FDA Executive Summary

Prepared for the
March 19, 2010 meeting of the
Circulatory System Devices Panel

P090013
REVO MRI SureScan Pacing System, Medtronic, Inc.

Introduction

This is an Executive Summary for the REVO MRI SureScan Pacing System (P090013). The device has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration.

The REVO MRI SureScan Pacing System, if approved, would be the first MR Conditional pacing system, allowing subjects implanted with the device to undergo MRI under certain conditions. The Executive Summary provides a discussion of the safety concerns and technical challenges that have limited access to MRI for pacemaker patients and describes FDA's review of the device description, preclinical, and clinical information provided by the Sponsor.

Contents

1 Proposed Indications for Use

1.1 Revo MRI SureScan IPG Indications for Use

The device is indicated for the following

- Rate adaptive pacing in patients who may benefit from increased pacing rates concurrent with increases in activity
- Accepted patient conditions warranting chronic cardiac pacing include:
  - Symptomatic paroxysmal or permanent second- or third-degree AV block
  - Symptomatic bilateral bundle branch block
  - Symptomatic paroxysmal or transient sinus node dysfunctions with or without associated AV conduction disorders
  - Bradycardia-tachycardia syndrome to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmia

The device is also indicated for dual chamber and atrial tracking modes in patients who may benefit from maintenance of AV synchrony. Dual chamber modes are specifically indicated for treatment of conduction disorders that require restoration of both rate and AV synchrony, which include:

- Various degrees of AV block to maintain the atrial contribution to cardiac output
- VVI intolerance (for example, pacemaker syndrome) in the presence of persistent sinus rhythm

Antitachycardia pacing (ATP) is indicated for termination of atrial tachyarrhythmia in bradycardia patients with one or more of the above pacing indications.

Atrial rhythm management features such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive Pacing (PMOP) are indicated for the suppression of atrial tachyarrhythmia in bradycardia patients with atrial septal lead placement and one or more of the above pacing indications.

The Revo MRI SureScan pacemaker has been designed for use in the MRI environment when used with the specified conditions of use.

1.2 5086MRI Lead Indications for Use

The Medtronic CapSureFix MRI Model 5086MRI steroid-eluting, bipolar, implantable, screw-in, ventricular/atrial, transvenous lead is designed to be used with a pulse generator as part of a cardiac pacing system. The lead has been designed for use in the MRI environment, but only when used with a Medtronic SureScan IPG. The lead has application where implantable atrial or ventricular, single chamber or dual chamber pacing systems are indicated.

2 Background – MRI Safety and Pacemakers

Magnetic Resonance Imaging is a high spatial and temporal resolution imaging modality that has unique soft tissue differentiation abilities. MRI also has the advantage of not exposing patients to tissue-ionizing radiation. For these reasons, MRI is the imaging modality of choice for many applications. For some conditions, there is not a reasonable imaging alternative. However, the MRI environment exposes patients to high static magnetic, gradient magnetic, and radio-frequency (RF) fields, each of which presents a unique set of risks for pacemaker patients.

MRI scanner manufacturers currently contraindicate MRI for pacemaker patients and the labeling for approved pacemakers cautions against MRI scanning for these patients due to a wide array of risks to the patient and the device in the MRI environment. Specifically, the following potential risks are of most concern:

- Lead heating: RF energy delivered by the MRI scanner may be dissipated at the tip of the lead and cause detrimental heating. This risk has been studied and presented in the scientific literature. *In vitro*[1,2] studies and acute animal studies[3], have shown considerable lead heating for some MRI conditions. Clinically, some patients have experienced increases in pacing threshold following MRI that are potentially due to tissue damage from lead heating[4].
- Unintended Cardiac Stimulation: There is the potential for the gradient magnetic field or the RF field in the MRI scanner to interact with the implanted system and cause unintended cardiac stimulation, potentially leading to an arrhythmia. In the literature, rapid pacing has been observed in isolated cases which may have been due to this phenomenon[5].
- Device Reset: Device resets during MRI have occurred in cases discussed in the literature for both pacemakers and ICDs [6,7]. The mechanisms behind these resets are not well understood.
- Inappropriate Sensing: The gradient magnetic fields of the MRI system switch with a frequency content that overlaps with frequencies found in the electrocardiogram (ECG). Therefore, if the device is in a sensing mode, the device will likely misinterpret gradient switching as being cardiac electrical activity, causing the device to pace either inappropriately or not at all. Hence, pacemakers must be placed in a non-sensing mode during MRI, either pacing asynchronously (for pacemaker-dependent patients) or not pacing at all.
- Battery Depletion: Decreases in device-reported battery voltage following MRI have been observed[8]. The mechanisms are not well understood but may be related to corruption of device diagnostics rather than actual battery depletion.
- Device Displacement and Torque: The strong static magnetic field may cause movement of the implantable pulse generator (IPG) or lead. This risk depends on the ferromagnetic properties of the device and the spatial gradient of the magnetic field. Validated bench tests used to assess this risk for a given device are well characterized.
- IPG Case Heating: IPG case heating is possible due to the switching gradient magnetic fields inducing eddy currents on the conducting IPG case. This could lead to patient discomfort and/or burns to adjacent body tissue.

- Vibration: The MRI system may induce mechanical vibration of the pacemaker due to the gradient magnetic field switching in the presence of a high static magnetic field causing device damage.
- Device Failure: Device failure requiring replacement has been reported in the literature for some ICD patients[9]. The mechanisms behind these failures are not well understood and, while not reported, the concern may also apply to pacemakers.

Small, published single-center retrospective and prospective studies reporting outcomes from pacemaker subjects who underwent MRI total approximately several hundred subjects[10,11,12,13,14]. The vast majority of published outcomes are positive, with no adverse effect to the subject or the device reported. Many pacemaker patients who receive MRIs when there are not appropriate diagnostic alternatives are not reported.

The REVO MRI SureScan Pacing System was specifically designed to reduce the risk of these failure mechanisms occurring in the MRI environment when the patient is scanned under certain MRI conditions. If approved, this would be the first MR Conditional pacing system.

3 Device Description

The Medtronic REVO MRI SureScan Pacing system consists of the Medtronic REVO MRI SureScan implantable pulse generator (IPG) and the Model 5086MRI lead. The dual chamber, rate responsive IPG is based on the market-approved Medtronic EnRhythm Pacing System. The Model 5086MRI lead is based upon the market-approved Medtronic Lead Model 5076.

3.1 IPG

The REVO MRI IPG under review has been changed from the market-approved device in several ways. The most notable changes are listed below:

- Radiopaque marker and shield engraving is used to identify the system visually or via x-ray.
- Changes were made to the internal electronics including reducing the feed-through capacitance in order to reduce induced voltage caused by gradient magnetic fields from the MRI system.
- The MRI SureScan device operation was added in firmware to be used during MRI. When programmed ON, MRI SureScan operation disables arrhythmia detection, magnet mode, and all user-defined diagnostics.
- MRI specific labeling was developed.

As with the market-approved system, the REVO MRI system is limited to bipolar therapy. Unipolar systems have a higher effective loop area which makes them more susceptible to induced current.

Figure 1: Picture of the REVO MRI SureScan IPG.

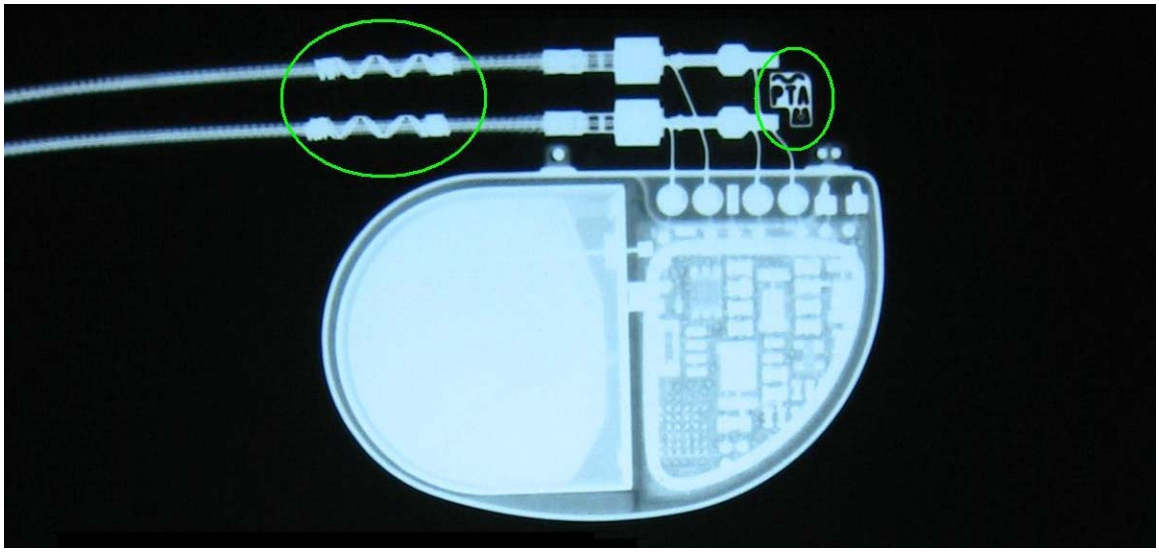

Figure 2: X-ray image of MRI labeled device with radiopaque symbols on the lead and IPG, indicating a complete MR Conditional system.

