and SAE • Table 7 add definition of non-invasive in complication section • Table 8 update classification parameters of relatedness and death classifications • Section 12.4 add device deficiencies in headline • Section 12.5 delete the device disposition requirement	

	• Section 13 update medical advisor review task detail • Section 15.1 clarify exemption of investigator qulicaficaion in GCP • Section 16.2 updated to delete the sentence of for CRFs and data collection elements that may be considered source.	

Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	China CIED 3.0T MRI Performance Study
Clinical Investigation Plan Identifier	MDT23009
Clinical Investigation Plan Version	2.0
Clinicaltrials.gov Identifier	NCT04060680
Sponsor/Local Sponsor	[redacted]
Document Version	1.0
Document Date	08-NOV-2024

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Benedict Orih, Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
APCT	Atrial Pacing Capture Threshold
CIED	Cardiac Implantable Electronic Device
CIP	Clinical Investigation Plan
CRTD	Cardiac Resynchronization Therapy Defibrillator
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
IPG	Implantable Pulse Generator
LV	Left Ventricular
MRI	Magnetic Resonance Imaging
OPC	Objective Performance Criterion
PMA-s	Pre-Market Application Supplement
RV	Right Ventricular
SAP	Statistical Analysis Plan
VPCT	Ventricular Pacing Capture Threshold

3. Introduction

This Statistical Analysis Plan (SAP) has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports. This SAP does not limit the analysis in reports. Additional analysis of the study data beyond this plan may be needed. This SAP is developed for the China 3T MRI performance study, based on the Clinical Investigation Plan (CIP) version 2 dated February 06, 2024.

Magnetic resonance imaging (MRI) has grown into one of the most widely used non-invasive imaging modalities. Various medical disciplines rely on the diagnostic capabilities of MRI because of its unique ability to discriminate soft tissues. In 2011, an estimated 32.0 million scan procedures were performed

in the U.S. alone, up 4% from the previous year[1]. It is estimated that 50% to 75% of patients with a cardiac implantable electronic device (CIED) will need an MRI scan after the implantation over their lifetime[2]. Since the release of the first MR conditional system, clinical studies report satisfactory results concerning safety and effectiveness of these systems in terms of device performance and patient safety. However, recent evolution of MRI system from the 1.5 Tesla(T) to the 3.0T technology, with stronger magnetic fields and gradients, has imposed the need to verify that existing implantable device are safe under more compelling criteria.

Medtronic has spent the last 15 years assessing the multiple interactions between cardiac devices and MRI machines via numeric modeling, bench testing, and animal studies. Modeling enables the evaluation of implanted system performance associated with differing patient anatomies, lead lengths, lead paths, scanner manufacturers, scan types, and patient positions within the scanner. Utilizing this model, market-released leads can be evaluated for potential MR conditional use.

Today in China, the majority of implanted CIED is applicable to the certification of 1.5 T MRI environmental. Lately multiple mode of CIEDs and leads were approved for 3.0T MRI scan in China market. Although the pre-clinical testing and clinical data have demonstrated the safety and efficacy of select CIEDs in a magnetic resonance environment when used according to labeling requirements, the safety and effectiveness data of 3.0T MRI scanning is limited in local market.

The China CIED 3.0T MRI Performance Study is a prospective, non-randomized, multi-site study conducted in mainland China. The purpose is to confirm safety of SureScan CIEDs in the clinical 3.0T MRI environment when subjects receive MRI scans.

4. Study Objectives

4.1 Objectives

4.1.1 Primary Objective

To demonstrate the safety of SureScan system CIED in clinical 3.0T MRI environment within 1-month post-MRI scan.

Endpoint Definition

The occurrence of any of the following within 30 days after the 3.0T MRI visit will be considered an MRI-related event for implantable pulse generator (IPG):

- Medical advisor-assessed MRI-related complication (as defined in CIP Table 7) within 30 days post-MRI

1. 2012 MR Benchmark Report, IMV Medical Information Division, Inc.
2. Kalin R and Stanton MS. Current Clinical Issues for MRI Scanning of Pacemaker and Defibrillator Patients. Pacing and Clinical Electrophysiology 2005 Apr: 28(4): 326-8.