3.2 Lead

The Medtronic Lead Model 5086MRI is a bipolar, silicone, steroid eluting, screw-in extendable/retractable pacing lead. The steroid is dexamethasone acetate and is identical to the steroid used in the market-approved Model 5076 lead. The lead body features a radiopaque anchoring sleeve for suturing down the lead and is designed for use in either the right atrium or the right ventricle. The major difference between the 5086MRI and the approved 5076 is the inner coil design which was modified to have a higher inductance in order to limit the amount of RF heating during an MRI procedure. To create an increased inductance coil, the inner conductor coil was reduced from a 4 filar design (Model 5076)

to a 2 filar design (Model 5086MRI). This change decreases the pitch and increases the number of turns in the coil, increasing its inductance. Due to larger wire diameter, however, the lead Model 5086MRI is overall slightly larger in diameter than the lead Model 5076 (7.0 Fr or 2.3 mm diameter as opposed to the Model 5076 diameter of 6.2 Fr or 2 mm). To limit gradient-induced voltage in the lead caused by the loop area formed between the IPG and the lead tip, the lead length for the lead Model 5086MRI will be limited to lengths of 45, 52, and 58 cm.

4 Basic Engineering Review Summary

FDA conducted an extensive basic (i.e., non-MRI) engineering review of the sponsor's preclinical testing. The following areas of review were included in FDA's basic engineering evaluation:

- Lead and IPG mechanical performance
- Lead and IPG electrical performance
- Electromagnetic compatibility
- Software
- Lead steroid validation
- Biocompatibility
- Sterilization
- Device and packaging shelf life

At this time, FDA has no outstanding basic engineering concerns.

5 Preclinical MRI Safety Testing

Preclinical testing was conducted to address the following concerns related to the MRI environment:

- Lead heating
- Unintended cardiac stimulation
- Force and torque
- Device interactions
- IPG case heating
- Vibration

5.1 Lead Heating

Lead heating is one of FDA's most serious concerns for MR Conditional pacing systems. The RF fields in the MRI environment can induce currents on a lead that may be dissipated in the form of heat at the tip/tissue interface during an MRI scan. There is extensive evidence in the literature demonstrating that lead heating can occur in the MRI environment and the potential for serious injury exists. However, historically the risk has been difficult to fully characterize and the worst-case conditions difficult to define. The conditions that contribute to lead heating include the following:

- Level of RF energy delivered by the MRI system
- Type of RF coil
- Patient location relative to RF coil

- Patient anatomy (including body size, fat and muscle content)
- Lead path
- Device characteristics including conductive length and inductance

FDA has experience reviewing MRI-induced heating validation for other electrically conductive implants such as cardiac stents. Such testing generally consists of data demonstrating that devices placed in beyond realistic worst-case MRI conditions in a phantom (human model) do not heat above a conservative acceptable limit, as measured with temperature probes. For devices that can meet such conservative test conditions, this type of testing is relatively simple to conduct and sufficient to support device safety in this regard. However, FDA recognizes that some devices may fail such conservative test requirements and yet may still be safe under clinically realistic worst-case conditions. For these devices, more sophisticated test methods are needed which better represent realistic worst-case conditions and assess the acceptability of any induced heating in the context of potential clinical implications.

FDA has been an active member of an international standards development group (JWG ISO TC150/SC6/JWG1-IEC SC62B/JWG2) which is developing a Technical Specification (ISO/TS10974) to describe the test methods for MRI safety validation for active medical implants, but that effort is not completed. Because the Technical Specification is intended for all active medical implants, and not just pacemakers, some of the methodology proposed may not be applicable or practical for some device areas. Device specific standards will likely be developed in the future which will provide more detail regarding the testing methods and requirements for a particular device area. The methodology used by the sponsor was developed prior to consensus being reached on the Technical Specification. As such, the sponsor's methods closely parallel but are not identical to the approach discussed in the current draft of the Technical Specification. A significant difference compared to the draft Technical Specification is the sponsor's proposed use of pacing capture threshold (PCT) as the indicator of myocardial damage associated with lead heating. The draft Technical Specification does not discuss the use of PCT and the general test methods it proposes are based on *in vivo* temperature rise. However, the draft Technical Specification does not offer specific guidance on how *in vivo* temperature rise should be assessed for pacing leads. For reasons discussed below, the sponsor argues that assessment of *in vivo* temperature rise for chronically implanted pacemaker leads is not practical.

Key elements of the sponsor's approach to lead heating are described below.

5.1.1 Pacing Capture Threshold

Unlike most device heating validation that FDA reviews, the sponsor's testing is not based on *in vivo* temperature assessments but instead relies on changes in PCT. The sponsor argues that temperature assessment at the lead tip (where heating is greatest) is not directly relevant given that in the chronic implant the lead tip is isolated from viable tissue by a fibrous encapsulation of variable thickness and temperature rise

drops off quickly with distance from the lead tip. The sponsor further argues that the temperature rise of interest is that of the viable tissue nearest to the lead tip, which is difficult to assess *in vivo* and difficult to accurately predict based on *in vitro* testing. In addition, it may be unclear what an acceptable temperature would be. Modest changes in temperature may cause no change to the myocardial tissue or changes that are induced may be recoverable. In addition, histopathology is of limited utility given its poor resolution to assess incremental changes in scar tissue around the lead tip and the fact that before and after comparisons are not possible. Change in PCT has been used in the clinical literature discussed earlier in this review as an indicator of myocardial damage from MRI. The sponsor proposes that PCT is a relevant metric for myocardial thermal damage from MRI for both the preclinical and clinical testing. Of note, the REVO MRI SureScan Pacing System is unable to detect pacing threshold changes smaller than 0.5V. This limitation has raised concern for FDA that smaller PCT changes may occur but remain unobserved and that those changes may be cumulative with multiple MRI exposures. An animal study discussed below was conducted to address this concern. The Panel will be asked to comment on the utility of PCT as an indicator of clinically relevant thermal damage from MRI.

5.1.2 RF Modeling

The sponsor's assessment of the potential for lead heating relied heavily upon a modeling approach, which was used to compute the RF power dissipated at the tip-tissue interface. The sponsor began this approach by simulating the electromagnetic field distribution in human body models during an MRI scan. The model was intended to account for a broad patient population and a wide range of clinical scenarios. The sponsor chose 100 anatomic lead paths in order to include worst-case conditions in the model. The sponsor also modeled the lead itself in order to predict the response to the field and the corresponding dissipated energy. Model validation was performed *in vitro* in a phantom by comparing the results of simulations and measurements for well-defined cases. During the review process, FDA asked extensive questions to confirm that the model was rigorously validated. FDA challenged the assumptions that the sponsor used in the model, and in some cases requested modifications (which were implemented), in order to ensure that the assumptions were based on worst case conditions. Using this approach, the sponsor determined that for the proposed MR Conditions of Use, the lead will dissipate less than 140 mW of power at the tip in 99.9% of human cases. These results were used to inform the animal studies discussed below.

5.1.3 Animal Studies

Due to the differences in body geometry, lead heating in an animal in the MRI environment may not be representative of the human situation. For this reason, the modeling approach was used to determine dissipated power in humans. However, if the relationship between heating (as measured by dissipated power) and thermal damage (as measured by PCT changes) is similar across species, then animal data can be used to estimate this effect to determine whether a particular level of dissipated power is likely to be clinically relevant. The sponsor conducted several studies as part of this project, many of which were used to inform the design

of later bench and animal studies and to support the initiation of the clinical trial. This review will focus on two later studies that that incorporate the information obtained from the modeling approach and, FDA believes, are most relevant to the critical concerns related to lead heating.

The first study (S1607) was designed to assess the dissipated power needed to cause changes in PCT. As discussed above, the sponsor determined that for the MR Conditions of Use proposed, the lead will dissipate less than 140 mW of power at the tip in 99.9% of cases. Using a direct RF injection animal preparation to systematically reproduce the RF energy that would be dissipated at the lead tip during MR scanning, the sponsor demonstrated that PCT changes do not occur until the dissipated power reaches more than 200 mW (Figure 3). The sponsor combined the RF modeling data and the animal study data into a single probability distribution function to characterize the likelihood that PCT changes will occur in humans under anticipated MRI conditions and concluded that clinically relevant changes in PCT are very unlikely to occur. FDA reviewed this study, including the methods used for direct RF injection, and concluded that the study was well conducted.