- Medical advisor-assessed right ventricular MRI-related loss of capture within 30 days post-MRI

The occurrence of any of the following within 30 days after the 3.0T MRI visit will be considered an MRI-related event for implantable cardioverter defibrillator / cardiac resynchronization therapy defibrillator (ICD/CRTD):

- Medical advisor-assessed MRI-related complication (as defined in CIP Table 7) within 30 days post-MRI
- Sustained tachyarrhythmia originating during SureScan programming, requiring immediate treatment (defined as ATP, device shock, or external shock) as assessed by medical advisor.
- Medical advisor-assessed right ventricular MRI-related loss of capture within 30 days post-MRI

Rationale

This endpoint was chosen to encompass adverse events related to the 3.0T MRI scan. MRI-related event rate will be is summarized and analyzed to evaluate the safety of SureScan CIED in 3.0T MRI environment.

4.1.2 Secondary Objective

To characterize changes in atrial and ventricular pacing capture thresholds (APCT and VPCT) from pre-MRI to 1-month post-MRI scan

Endpoint Definition

The effectiveness of the SureScan MRI CIED device will be measured by the following parameters

- Atrial pacing capture threshold (if applicable)
- Ventricular pacing capture threshold (both right and left ventricular lead if applicable)

These parameters will be measured pre-MRI scan, immediately post MRI scan and 1-month post MRI scan.

Rationale

While PCT and sensing amplitude changes will contribute to the effectiveness objective, the increased PCT will affect the pacing effectiveness and the lifetime of device.

5. Investigation Plan

The China CIED 3.0T MRI Performance study is a prospective, non-blinded, multi-site, interventional post-market study. The study is expected to be conducted at mainland China. Participating devices are expected to include single/dual chamber transvenous IPG, single/dual chamber ICD and CRTD.

The number of enrolled subjects in the study is 64 considering the attrition. To ensure a reasonable distribution of experience and minimize site bias in study results, the maximum number of subjects enrolled at each site will be capped at 30% of total subjects enrolled. All subjects will have required follow-up visits at baseline, MRI visit, 1-month post-MRI. The MRI scans will occur at the MRI visit. The MRI scan region will be determined by investigator according to the subject's clinical condition.

Ethics Committee approval of the study CIP and informed consent must be obtained prior to the site enrolling patients. Subject medical history will be verified to ensure patients meet all the inclusion and none of the exclusion criteria. Subject inclusion/exclusion criteria can be found in CIP section 9.

5.1 Duration

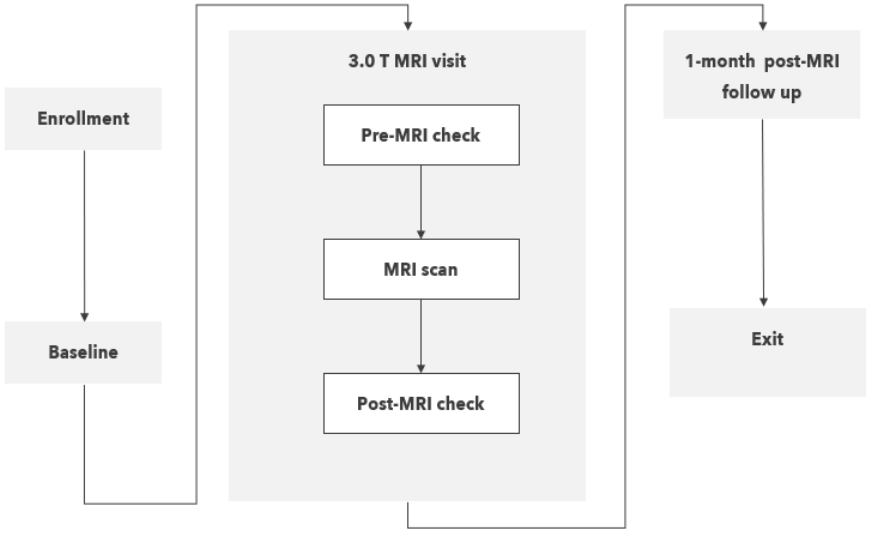
The expected study duration is approximately 9 months, representing 7months of enrollment and 2 months of subject follow-ups. The duration of individual subject participation will vary based on timing of site activation and their enrollment.

5.2 Rationale

The main purpose of this study is to demonstrate safety of SureScan CIED in 3.0T MRI environment. The performance goals for the primary safety objective are chosen based on the known performance of Medtronic SureScan Post-Approval Study and the objectives are designed to show that the SureScan CIED will perform comparably with regard to safety and efficacy in 3.0T MRI environment.

The following diagram provides an overview of the China CIED 3.0T MRI Performance study. This can also be found in CIP section 10.

Figure 1: Overview of the China CIED 3.0T MRI Performance Study



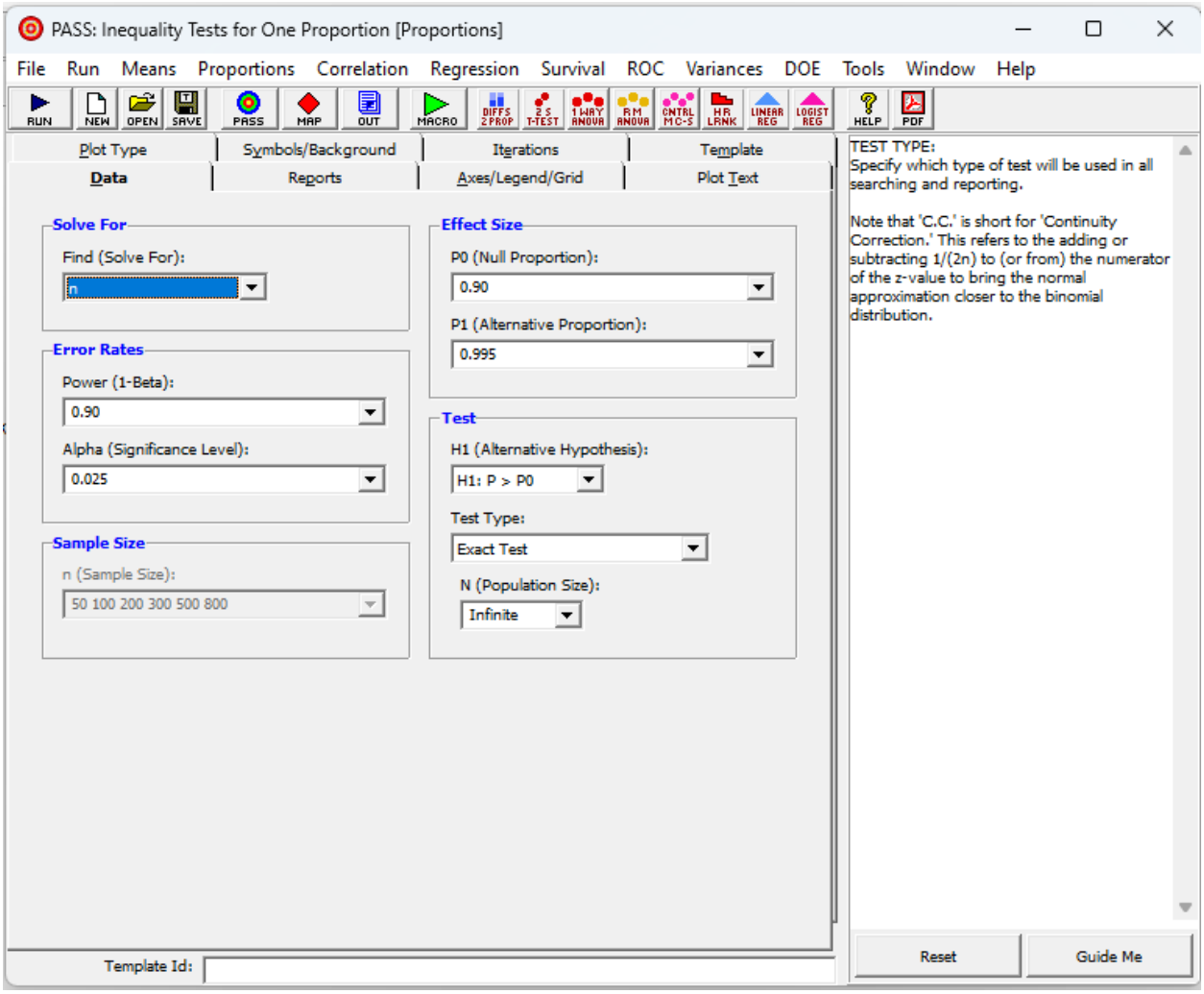
6. Determination of Sample Size

The primary objective of the study is to demonstrate the safety of SureScan system CIED in clinical 3.0T MRI environment within one month post MRI scan. An Objective Performance Criterion (OPC) of 90% for the primary objective was chosen based on prior precedents. If the one-sided 97.5% lower (Clopper-Pearson) confidence bound for the proportion of subjects free of an MRI-related event within one month post MRI is greater than 90%, the primary objective will be met.