Figure 3: **ower.**

The second study discussed in this review (S2167) was intended to demonstrate that small changes in pacing threshold are not cumulative with multiple MRI exposures, a question that was not assessed in the clinical study. In this study, were each implanted with in the right ventricle and in the right atrium). After the leads matured, the animals were exposed to multiple direct RF injections at weeks 6, 8, 10, 12 and 14 post-implant. Some of the leads

were exposed to approximately 131 mW of dissipated power (near worst case clinically, according to the modeling data) while other leads were exposed to approximately 390 mW of dissipated power (well beyond worst case clinically, according to the modeling data). The lower energy data is shown in Figure 4 and the higher energy data in Figure 5. At 131 mW of dissipated power, no measurable change in PCT was noted after repeat exposures. At 390 mW of dissipated power, transient changes in PCT were seen but PCT recovered prior to the following RF injection with no cumulative effect noted. The sponsor notes that the outlier data seen in the week 14 assessments were all measured sequentially on the same day using the same equipment, indicating that equipment malfunction was the likely cause of the abnormality. FDA reviewed this animal study and concluded that it was well conducted. The Panel will be asked whether the data presented support the safety of multiple MRI scans for patients.

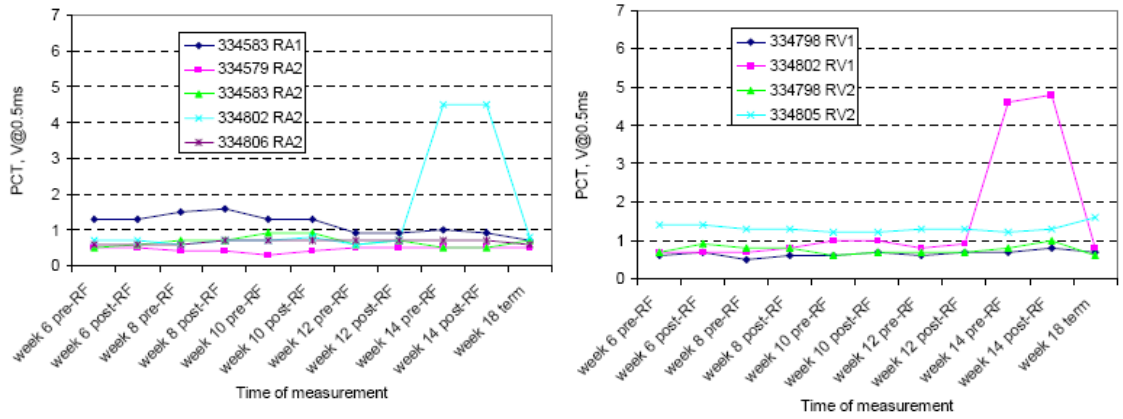

Figure 4: Atrial (left) and ventricular (right) PCT before and after repeat RF injection at approximately 131 mW dissipated power (near worst case clinically). No measurable change in PCT was noted after repeat exposures. Outlier data points are discussed in the text above.

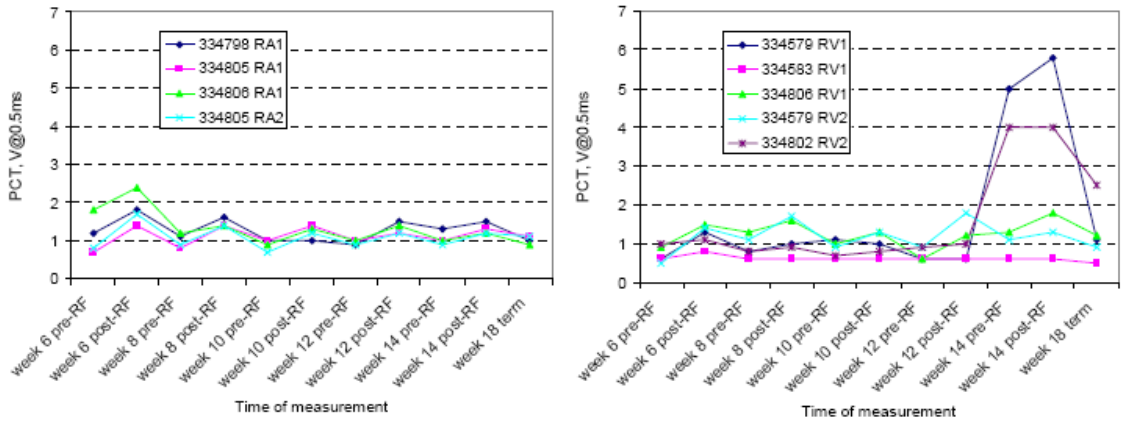

Figure 5: Atrial (left) and ventricular (right) PCT before and after repeat RF injection at approximately 390 mW dissipated power (beyond worst case clinically). Transient changes in PCT were seen but PCT recovered prior to the following RF injection Outlier data points are discussed in the text above.

5.2 Unintended Cardiac Stimulation

The sponsor's basic approach to validation with regard to unintended cardiac stimulation was to demonstrate that any gradient- or RF-induced currents are below the cardiac stimulation threshold and are therefore not of clinical consequence. The sponsor made several worst-case assumptions regarding the potential for stimulation and the clinical consequences should stimulation occur. For example, the sponsor assumed that any instance of induced current equal to or greater than the patient's stimulation threshold would result in hemodynamic collapse that continued until the scan was stopped. It was further assumed that if the induced currents reached or exceeded the stimulation threshold, all susceptible patients would experience an induced arrhythmia that would continue after the scan was stopped and induced electrical stimulation ended.

The sponsor described how the worst-case conditions for gradient field, RF field, and lead path were characterized. Under worst-case conditions in terms of loop area and gradient strength, a 3 standard deviation induced voltage of 3.77V peak (or 7.54V peak-peak) was observed. Using an animal model in which the lead was looped multiple times to increase the effective loop area, it was determined that gradient-induced lead voltages larger than 5.4V peak were needed to produce cardiac stimulation. Such high voltages were required to produce stimulation due to the short pulse width of the gradient waveform. For RF-induced stimulation, [redacted] testing was used to demonstrate that in order for stimulation to occur, the pacing system must rectify the currents that flow through the IPG lead interface as a result of RF-induced lead voltage. Bench testing was used to demonstrate that the RF voltage was not rectified when tested at the worst case RF voltage.

The sponsor determined that, under some circumstances, unintended cardiac stimulation could occur when several unrelated factors were near worst case in their ranges simultaneously. Therefore, the sponsor asserts that the probability of occurrence is low. FDA concurs. However, FDA believes that the preclinical testing is not sufficient alone to support the low estimated probability of occurrence and that the clinical results are essential for confirmation of this assessment.

5.3 Force and Torque

FDA reviewed testing intended to demonstrate that the device will not experience motion due to the static magnetic field in the MRI environment. The sponsor demonstrated that the worst-case displacement force on the device is approximately equal to the gravitational force on the device. The sponsor provided a rationale for why this force will not have clinical consequence. FDA concluded that the device has been adequately validated with regard to this issue.

5.4 Device Interactions

FDA reviewed device interaction testing which was intended to demonstrate that the device continues to perform appropriately under the expected worst-case static magnetic field, gradient magnetic field, and RF field conditions. FDA concluded that the device has been adequately validated with regard to this issue. One goal of the clinical study was to offer confirmation in this regard.

5.5 IPG Case Heating

IPG case heating is possible due to the switching gradient magnetic fields inducing eddy currents on the conducting IPG case. This could lead to patient discomfort or harm due to damage to adjacent body tissue. This risk from gradient induced heating increases directly with in gradient slew rate. Therefore it is essential that validation of the device in terms of IPG case heating must involve testing at high gradient slew rates. The sponsor determined that a reasonable worst-case slew rate is 100T/s. Of note, this is consistent with the proposed MR Conditions of Use which restrict MRI to scanners with a maximum slew rate less than 200 T/m/s, using the unit of measure generally used in MRI labeling. The sponsor notes that most clinical scanners cannot achieve this high slew rate. Therefore, testing was conducted using a custom high gradient field tester simulating worst-case MRI gradient magnetic fields. FDA reviewed the test data provided by the sponsor and concluded that the issue has been appropriately addressed.

5.6 Vibration

The MRI system may induce mechanical vibration of the device due to the gradient magnetic field switching in the presence of a high static magnetic field. The sponsor presented data demonstrating that the worst-case condition is characterized by the product of the maximum gradient slew rate and the static magnetic field and that after exposure to beyond worst-case conditions with regard to MRI-induced vibration, the device continued to perform without failure. FDA reviewed the test data provided by the sponsor and concluded that the issue has been appropriately addressed.

5.7 Preclinical Testing Conclusions

Many aspects of the preclinical testing approach are novel for this first-of-a-kind device, particularly with regard to lead heating and unintended cardiac stimulation. Notably, given the limitations of the clinical study that are discussed later in this document, rigorous preclinical data are particularly important to support the safety and effectiveness of this device with regard to MRI exposure. The Panel will be asked to comment on whether the preclinical testing conducted to assess the safety of the REVO MRI pacing system when used according to the proposed MR Conditions of Use is appropriate.