The sample size estimation for evaluating the primary objective is based on the following assumptions:

- α (the type I error rate) = 0.025
- power $(1 - \beta)$ = 90%
- P_0 (proportion under null hypothesis) = 0.90
- P_1 (assumed true proportion) = 0.995. Rationale for 0.995: There have been 0 MRI-related events in previous MRI studies (EnRhythm MRI, Advisa MRI and 5076 MRI for IPG devices and Evera MRI for ICD devices).

The sample size calculation is performed using the inequality tests for one proportion with a one-sided, one-sample proportion exact test in PASS (2008). Under the above assumptions, the minimum required sample size is 54 subjects to undergo a 3.0T MRI scan and be followed for at least 1 month post MRI procedure. Details on sample size estimation using PASS 2008 are as follows.


PASS: Inequality Tests for One Proportion [Proportions]
File Run Means Proportions Correlation Regression Survival ROC Variances DOE Tools Window Help
RUN NEW OPEN SAVE PASS MAP OUT MACRO DIFFS 2 PROP 2 S T-TEST 1 WAY ANOVA RM ANOVA CNTRL MC-S HR LRNK LINEAR REG LOGIST REG HELP PDF
Plot Type Symbols/Background Iterations Template
Data Reports Axes/Legend/Grid Plot Text
Solve For
Find (Solve For):
n
Error Rates
Power (1-Beta):
0.90
Alpha (Significance Level):
0.025
Sample Size
n (Sample Size):
50 100 200 300 500 800
Effect Size
P0 (Null Proportion):
0.90
P1 (Alternative Proportion):
0.995
Test
H1 (Alternative Hypothesis):
H1: P > P0
Test Type:
Exact Test
N (Population Size):
Infinite
TEST TYPE:
Specify which type of test will be used in all searching and reporting.
Note that 'C.C.' is short for 'Continuity Correction.' This refers to the adding or subtracting 1/(2n) to (or from) the numerator of the z-value to bring the normal approximation closer to the binomial distribution.
Template Id:
Reset
Guide Me

Power Analysis of One Proportion

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Numeric Results for testing H0: P = P0 versus H1: P > P0
Test Statistic: Exact Test

Power	N	Proportion Given H0 (P0)	Proportion Given H1 (P1)	Target Alpha	Actual Alpha	Beta	Reject H0 If R>=This
0.9699	54	0.9000	0.9950	0.0250	0.0237	0.0301	53

References

Chow, S.C.; Shao, J.; Wang, H. 2003. Sample Size Calculations in Clinical Research. Marcel Dekker. New York.
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Zar, Jerrold H. 1984. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey.

Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.
N is the size of the sample drawn from the population. To conserve resources, it should be small.
Alpha is the probability of rejecting a true null hypothesis. It should be small.
Beta is the probability of accepting a false null hypothesis. It should be small.
P0 is the value of the population proportion under the null hypothesis.
P1 is the value of the population proportion under the alternative hypothesis.

Summary Statements

A sample size of 54 achieves 97% power to detect a difference (P1-P0) of 0.0950 using a one-sided binomial test. The target significance level is 0.0250. The actual significance level achieved by this test is 0.0237. These results assume that the population proportion under the null hypothesis is 0.9000.

Attrition from enrollment to completion of an MRI scan and being following for one month post MRI ranges from 12% to 18% in historical MRI studies (Table 1, i.e. CIP section 14.5 Table 11). Assuming an attrition rate of 15%, a total enrollment of 64 subjects is needed in the China 3.0T MRI study. If the actual attrition rate exceeds 15%, further evaluation may be considered.

[redacted]

7. Statistical Methods

The CIP version 2 dated February 06, 2024, is the latest version as of the approval date of this document.