6 Clinical Study

6.1 Study Design

The clinical study was designed as a prospective, randomized, controlled, unblinded, multi-center study of typical Class I or II indicated pacemaker patients comparing outcomes between those with and without exposure to a single investigational protocol MRI scan. The protocol MRI scan, which was not intended to address any clinical indication for the subject, was determined by FDA to represent an appropriate range of realistic clinical scenarios within the confines of the proposed MR Conditions of Use. No clinically indicated MRI scans for purposes of medical care were allowed in the study and those that occurred were considered study deviations.

Pacemaker function and adverse events were assessed at implant, at two months, before and after MRI at 9-12 weeks post-implant, at 3, 4 and 6 months post-implant (one week, one month and 3 months after MRI) and every 6 months thereafter. MRI scanning of the test group subjects was only performed if electrical function was stable, pacing thresholds low, and 6 weeks had passed to allow implant maturation. The study flow is shown in Figure 6.

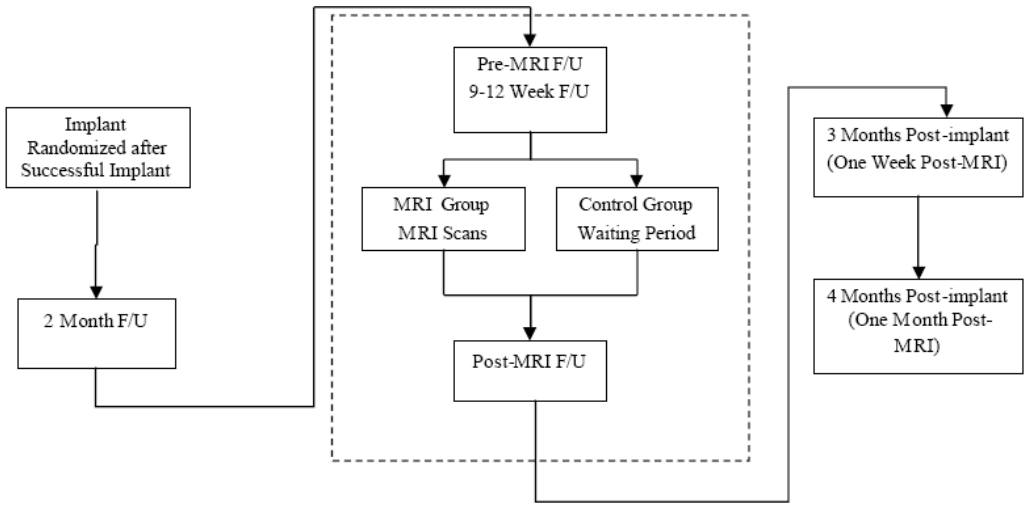

Figure 6: Study Visit Flowchart

6.2 Enrollment Criteria

6.2.1 Inclusion

- Subjects who have a Class I or II indication for implantation of a dual chamber pacemaker according to the ACC/AHA/NASPE guidelines.
- Subjects must be able to undergo a pectoral implant.
- 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 center for the length of the study.

6.2.2 Exclusion

- Subjects who require a legally authorized representative to obtain consent
- Subjects with a mechanical tricuspid heart valve.
- Subjects with a history of tricuspid valvular disease.
- Subjects for whom a single dose of 1.0 mg dexamethasone acetate may be contraindicated.
- Subjects who have a previously implanted pacemaker or implantable cardioverter defibrillator (ICD) (abandoned pacemaker and/or defibrillator leads not permitted; however, subjects with complete system explants are not excluded)
- Subjects who are immediate candidates for an ICD.

- Subjects currently indicated or expected to be indicated for another MRI-scan procedure other than those specifically described in the study during the period of required study follow-up.
- Subjects with previously implanted active medical devices.
- Subjects with non-MRI compatible device (such as ICDs or neurostimulators) or material implant (e.g. non-MRI compatible sternal wires, neurostimulator, biostimulator, metals or alloys).
- Subjects with medical conditions that preclude the testing required by the protocol 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 this clinical study.
- Pregnant women, or women of child bearing potential and who are not on a reliable form of birth control.
- Subjects with exclusion criteria required by local law (e.g. age, breast feeding).

6.3 Primary Study Objectives

The primary objectives are as follows:

1) To assess the one month post scan MRI-related complication-free rate. The hypothesis is that the MRI-related complication-free rate between the MRI procedure and one month post-MRI is greater than 90%, tested with one-sided type I error, α, at 0.025.

2) To compare the changes in 1) atrial and 2) ventricular voltage thresholds before and one month after MRI measured at 0.5 ms between the MRI and control groups. The hypotheses are that the proportion of subjects who experience an increase greater than 0.5 V in atrial and ventricular voltage thresholds are non-inferior across treatment and control, with margin = 10%.

3) To compare the changes in 1) atrial and 2) ventricular sense amplitudes before and one month after MRI between the MRI and control groups. The hypotheses are that the proportion of subjects who experience atrial and ventricular sense amplitude decreases less than or equal to 50% and whose atrial and ventricular sense amplitudes remained above an acceptable minimum at one-month post-MRI/waiting period (four months post-implant) is non-inferior between the MRI and control groups (margin = 10%).

All three primary objectives must be met in order to consider the study successful.

6.4 Secondary Study Objectives

The secondary objectives are as follows:

1) Characterize all system-related complications. The hypothesis is that the system-related complication-free rate between the implant procedure and the four-month post-implant follow-up visit is greater than 80%.
2) Confirm that labeling instructions for completing the MRI scans were followed to ensure subject safety.
3) Characterize occurrence of sustained ventricular arrhythmias and asystole seen during MRI scans.
4) Characterize all implant procedure, pacing system- and MRI procedure-related adverse events through the one-month post-MRI visit for the MRI group, and the corresponding visit for the control group.
5) Characterize atrial and ventricular lead impedance through four months post-implant.
6) Characterize the lead handling of the CapSure Fix MRI lead Model 5086MRI in relation to the commercially available lead Model 5076.
7) Characterize four-month pacing thresholds and sense amplitudes of the MRI group and control group in relation to the commercially available lead Model 5076.

Secondary objectives #1, 6, and 7 were evaluated under the "fixed-sequence method" in order to preserve the overall type I error rate from the secondary objectives. Secondary objectives #2-5 are descriptive only, and were not tested using formal statistical analyses.

6.5 Additional Analyses

The additional analyses are as follows:

1) Demonstrate that the EnRhythm MRI SureScan Pacing System (both device and leads) can be identified as MRI-Labeled via X-ray.
2) Summarize aberrant or undesirable behavior of the SureScan MRI mode.
3) Summarize whether safeguards and procedures were followed at the time of the MRI scans.

6.6 Device Programming during MRI

Key elements of the device programming requirements for the MRI procedure were as follows:

- Prior to the MRI, atrial and ventricular pacing outputs were programmed to 5V at 1.0ms until the 3 month follow-up visit (one week post-MRI).
- Prior to the MRI, the SureScan feature was to be set to ON. The SureScan feature was to be set to OFF immediately following the MRI
- The pacing mode was left to the physician's discretion. Based on whether pacing support was needed, the device could be programmed to asynchronous pacing or a sensing only mode.

6.7 MRI Scan Conditions

The protocol specifically defined the MRI scans used for the study. Key elements of those requirements are as follows:

- Eight brain sequences
- Six lumbar sequences
- Covered the range of commonly used sequence types
- Maximized gradient slew rate (dB/dt) up to 200 T/m/s
- Maximized whole body averaged SAR up to 2 W/kg
- Only 1.5 Tesla MR systems

The protocol defined MRI scans were consistent with the proposed MR Conditions of Use discussed later in this document, including the restriction regarding thoracic scans (isocenter may not be between C1 and T12).

6.8 Patient Monitoring and Safety Precautions during MRI

During the entire MRI scan, the subject's cardiac function was required to be monitored using pulse oximetry by a study trained center electrophysiologist, cardiologist, or Advanced Cardiac Life Support (ACLS) trained clinician who is capable of delivering external cardiac pacing defibrillation and advanced cardiac life support. Other subject monitoring including ECG was recommended. Verbal communication with the subject must also take place to assess or confirm any clinically significant changes noted in the subject's oxygen saturation or heart rate, as well as any clinically significant complaints not obvious during pulse oximetry. It was required that an emergency code cart with an external defibrillator, as well as a programmer were available. If the subject's hemodynamic function was compromised during the MRI scan, the MRI procedure was to be discontinued and proper measures taken to restore the subject's hemodynamic function. If there were any lapses in patient monitoring or if procedures and/or safeguards were not followed, a Study Deviation case report form was to be used.

6.9 Patient Accountability

The following chart describes the enrollment and follow-up that occurred in the study.

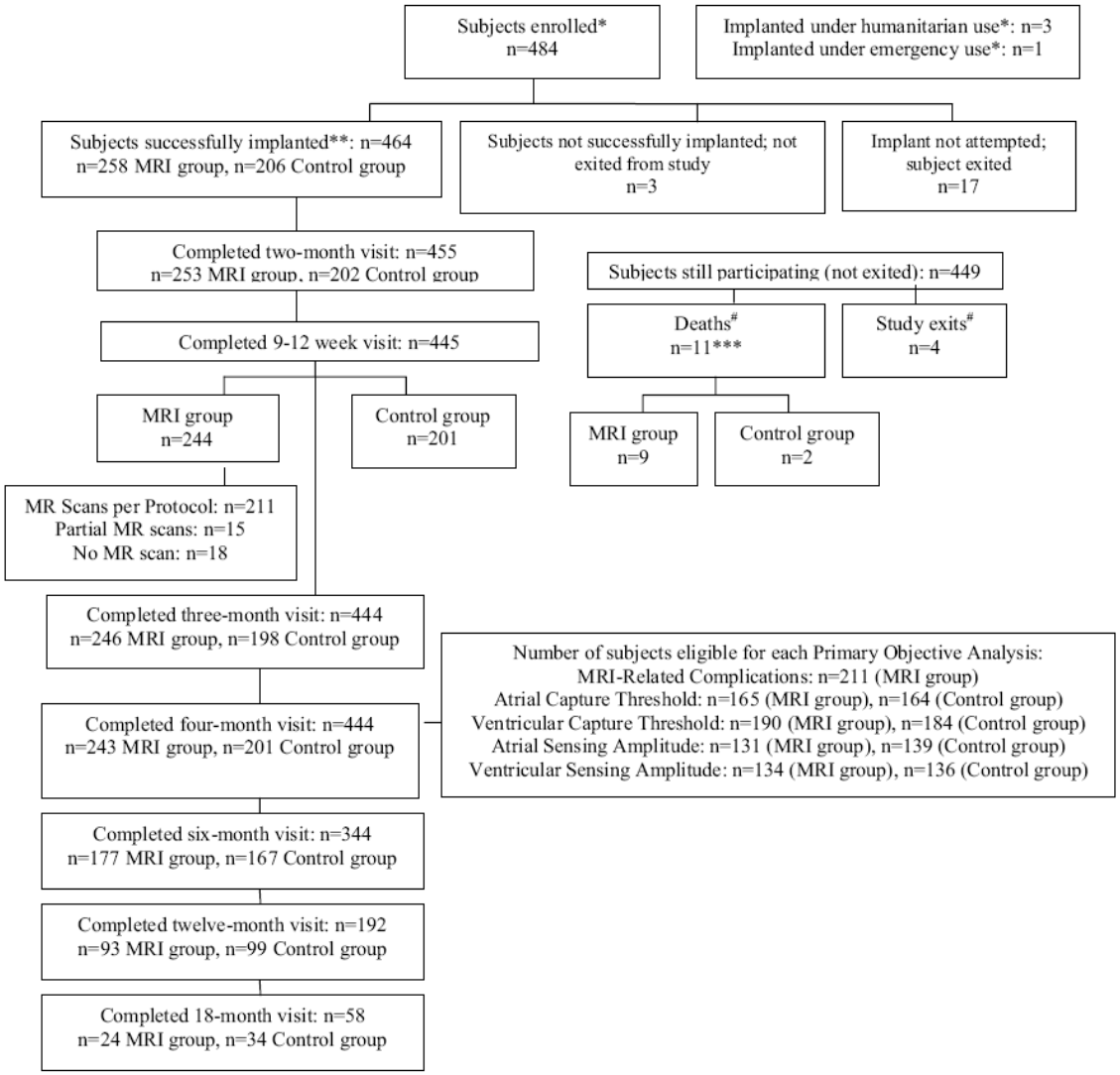

Figure 7: Patient Accountability.

* Includes all subjects who signed and dated informed consent.
** Complete system implant of the EnRhythm MRI SureScan Pacing System with the pulse generator implanted in the pectoral region with an atrial and a ventricular CapSure Fix 5086MRI lead.
*** All deaths have been reviewed by the Adverse Events Adjudication Committee (AEAC) and none were considered related to the REVO MRI SureScan Pacing System, implant procedure, or MRI procedure.
# Includes all deaths and study exits that occurred during the study regardless of timeframe.

6.10 Demographics

The following tables summarize the subject demographics and medical history.

Demographic	MRI Group (n=258)	Control Group (n=206)
Age at Implant		
Mean ± SD	69.3 ± 12.9	68.0 ± 12.6
Median	71.5	71.0
Range	27.8-95.4	19.2-87.3
Gender		
Male	154 (59.7%)	135 (65.5%)
Female	104 (40.3%)	71 (34.5%)
New York Heart Association		
Class I	53 (20.5%)	42 (20.4%)
Class II	57 (22.1%)	35 (17.0%)
Class III	5 (1.9%)	14 (6.8%)
Class IV	1 (0.4%)	1 (0.5%)
Does not meet classification criteria	142 (55.0%)	114 (55.3%)
Height (inches)		
Mean ± SD	66.8 ± 3.8	Not collected
Median	66.9	
Range	58	
Collected at the 9-12 week follow up for the MRI group only	77.5	
Weight (Lbs)		
Mean ± SD	177.8 ± 34.1	Not collected
Median	176	
Range	99	
Collected at the 9-12 week follow up for the MRI group only	315	
Primary indication for implant*		
Atrial tachyarrhythmias	19 (7.4%)	15 (7.3%)
AV block	95 (36.8%)	84 (40.8%)
Cardial sinus hypersensitivity	5 (1.9%)	4 (1.9%)
Sinus node dysfunction	122 (47.3%)	90 (43.7%)
Vasovagal syncope	4 (1.6%)	4 (1.9%)
Sick Sinus Syndrome	2 (0.8%)	6 (2.9%)
Other	11 (4.3%)	3 (1.5%)

Table 1: Subject Demographics

* Whether subjects were pacing dependent was not recorded. However, of the 226 subjects in the MRI group who received an MRI scan, 158 (69.9%) were paced asynchronously during the MRI scan, 67 (29.6%) were not paced, and 1 subject was unknown (0.4%).

Medical History	MRI Group (n=258)	Control Group (n=206)
General cardiovascular history		
Coronary artery disease	80 (31.0%)	72 (35.0%)
Hypertension	168 (65.1%)	135 (65.5%)
Syncope	80 (31.0%)	70 (34.0%)
Valve dysfunction	72 (27.9%)	52 (25.2%)
Surgical cardiovascular history		
Ablation	17 (6.6%)	10 (4.9%)
CABG	29 (11.2%)	32 (15.5%)
Valve surgery	19 (7.4%)	14 (6.8%)
Atrial arrhythmia history		
Atrial fibrillation*	116 (45.0%)	68 (33.0%)
Paroxysmal	99 (38.4%)	54 (26.2%)
Persistent	13 (5.0%)	12 (5.8%)
Permanent	7 (2.7%)	6 (2.9%)
Brady-tachy syndrome	40 (15.5%)	35 (17.0%)
Sinus arrest	62 (24.0%)	59 (28.6%)
Sinus bradycardia	108 (41.9%)	77 (37.4%)
AV junctional arrhythmia history		
None	98 (38.0%)	75 (36.4%)
1st degree AV block	61 (23.6%)	46 (22.3%)
2nd degree AV block	57 (22.1%)	46 (22.3%)
3rd degree AV block	59 (22.9%)	50 (24.3%)
AV junctional rhythm	20 (7.8%)	15 (7.3%)
LBBB	18 (7.0%)	17 (8.3%)
RBBB	46 (17.8%)	39 (18.9%)
Vascular history		
None	174 (67.4%)	152 (73.8%)
Carotid artery disease	23 (8.9%)	12 (5.8%)
Cerebrovascular accident	22 (8.5%)	7 (3.4%)
Peripheral vascular disease	27 (10.5%)	18 (8.7%)
Diabetes	57 (22.1%)	43 (20.1%)
Myocardial Infarction	31 (12.0%)	32 (15.5%)

Table 2: Subject Medical History

6.11 Implant Location

Implant location may be an important factor with regard to device safety and performance in the MRI environment. The following tables characterize the range of lead and IPG implant locations that were used in the clinical trial.

Location	n	Percent
RA appendage	320	69.0%
High right atrium	43	9.3%
RA lateral free wall	79	17.0%
High septum	8	1.7%
Middle septum	3	0.7%
Other*	11	2.4%

* Includes anterior RA (2), anterior wall (2), anterolaterally (2), atrial root (1), Bachman's Bundle (1), high lateral (1), low anterior wall (1), and low posterior septal (1).