7.1 Study Subjects

7.1.1 Disposition of Subjects

This is a prospective, non-randomized, single-arm, multi-site, interventional post-market study. The target study population is subjects who were implanted an SureScan system CIED over 6 weeks at the time of signing informed consent form (ICF). A subject is considered enrolled when the consent process has been finalized. The date the subject signed the IC must be documented in the subject's medical records. Confirmation of Inclusion/Exclusion Criteria of subject will be performed by investigator at enrollment visit. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. Once consent is obtained, report adverse events, device deficiency, study deviations and subject exits as they occur. All subjects will have required follow-up visits at baseline, MRI visit, and 1-month post-MRI. The MRI scans will occur at the MRI visit. The MRI scan region will be determined by investigator according to the subject's clinical condition.

Subject disposition will be presented using a flow diagram where completed visits, missed visits, and attrition due to exit or death will be indicated.

7.1.2 Clinical Investigation Plan (CIP) Deviations

A study deviation is defined as an event within a study that did not occur according to the CIP or the Clinical Trial Agreement. Examples of study deviations include but are not limited to:

- Failure to obtain proper IC.
- Failure to collect required study data.
- Inclusion/exclusion criteria not met.
- Missing required device interrogation files
- Missing visit

All study deviations must be reported on the CRF. Deviations will be summarized with descriptive statistics including, for each type of deviation, how many occurrences there were in the study, and the number of subjects experiencing each type of deviation.

7.1.3 Analysis Sets

All subjects implanted with a SureScan study device who have a 3.0T MRI scan after enrollment and have completed their one-month post-MRI scan follow-up or have had an MRI-related event without completion of their one-month post-MRI scan follow-up will be included in the analysis for the primary objective. Results from the primary analysis will determine if the primary objective is met. In addition, sensitivity analysis will be considered when there is missing data for the primary endpoint.

7.2 General Methodology

Data analysis will be performed by Medtronic statisticians or designees.

The cohort will include all enrolled subjects. There are no pre-specified subgroups for assessment.

7.3 Poolability

This study plans to enroll up to 64 subjects in China. Poolability analysis will not be performed due to small sample size, single geographical region, and few sites.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

All available data will be included in the data listings and tabulations.

Subjects who have a 3.0T MRI scan after enrollment and have completed their one-month post-MRI scan follow-up or have had an MRI-related event without completion of their one-month post-MRI scan follow-up will be included in the main analysis for the primary endpoint. Other enrolled subjects will be included in a sensitivity analysis. Specifically, a tipping point analysis will be performed based on all subjects that are enrolled to determine the robustness of the results with respect to missing data.

Common examples of missing the primary endpoint include:

- Withdraw or exit the study prior to MRI visit
- Miss the MRI visit
- Attend the MRI visit but the 3.0T MRI scan is not performed or completed
- Withdraw or exit the study after the MRI scan but prior to the one-month post MRI visit
- Miss the one-month MRI visit

7.5 Adjustments for Multiple Comparisons

There is no adjustment for multiple comparisons. For the primary objective, the type I error rate is set to 0.025 to be consistent with previous 1.5T MRI clinical trials.

7.6 Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize demographic, physical exam, cardiovascular medical history and other baseline characteristics. For categorical data, counts and percentages will be employed, while for continuous variables, means, standard deviation, quartiles, minimum, and maximum will be provided. These statistics will be calculated for all enrolled subjects.

7.7 Treatment Characteristics

Descriptive statistics will be used to summarize electrical performance data such as lead impedances, sensing amplitudes and pacing capture thresholds collected before and after 3T MRI procedure.

7.8 Interim Analyses

There are no interim analyses in this study.

7.9 Evaluation of Objectives

7.9.1 Primary Objective(s) Primary Objective for Safety: MRI-related Events

To demonstrate the safety of SureScan system CIED in clinical 3.0T MRI environment within 1-month post-MRI scan.

7.9.1.1 Hypothesis

The MRI-related event-free rate within 1-month post-MRI is greater than 90%.

H_0: $p \leq 0.90$

H_A: $p > 0.90$

Where p is the percentage of subjects free of an MRI-related event within 1-month post-MRI.