Table 3: Right atrial lead tip location

Location	n	Percent
RV apex	305	65.7%
RV septum	132	28.5%
RV outflow tract	12	2.6%
RV freewall	7	1.5%
Other*	8	1.7%

* Includes apical septum (5), inferior wall (1), near tricuspid site (1), and outflow septum (1).

Table 4: Right ventricular lead tip location

Location	n	Percent
Left subcutaneous	311	67.0%
Left submuscular	10	2.2%
Left subfascial	37	8.0%
Right subcutaneous	84	18.1%
Right submuscular	5	1.1%
Right subfascial	17	3.7%

Table 5: IPG location

6.12 Primary Objective Results

FDA's analyses for the primary objectives were performed for the per-protocol (PP) population. The PP population includes subjects who met the following criteria:

- Successfully implanted with the study device and randomized
- Have 9-12 week visit data(pre-MRI/waiting period)
- Met the MR Conditions of Use
- Received an MRI scan (if in the MRI group)
- Have 4-month visit data

For these evaluable patients, all of the primary objectives were met as shown in the following tables. FDA's analyses differ slightly from those presented by the sponsor because the sponsor's analyses include control subjects who did not meet the MR Conditions of Use and, had they been in the MRI arm, would not have received an MRI scan.

6.12.1 Primary Objective #1 - MRI-related complication free rate

The result for Primary Objective #1 is shown in Table 6.

Success Criteria	Subjects	Complication-Free Rate	One-sided 97.5% Confidence Boundary and p-value	Conclusion
The MRI-related complication-free rate is greater than 90%	211	100%	98.3% $p < 0.001$	Objective Met

Table 6: Result of MRI-Related Complications Primary Objective

6.12.2 Primary Objective #2 – Pacing capture threshold

The results for Primary Objective #2 are shown in **Table 7**.

Success Criteria	Comparison	Subjects MRI/ Control	Success Rates MRI/ Control	Conclusion
The proportions of subjects who experienced an increase less than or equal to 0.5 V are clinically equivalent, defined as within 10%.	Atrial	165/ 157	100%/ 100%	Objective met
	Ventricular	190/ 177	100%/ 100%	Objective met

Table 7: Results of Pacing Capture Threshold Primary Objective. Since the success rates were both 100%, the one-sided 97.5% confidence boundary and p-value could not be calculated.

6.12.3 Primary Objective #3 – Sensing amplitude

The results for Primary Objective #3 are shown in Table 8.

Success Criteria	Comparison	Subjects MRI/ Control	Success Rates MRI/Control	One-sided 97.5% Confidence Boundary and p-value	Conclusion
The proportions of subjects who experienced a sensing amplitude decrease not exceeding 50%, and a one-month post-MRI/waiting period sensing amplitude not less than 1.5 mV for atrial measurement and not less than 5.0 mV for ventricular measurements, are clinically equivalent, defined as within 10%.	Atrial	131/ 133	94.7%/ 92.5%	8.9% p = 0.01	Objective met
	Ventricular	134/ 131	97.0%/ 95.4%	6.9% p = 0.003	Objective met

Table 8: Results of Sensing Amplitude Primary Objective

Secondary Objective Results

For evaluable subjects, all of the secondary objectives with defined success criteria were met. The secondary objective results are discussed below.

6.12.4 Secondary Objective #1 - Pacing system-related complication free rate

The result for Secondary Objective #1 is shown in Table 9.

Success Criteria	Subjects	Complication Free Rate	One-sided 95% Confidence Boundary and p-value	Conclusion
The pacing system-related complication-free rate is greater than 80%	447	91.7%	89.3% $p < 0.001$	Objective Met

Table 9: Secondary Objective #1

A list of the complications that contributed to the result is provided in Table 10.

Complication Key Term	Number of Complications	Number (%) of Subjects (n=467*)
Lead dislodgement	18	18 (3.9%)
Elevated pacing threshold	9	8 (1.7%)
Failure to capture	3	3 (0.6%)
Pericardial effusion	3	3 (0.6%)
Thrombosis	2	2 (0.4%)
Cardiac perforation	2	2 (0.4%)
Implant site infection	2	2 (0.4%)
Inappropriate device stimulation of tissue	1	1 (0.2%)
Atrial fibrillation	1	1 (0.2%)
Cardiac pacemaker revision	1	1 (0.2%)
Chest pain	1	1 (0.2%)
Endocarditis	1	1 (0.2%)
Medical device complication	1	1 (0.2%)
Pain in extremity	1	1 (0.2%)
Subclavian vein thrombosis	1	1 (0.2%)
Total	47	39 (8.4%)

Table 10: Pacing system-related complications through the four-month post-implant follow-up visit.
*Some subjects had more than one event.

6.12.5 Secondary Objective #2 – Labeling instructions

This objective was intended to confirm that labeling instructions for completing the MR scans were followed to ensure subject safety. There were no defined success criteria. However, the sponsor noted that there were no subjects who experienced a system-related adverse device effect that that was attributed to labeling insufficiencies or incorrect following of MRI labeling instructions.

6.12.6 Secondary Objective #3 – Occurrence of arrhythmias

There were no subjects with sustained ventricular arrhythmias or asystole attributed to the MRI scan. There were no defined success criteria for this endpoint.

6.12.7 Secondary Objective #4 - Implant procedure, pacing system- and MRI procedure-related complications and observations through the one-month post-MRI visit for the MRI group, and the corresponding visit for the control group

The adverse event free rate was 80.3%. There were no defined success criteria for this endpoint.

6.12.8 Secondary Objective #5 – Lead impedance

The result for Secondary Objective #5 is shown in Table 11. There were no defined success criteria for this endpoint.

Success Criteria	Comparison	Mean ± SD Impedance (Ω) changes from pre-MRI to one-month post-MRI: MRI Group	Mean ± SD Impedance (Ω) changes from pre-waiting period to one-month post-waiting period: Control Group
None Defined	Atrial	-0.6 ± 61.8	7.3 ± 50.4
	Ventricular	-9.0 ± 48.5	-5.7 ± 51.8

Table 11: Secondary Objective #5

6.12.9 Secondary Objective #6 – Lead handling

The comparison group for this evaluation was the cohort reported in the clinical study report for PMA supplement approval of Medtronic Lead Model 5076. This objective was evaluated by analyzing implanting physician responses regarding lead handling, and comparing the responses to the Medtronic Lead Model 5076 study cohort. The result for Secondary Objective #7 is shown in Table 12. This analysis did not account for potential imbalances in characteristics between the two cohorts.

Success Criteria	Comparison	Difference in Mean Lead Handling Scores	One-sided 95% Confidence Boundary and p-Value	Conclusion
Differences in overall lead handling characteristics are statistically equivalent (Δ=1.5 units on a scale of -3 to +3)	Atrial	0.15	0.43 $p < 0.001$	Objective Met
	Ventricular	0.18	0.39 $p < 0.001$	Objective Met

Table 12: Secondary Objective #6

6.12.10 Secondary Objective #7 – Lead performance

This objective compared the four-month pacing thresholds and sensing amplitudes of the Model 5086MRI leads in both the MRI and control groups to those of the commercially available Medtronic Lead Model 5076 study cohort's three-month follow-up data. The results for Secondary Objective #7 are shown in Table 13 and Table 14. These analyses did not account for potential imbalances in characteristics between the two cohorts.

Pacing Capture Thresholds				
Success Criteria	**Comparison**	**Model 5086MRI Mean ± SD (V)**	**One-sided 95% Confidence Boundary and p-Value**	**Conclusion**
Pacing thresholds are statistically equivalent (Δ=0.5 V)	Atrial	MRI: 0.78 ± 0.28 Control: 0.77 ± 0.66 5076: 0.61 ± 0.23	0.23 ($p < 0.001$) 0.25 ($p < 0.001$)	Objective Met
	Ventricular	MRI: 0.82 ± 0.30 Control: 0.90 ± 0.70 5076: 0.75 ± 0.77	0.23 ($p < 0.001$) 0.32 ($p < 0.001$)	Objective Met

Table 13: Secondary Objective #7 pacing capture thresholds

Sensing Amplitude				
Sensing amplitudes are statistically equivalent (Δ=0.9 mV for atrial sensing, 2.5 mV for ventricular sensing)	**Lead Implant Site**	**Model 5086MRI Mean ± SD (mV)**	**Model 5076 Mean (mV)**	**Conclusion**
	Atrial	MRI: 3.0 ± 1.3 Control: 3.1 ± 1.4 5076: 3.2 ± 1.7	0.56 ($p < 0.001$) 0.47 ($p < 0.001$)	Objective Met
	Ventricular	MRI: 10.1 ± 5.0 Control: 10.2 ± 5.2 5076: 10.0 ± 4.3	0.94 ($p < 0.001$) 0.86 ($p < 0.001$)	Objective Met

Table 14: Secondary Objective #7 sensing amplitudes

6.13 Additional Analyses Results

The additional analyses results are discussed below.

6.13.1 Additional Analysis #1 – Identification of radiopaque markings

The analysis was based on data collected in 240 cardiac staff and 239 radiologist questionnaires. The questionnaires rated the ease of identifying the IPG and lead radiopaque markings by rating it on a scale of -3 (well below expectations) to 3 (well above expectations). The results are shown in Table 15.

Radiopaque	Questionnaire	Results (Median Scores)
IPG	Cardiac Staff	1 (Slightly above expectations)
	Radiologists	2 (Moderately above expectations)
Lead	Cardiac Staff	2 (Moderately above expectations)
	Radiologists	2 (Moderately above expectations)

Table 15: Additional Analysis #1

6.13.2 Additional Analysis #2 – SureScan feature performance

The analysis was based on data collected in 82 questionnaires completed by cardiac staff. The questions, which were rated on a scale of 1 (extremely difficult) to 7 (extremely easy), were in regard to the ease of locating the SureScan feature, verifying items on the software application's checklist, selecting the appropriate SureScan pacing mode, and identifying that the SureScan mode was turned on. The results are shown in Table 16.

Question	Results (Median Scores)
Ease of locating the SureScan feature	6 (Easy)
Ease of verifying all of the items on the MRI SureScan software application's check list	6 (Easy)
Ease of selecting the appropriate SureScan pacing mode	6 (Easy)
Ease of identifying that the SureScan mode was turned on	6 (Easy)
Clarity of the device's sensing and diagnostic capabilities when in SureScan mode	6 (Clear)

Table 16: Additional Analysis #2

6.13.3 Additional Analysis #3 – Analysis of procedure

This analysis summarizes whether safeguards and procedures were followed at the time of the MR scans. The data were collected in 82 cardiac staff questionnaires and 84 radiology staff questionnaires and asked questions, each on a scale of 1 to 7, pertaining to patient monitoring, equipment availability, and communication between the radiology and cardiac teams. Some of the key questions are summarized in the Table 17.

Question	Results (Median Scores)
Cardiac staff's ease of scheduling the appointment with radiology	6 (Easy)*
Radiology staff's ease of scheduling the appointment with cardiology	6 (Easy)*
Radiology staff's level of comfort with monitoring and potentially resuscitating the patient if the staff was ACLS trained	6 (Comfortable)**
Radiology staff's opinion on the clarity of information in the manual if the manual was reviewed	6 (Clear)***

* Numerical range was 1 to 7, extremely difficult to extremely easy
** Numerical range was 1 to 7, extremely uncomfortable to extremely comfortable
*** Numerical range was 1 to 7, extremely unclear to extremely clear

Table 17: Additional Analysis #3

6.14 Missing Data

6.14.1 Summary of Missing Data

The number of subjects analyzed for each primary endpoint was substantially lower than the number of subjects enrolled and randomized in the study. Table 18 below shows the proportions of missing for each primary objective.

	MRI (N=258)		Control (N=206)
	All missing n (%)	Missing other than MR scan issues n (%)	All missing n (%)
MRI-Related Complications	47 (18.2%)	NA	NA
Pacing Capture Threshold			
Atrial	93 (36.0%)	61 (23.6%)	42 (20.4%)
Ventricular	68 (26.4%)	36 (14.0%)	22 (10.7%)
Sensing Amplitude			
Atrial	127 (49.2%)	95 (36.8%)	67 (32.4%)
Ventricular	124 (48.1%)	92 (35.7%)	70 (34.0%)

Table 18: Distribution of missing by treatment group

During the review, FDA asked the sponsor for additional information regarding the reasons why those data were missing or excluded. Reasons for missing data included the following:

- MRI scan not conducted (18), for reasons including:
  - High PCT (3)
  - Unknown PCT (2)
  - Non-MRI compatible stent (1)
  - Pacemaker stimulation of the diaphragm (2)
  - Presence of an MRI-incompatible lead (1)
  - Pregnancy (1)
  - Subject refusal (8)
- MRI scan not conducted according to protocol (15), with deviations including
  - SAR exceeded 2 W/kg (8)
  - Patient discomfort (4)
  - MRI system malfunction (1)
  - Ventricular threshold exceeded 2V at pre-MRI check (scan completed) (1)
  - Inability to fit the patient into the scanner (head sequences completed) (1)
- Follow-up visits missed or outside of follow-up window (30)
- PCT increase exceeding 0.5 V from 2 months to 9-12 weeks (6)
- Atrial arrhythmia at follow up and therefore no threshold obtained (45)
- Incomplete sensing test at 9-12 weeks or four-month visit (26 atrial, 51 ventricular)
- Sensing values less than 1.5 mV (atrial) or 5.0 mV (ventricular) at 9-12 weeks (38 atrial, 53 ventricular)

For each reason for missing data, the proportions of missing data between the two treatment groups were comparable. Where possible, the sponsor provided FDA with the partial data for subjects with missing data. The partial data were generally consistent with the overall study results. FDA concluded that, from a clinical perspective, the causes for missing data were reasonable. As discussed in the following sections, statistical analyses were also performed to assess the likelihood that missing data could bias the conclusions from the study.

6.14.2 Missing data for MRI-Related Complications Primary Objective

As shown in Table 18, there were 47 out of 258 (18.2%) missing data points for the primary safety objective, MRI-related complications. FDA determined the success rate that would be needed for those subjects with missing data in order preserve the success determination for the objective. A minimum of 241 out of 258 subjects would need to be free of an MRI-related complication in order to meet the primary safety objective. If we consider the eight subjects whose SAR exceeded 2 W/kg and who were free of an MRI-related complication as defined in the protocol, only 22 additional subjects among the 39 missing data points (56.4%) need to be successes in order to meet the performance goal of 90% MRI-related complication free. Note that there were no MRI-related complications observed for the subjects without missing data in the per-protocol analysis.

6.14.3 Tipping Point Analyses

FDA asked the sponsor to perform tipping point analyses for the pacing capture threshold and sensing amplitude primary objectives. Tipping point analyses for dichotomous outcomes (e.g., success/failure), as in this clinical study, assess the statistical results for all possible combinations of missing data from two treatment arms. For these tipping point analyses, the eight subjects in MRI group who were excluded in the primary analyses because SAR exceeded 2 W/kg were not considered missing if they had endpoints determined as defined in the protocol.

Considering the atrial PCT assessment as an example, there were 49 missing subject data points in the control group and 86 missing subjects data points in the MRI group. Depending on the outcomes that one assumes for the missing data points in each group, the non-inferiority hypothesis for this objective may succeed or fail. For example, if only 20 out of 93 missing data points in the MRI group were successes and only 20 out of 49 in the control group were successes, the non-inferiority test would fail.

For each objective, FDA made the conservative assumption that all of the missing subject data points from the control group would have been successes. FDA then assessed the needed success rate for missing subjects in the MRI group in order to preserve the success determination for the objective. For the atrial PCT objective, if all 49 of the missing subject data points from the control group would have been successes, then at least 70 out of the 86 missing data points in the MRI group (81.4%) would need to be successes in order to declare non-inferiority. The success rates from the observed data in the per-protocol analysis for this objective were 100% in both groups. Therefore the tipping point analysis indicates that the extent of missing data could have biased the analysis of this objective if the MRI group subjects with missing data performed substantially worse than the MRI group subjects with complete data. Similarly, for the ventricular PCT objective, if all 29 controls with missing data points were assumed to be successes, only 45 out of 60 subjects (75.0%) in the MRI group would need to be successes to meet this objective, while 100% success was observed for subjects with complete data. For the atrial sensing amplitude objective, when all missing data points in the control groups were assumed to be successes, 107 out of 120 (89.2%) successes are needed from the MRI group, while 94.7% success was observed for subjects with complete data. For the ventricular sensing amplitude objective, 100 out of 116 subjects

(86.2%) successes are needed from the MRI group, while 97.0% was observed for subjects with complete data. These comparisons are summarized in Table 19 below.

	Missing	Success needed to meet objective	Success observed from complete data
	n	%	%
Pacing Capture Threshold			
Atrial	86	81.4	100.0
Ventricular	60	75.0	100.0
Sensing Amplitude			
Atrial	120	89.2	94.7
Ventricular	116	86.2	97.0

Table 19: Percentage of successes needed in the MRI group if all missing data points in the control group are assumed to be successes

The complete tipping point analyses are provided in the Appendix.

6.15 Multiple MRI Exams

FDA has expressed concern regarding the potential for cumulative effects from exposure to multiple MRI exams. This clinical trial was not designed to address this question. However, there were 15 study subjects who received multiple MRI exams based on clinical need. As shown in Table 20, most of these subjects received two MRI exams but one subjects received seven exams. The sponsor provided FDA with the electrical performance and adverse event data for these subjects. There were no MRI-related adverse events or changes in electrical performance observed in these subjects. FDA recognizes that, due to the limited sample, these data are inconclusive with regard to the potential for cumulative effects from multiple MRI exposures. As discussed previously in this document, the sponsor also conducted an animal study to address this question.