7.9.1.2 Endpoint Definition

For subjects with IPG devices, the occurrence of any of the following within 30 days after a 3.0T MRI procedure will be considered an MRI-related event:

- Medical advisor-assessed MRI-related complication within 30 days post-MRI
- Medical advisor-assessed right ventricular MRI-related loss of capture within 30 days post-MRI

For subjects with ICD or CRT-D devices, the occurrence of any of the following within 30 days after a 3.0T MRI procedure will be considered an MRI-related event:

- Medical advisor-assessed MRI-related complication within 30 days post-MRI
- Sustained tachyarrhythmia originating during SureScan programming, requiring immediate treatment (defined as ATP, device shock, or external shock), as assessed by a medical advisor.
- Medical advisor-assessed right ventricular MRI-related loss of capture within 30 days post-MRI

Definitions of “MRI procedure related” and “complication” can be found in the CIP section 12.3 Table 7.

7.9.1.3 Performance Requirements

The null hypothesis will be rejected if the one-sided 97.5% lower confidence bound is greater than 90% or, equivalently, if the p-value is less than 0.025.

7.9.1.4 Rationale for Performance Criteria

All events that can be attributed to the MRI are expected to occur within one month. There is no evidence of lingering effects of MRI scans on devices. Therefore, assessing this objective one-month post-MRI will capture all MRI-related events that result following the MRI procedure.

Previous 1.5T MRI clinical studies including EnRhythm MRI, Advisa MRI and 5076 MRI for IPG devices and Evera MRI for ICD devices have used an Objective Performance Criterion (OPC) of 90% for a similar safety objective, and all of them have met their safety objective with 0 MRI-related events observed (Table 2).

[redacted]

7.9.1.5 Analysis Methods

The objective will be evaluated using a one-proportion binomial exact test along with a one-sided 97.5% lower (Clopper-Pearson) confidence bound. The proportion of subjects free from MRI-related events

will be calculated by dividing the number of subjects without an MRI-related event by the number of subjects at risk for an event. The denominator is all subjects implanted with a SureScan study device who underwent a 3.0T MRI scan and completed the one-month post-MRI scan visit (or later follow-up, if any), or have had an MRI-related event prior to completing the one-month post-MRI scan visit. The numerator will be the subjects included in the denominator who are free from MRI-related events. Subjects who are lost to follow-up or withdraw for other reasons prior to the one-month post-MRI scan follow-up will not be included in the analysis unless they have had an MRI-related event.

Medical advisor's assessment on the relatedness and complication of events will be used for the analysis. The analysis will be performed with SAS code similar to

```
proc freq data=MRI;
     exact binomial;
     tables MRIEVENT/binomial(p=0.9) alpha=0.05;
run;
```

where MRIEVENT is a variable coding whether a patient has an MRI-related event one month post MRI scan; exact statement requests both one- and two-sided exact test for the binomial proportion of MRIEVENT; p = 0.9 in the binomial option specifies the null hypothesis proportion for the binomial test; the alpha=0.05 option sets the confidence level of two-sided confidence interval (CI) for the binomial proportion as 95%, hence the lower confidence limit of this 95% CI is the one-sided 97.5% confidence boundary. If it is greater than 90%, we reject the null hypothesis at a significance level of 0.025.

For patients who are enrolled but unable to complete MRI scan and/or one-month post-MRI visit, their primary endpoint will be missing. To assess the robustness of main analysis to missing data, a tipping point analysis[2, 3] will be performed based on all subjects enrolled.

Let $n_{missing}$ be the number of subjects with an MRI scan attempt who are not included in the denominator for the main analysis mentioned above. Starting at 0 and ending at $n_{missing}$, the MRI-related event-free rate is changed by adding 1 failure at a time and a two-sided 95% CI will be produced each time. If its lower confidence limit is less than or equal to 90%, then the number of failures in the missing subjects that results the study fails to reject the null hypothesis of this objective is a tipping point. The algorithm of the tipping point analysis is below.

Do i = 0 to $n_{missing}$;

p = $1-(n_{failure}+i)/n$

If the lower limit of two-sided 95% CI <= 90% then tipping point index = 1;

2 Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. Journal of Biopharmaceutical Statistics. 2009,19:1085-1098.
3 Campbell G, Pennello G, Yue L. Missing data in the regulation of medical devices. *J Biopharm Stat*. 2011 Mar; 21(2): 180-95.

else tipping point index = 0;

End;

where $n_{missing}$ is the number of missing data points; $n_{failure}$ is the number of subjects who has MRI-related events one month post-MRI scan (failure); n is the number of randomized MRI subjects included in the analysis.

The percentage of successes (free from MRI-related events) among the missing subjects needed to meet the objective will be compared to the observed success rate, which will be used to assess if the study conclusion is robust in regard to the missing data.