Total MRI Exams Received	Number of Subjects
2	10
3	2
4	2
7	1

Table 20: Subjects who recieved multiple MRI exams

<u>The Panel will be asked to comment on whether the preclinical and clinical data support the safety of exposure to multiple MRI exams for patients implanted with the REVO MRI Pacing System.</u>

6.16 Study Limitations

FDA recognizes that the clinical study has several notable limitations including the following:

- The study sample size would not be adequate to detect very low rate safety events associated with MRI exposure.
- The study was not designed to characterize worst-case patient conditions in terms of patient anatomy, device placement, etc.

- The study did not directly assess lead heating or thermal injury, instead relying on changes in PCT and sensing amplitude as indicators of heating induced changes.
- The study did not assess the possible cumulative impact of multiple MRI exposures for patients.
- There was substantial missing or excluded data for the primary endpoint analyses.

Many of these limitations were recognized by FDA prior to initiation of the study. FDA approved the study based on the understanding that it was designed to provide important real-world confirmatory data to support the more expansive preclinical testing. The Panel will be asked to comment on whether the clinical study design was appropriate and whether the preclinical and clinical data provided demonstrate that it is safe for patients implanted with the REVO MRI pacing system to receive an MRI according to the proposed MR Conditions of Use.

7 Proposed MR Conditional Labeling

7.1 MR Conditions of Use

The sponsor has proposed the following MR Conditions of Use:

- Cylindrical bore magnet, clinical MRI systems with a static magnetic field of 1.5 Tesla (T) must be used
- Gradient systems with maximum gradient slew rate performance per axis of ≤ 200 T/m/s must be used.
- Whole body averaged specific absorption rate (SAR) as reported by the MRI equipment must be ≤ 2.0 W/kg; head SAR as reported by the MRI equipment must be < 3.2 W/kg.
- Patients and their implanted systems must be screened to meet the following requirement:
    - No previously implanted (active or abandoned) medical devices, leads, lead extenders, or lead adaptors
    - No broken or intermittent leads
    - A SureScan pacing system that has been implanted for a minimum of 6 weeks
    - A SureScan pacing system implanted in the left or right pectoral region.
    - Pacing capture threshold values of ≤ 2.0 V at a pulse width of 0.4ms.
    - No diaphragmatic stimulation at a pacing output of 5.0 V and at a pulse width of 1.0 ms in patients whose device will be programmed to an asynchronous mode when MRI SureScan is on
    - A lead impedance value of ≥ 200 Ω or ≤ 1500 Ω
- The patient must be positioned within the bore such that the isocenter (center of the MRI bore) is superior to C1 vertebra or inferior to the T12 vertebra
- There are no restrictions on the placement of any receive-only coils.
- There are no restrictions on the use of local transmit or local transmit/receive coils for imaging the head or of the extremities.
- Proper patient monitoring must be provided during the MRI scan. This includes continuous monitoring of the patient's hemodynamic function. Since the MRI environment may interfere with the patient monitoring system, it is recommended that more than one of the following systems be used:

    - Electrocardiography
    - Pulse oximetry
    - Noninvasive blood pressure measurements
- The implanted system must consist solely of a Medtronic Revo MRI SureScan Model RVDR01 device and 2 CapSureFix MRI SureScan Model 5086MRI leads.

7.2 Proposed MR Conditional Contraindications

The sponsor has proposed the following MR Conditional Contraindications:

- Patients with broken or intermittent leads are contraindicated for an MRI scan.
- Patients with a lead impedance value of < 200 Ω or > 1500 Ω are contraindicated for an MRI scan.
- Patients with a SureScan pacing system implanted in sites other than the left and right pectoral region are contraindicated for an MRI scan.
- Patients who do not have a complete SureScan pacing system, which includes a SureScan device and both atrial and ventricular SureScan leads, are contraindicated for an MRI scan.

7.3 Proposed MR Conditional Precautions

The sponsor has proposed the following MR Conditional Precautions:

- Do not scan the patient positioned such that the isocenter (center of the MRI bore) is inferior to the C1 vertebra and superior to the T12 vertebra as it may cause myocardial damage due to lead heading, resulting in an increase in pacing capture threshold. This has not been studied clinically.
- Do not scan patients with a SAR level exceeding 2W/kg. A scan above 2W/kg may increase the risk of myocardial tissue damage due to lead tip heating, resulting in an increase in the Pacing Capture Threshold.
- Do not scan patients with pacing capture threshold values of > 2.0 V at a pulse width of 0.4 ms. The higher pacing capture threshold indicates there may be an issue with the implanted lead.
- Do note scan patients with previously implanted (active or abandoned) medical devices, leads, lead extenders, or lead adaptors as it may increase the risk due to lead tip heating and other MRI RF field related hazards. The interaction of other devices has not been evaluated.
- Do not scan patients whose device will be programmed to an asynchronous pacing mode when MRI SureScan is on, and who have diaphragmatic stimulation at a pacing output of 5.0 V and at a pulse width of 1.0 ms. It may be difficult for the patient to remain still in order to obtain a quality image.

<u>The Panel will be asked to comment on whether the MR Conditional Labeling is appropriate.</u>

8 Proposed Post-Approval Study

FDA believes that, should the REVO MRI SureScan Pacing System be approved, a post-approval study in a larger and more heterogenous population will be needed in order to address the following primary questions:

- Do the study results continue to support the safety of the device for patients who receive an MRI scan according to the MR Conditions of Use?
- Is the chronic performance of the Model 5086MRI lead acceptable?

FDA has worked interactively with the sponsor to develop a draft post-approval study protocol to address these questions. The sponsor has proposed a five-year post-approval study that will enroll at least [redacted] subjects.

8.1 Proposed Primary Objectives

The following primary objectives are proposed:

1) To demonstrate MRI-related complication rate will be less than [redacted] The Adverse Event Adjudication Committee will classify the relatedness to MRI of a complication that occurred within one-month of the MRI scan. The analysis of this primary objective will include all complications adjudicated as MRI-related. A final list of MRI-related complications that contributed to the primary objective will be presented when the primary objective is analyzed.

2) To demonstrate that the complication free survival probability for Model 5086MRI lead placed in the right atrium (RA) is greater than 92.5% at 5 years post-implant.

3) To demonstrate that the complication free survival probability for Model 5086MRI lead placed in the right ventricle (RV) is greater than 92.5% at 5 years post-implant.

For Primary Objective #2 and #3, complications related to lead hardware or design failure regardless of MRI scans will be included in the analysis.

8.2 Proposed Secondary Objectives

The following secondary objectives are proposed:

1) Characterize chronic SureScan Pacing System electrical performance by MRI exposure
    a. Atrial and ventricular PCT measurement changes for each scheduled visit will be summarized by MRI: i.e., no MRI, Single MRI, Multiple MRIs.
    b. Atrial and ventricular sensing measurement changes for each scheduled visit will be summarized by MRI: i.e., no MRI, Single MRI, Multiple MRIs
    c. Atrial and ventricular PCT measurement changes for subjects with follow-up due to an observed clinically significant change between pre and post will be summarized
    d. Atrial and ventricular sensing measurement changes for subjects with follow-up due to an observed clinically significant change between pre and post will be summarized.

2) Summarize all MRI system and scan conditions collected at time of MRI.

3) Summarize all SureScan system related adverse device effects including failure modes by key term (including lead failure modes) occurring up to five years post-implant.

4) Characterize atrial and ventricular lead impedance.

A complete post-approval study summary is provided in the Panel Pack. The Panel will be asked to comment on the need for a post-approval study and the key elements that should be included in such a study.

9 Conclusions

The REVO MRI SureScan Pacing System, if approved, would be the first MR Conditional pacing system and several aspects of the validation strategy are new. As discussed in this document, the preclinical testing approach is novel. FDA asks the Panel to comment on several important questions regarding the validity of this approach. The clinical study that was conducted to characterize the safety and effectiveness of the device with regard to MRI met all of its objectives. However, FDA recognizes that the study had several important limitations. Notably, the study was modest in size, did not directly assess thermal injury, did not assess multiple MRI exams, and had a substantial amount of missing data. As such, FDA views the study design as one intended to be confirmatory to more comprehensive preclinical testing. The Panel is asked to comment on appropriateness of the study design and the quality of the results. FDA also recognizes that the MR Conditions of Use include several important limitations. Notably, MRI is limited to only 1.5 Tesla systems and patients must be positioned such that the isocenter of the magnet is not in the thoracic region. The Panel is asked to comment on whether the MR Conditions of Use are supported by the data and are practical in the clinical environment. Finally, the Panel is asked to advise FDA as to whether the totality of the data supports the safety and effectiveness of the device and offers a positive risk-benefit profile.

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