7.9.1.6 Determination of Subjects/Data for Analysis

All subjects implanted with a SureScan study device who have a 3.0T MRI scan after enrollment and have completed their one-month post-MRI scan follow-up, or have had an MRI-related event without completion of their one-month post-MRI scan follow-up will be included in the main analysis.

7.9.2 Secondary Objective(s) Atrial and Ventricular Pacing Capture Thresholds

To characterize changes in atrial and ventricular pacing capture thresholds (APCT and VPCT) from pre-MRI to 1-month post-MRI scan

7.9.2.1 Hypothesis

There is no hypothesis for this objective.

7.9.2.2 Endpoint Definition

If applicable, PCTs to be evaluated include:

- APCT of atrial lead for subjects with an IPG device
- APCT of atrial lead and VPCT of right ventricular (RV) lead for subjects with an ICD device
- APCT of atrial lead and VPCTs of right ventricular (RV) and left ventricular (LV) leads for those with a CRT-D device.

PCTs of each subject will be measured prior to the 3.0T MRI scan and at the one-month post-MRI. Change in PCT is defined as PCT measured at one-month post-MRI subtracts that measured prior to a 3.0T MRI scan. Proportion of subjects with an increase less than or equal to 0.5V in APCT or VPCTs from pre-MRI to one-month post-MRI will also be used to characterize the efficacy performance of SureScan with respect to PCTs.

If the 1-month post-MRI APCT or VPCT is missing, the PCT measured immediately post-MRI will be used instead.

7.9.2.3 Performance Requirements

There are no performance requirements.

7.9.2.4 Rationale for Performance Criteria

Although there are no performance requirements for PCTs, the interest to check an increase of $\leqslant$ 0.5V in a PCT from pre-MRI to one-month post-MRI is consistent with what have done in the FDA approved pre-market MRI studies such as EnRhythm MRI, Advisa MRI, and Evera MRI.

7.9.2.5 Analysis Methods

The change in PCT is the PCT measured at one-month post-MRI visit subtracts that measured prior to a 3.0T MRI scan. Descriptive statistics will be provided for changes in APCT and VPCTs, respectively.

In addition, the percentage of subjects with an increase less than or equal to 0.5V from pre- to one month post-MRI in APCT and VPCTs will be determined.

7.9.2.6 Determination of Subjects/Data for Analysis

To be included in the analysis, all the following must be met:

- The subject must undergo a 3.0T MRI scan.
- The subject must have valid PCT measurements pre- and post-MRI (see paragraph below for definitions).
- The (atrial, right or left ventricular) lead is not dislodged within 6 weeks prior to MRI scan.
- The (atrial, right or left ventricular) lead has not been replaced or repositioned within 6 weeks prior to MRI scan or between MRI scan and the one-month post-MRI visit.
- The VPCTs of RV at the pre-MRI must be ≤ 2.0V. This is because subjects with a higher VPCT cannot have an MRI per CIP

To be a valid PCT measurement, the pulse width must be set to 0.4ms and a printed pacing capture threshold testing strip must be available to confirm the pulse width and capture threshold reported.

The pre-MRI period value will be the pre-MRI period PCT measurement. For the post-MRI period PCT value, the PCT value on the one-month post-MRI period CRF will be used. If that does not exist or is not valid, the PCT measured immediately post-MRI will be used instead.

[redacted]

[redacted]

7.10 Safety Evaluation

Adverse events collected from enrolled subjects will be summarized using descriptive statistics. Counts and percentages of subjects experiencing system-related or MRI procedure-related adverse events will be reported, as well as, in the case of system-related events, the specific components of the system to which the event was related. The seriousness of adverse events will also be summarized. Details of individual adverse events will be listed. When deemed necessary, individual adverse events where

center investigator classification on relatedness differs from medical advisor will be identified for reporting.

In addition, the term and center description of individual device deficiencies and whether they could have led to a serious adverse device effect will be reported. Individual deaths (if any) including death classification per center investigator and per medical advisor will also be listed.

7.11 Changes to Planned Analysis

There are no changes to planned CIP.

8. Validation Requirements

Level I validation will be performed on programs related to the primary objective, while level II validation will be performed for programs related to all other objectives, as well as for programs summarizing non-objective related information such as baseline demographics, study deviations, adverse events, and study exits.