SUMMARY OF:
P980016/S536
Bundled with
P920015/S151, P890003/S329, P930039/S138, P090013/S200

EXECUTIVE SUMMARY/BACKGROUND

The Evera MRI SureScan Defibrillation System (Evera MRI System) is an MR conditional system that provides Medtronic's ICD feature set approved for the Viva / Brava/ Evera family of Implantable Cardioverter Defibrillators. The Evera MRI system includes full-featured, dual and single chamber implantable cardioverter defibrillators (ICD) that are compatible with the Sprint Quattro Secure MRI SureScan Lead Models 6935M and 6947M and has system software Model SW033 that supports the SureScan features in order to provide a complete MR conditional system. The firm indicated that dual chamber Evera MRI devices are also compatible with current approved SureScan right atrial pacing leads and SureScan defibrillation leads, including the SureScan Model 5086MRI (approved February 2011, P090013) and CapSureFix Novus MRI SureScan Model 5076 leads (approved October, 2014, P930039/S107). Compatibility data for all lead families were provided in Module 003 of the modular PMA M140016.

The Evera MRI ICDs are an addition to the Viva Brava Evera ICD family and based on the non-MR Conditional labeled Evera ICDs approved in April 2013 (P980016/S382). The Evera MRI devices leverage the form and functionality of the Evera devices, while additionally providing for the device and lead system to be labeled as MR Conditional. The Evera MRI system labeling permits scans at 1.5T that occur in the normal operating mode (whole body SAR ≤2W/kg) with no patient positioning restrictions, similar to the Advisa DR MRI IPG.

At a high level, the device changes required to address this additional environmental functionality consist of updates to the firmware, identifying radiopaques in the connector modules, and product labeling (device markings, as well as manual content). The design of the Sprint Quattro Secure MRI SureScan Leads continues to be the same as the non-MR Conditional labeled predecessors.

The Evera MRI System can most clearly be described as the Evera ICD system with the addition of MR conditional functionality, similar to the Advisa DR / SR MRI systems.

The firm requested and was granted the ability to pursue a modular 180 Day PMA Supplement approach, even though the modular process is typically used for original PMA submission. The modular approach was deemed appropriate since the MRI Hazard Assessment module (M140016/M003) was expected to require additional review time possibly exceeding the typical 180 Day Supplement limit; Table 1 on the next page lists the contents and status of each module at the time of the conversion (March 16, 2015) into this PMA supplement (P980016/S536).

Module M003 (MRI Hazard Assessment) had resulted in a major deficiency letter on January 27, 2015 during its original review and resulted in an amendment M140016/M003/A001 on February 20, 2015. The responses were reviewed but required additional information (requested May 19th, 2015). The information was received interactively from the firm on June 02 and June 05, 2015 and the response was deemed acceptable.

Module M006 (Manufacturing) was inadvertently assigned to the Office of Compliance; a normal process for a modular original PMA but not for a modular 180-Day supplement. The review based on the assumption of dealing with an original PMA resulted in a deficiency letter on May 15th, 2015. The firm's response to the deficiency letter was received on June 17th, 2015 as an amendment to the PMA supplement (P980016/S536/A001). After verbal consultation with the Office of Compliance, the response was deemed acceptable.

An internal meeting was held on May 01, 2015 to discuss the need for a Panel Meeting. Even though the Evera MRI ICD system will be the first ICD to receive MR Conditional Labeling, the team concluded that the technical and clinical questions with regards to the use of ICDs in the MRI system environment are very similar to those encountered for pacemaker systems. Given the experience the field (Clinicians, Industry and FDA) has gained over the past 5 years since the first MR Conditional Labeling was granted for the Revo pacemaker system and the emergence of a standardized test approach based to a large extend

on the ISO/TS 10974:2012(E) Technical Specification the team concluded that no Advisory Panel input would be required to arrive at a safety / efficacy decision for Evera MRI ICD.

In the same meeting it was also concluded that the by the firm proposed Post Approval Study was not sufficient to address remaining open questions. Even though the bench tests, animal studies and the IDE clinical study provide a reasonable assurance of safety and efficacy for the Evera MRI ICD when operated in the MRI environment following the MR Conditional Labeling, the ability to study the system's ability to delivery VF therapy without out delay after its MRI exposure was very limited in a pre-approval setting due to the low incident rate of true VF episodes. A total of 34 VT/VF episodes occurred after MRI in 24 subjects; 20 of these were induced. The team was of the opinion that additional data should be collected in a Post Approval Study, with the target of post MRI true VF episodes being investigated for therapy delay in 25 subjects. Interactive discussions with the firm resulted in a revised Post Approval Study Protocol filed via an amendment (P980016/S536/A002) on July 02, 2015. The protocol was reviewed internally and required minor modifications. The requested modifications were incorporated by the firm and a final version of the PAS Protocol was received via e-mail on July 27th, 2015.

Table 1: Content of the Modular Submission M140016

Module	Contents	Submitted Status	Notes
M001 Non-clinical Testing by Equivalency	Biocompatibility, Sterilization, Shelf Life	08/01/2014 Acceptable 10/31/2014	All testing is by equivalency to Evera ICD (Blackwell). Reports were included in IDE, no new info.
M002 Care Pathway/ Patient Management/ Risk Management	Care Pathway Description, Human Factors Testing, Risk Management Documentation, Patient Management Documentation, Bibliography for M002: Care Pathway and ICD operation	09/11/2014 Acceptable 01/13/2015	System Description is now up-dated to include models not studied under IDE. Care Path-way discussion and Human Factors testing is new content compared to IDE. Patient Manage-ment section includes addition of Encore programmer and MyCareLink monitor (already approved for predecessor products)
M003 MRI Hazard Assessment	System Level MRI Environment Potential Hazards (Pre-Clinical Testing and Modeling) Lead Heating, Case Heating, Unintended Cardiac Stimulation, Vibration, Force and Torque, Device Interactions, Other Interactions MRI pre-clinical bench testing, Animal study test plans and reports, Lead Heating Modeling Results Bibliography for M003: MRI Environment Hazards	10/24/2014 Deficient 01/27/2015 PMRR 03/16/2015	Includes same MRI related design validation reports and animal studies as IDE. Includes new Confirmatory Animal Study using final level devices. Includes LHM 1.5 and 2.0 numerical modeling results using theoretical SAR limits and clinical worse case limits with associated Risk Assessment. Includes new final device testing post Tel M Module change per April 9, 2014 Conditional Approval Letter.
M004 Non-MRI Design Validation and System Validation Testing	Non-MRI Design Validation Testing, System Validation testing	12/05/2014 Accepted 02/25/2015	Contents are the same as the IDE
M005 Software and Firmware	Software Verification Testing, Firmware Verification Testing	01/16/2015 PMRR 03/16/2015	Contents are the same as the IDE but will reflect additional information provided in IDE deficiency
M006 Manufacturing	Manufacturing Section which includes Previously Approved Changes.	02/26/2015 PMRR* 03/16/2015	Updated Manufacturing information with Previously Approved Changes since IDE submission.
Final Module M007 Clinical Study Results, Post Approval Study Plan, and System Labeling	Clinical Investigational Study Plan and Report Financial disclosures Post Approval Study Plan, Package Labels, Labeling, Bibliography for full PMA submission. Any additional previously approved manufacturing changes that apply will also be included.	03/13/2015	None.

Note: Each module contains an Executive Summary for the module, a Regulatory History summary as well as a System Introduction and Description.

INDICATIONS FOR USE

The non-MRI indications for use of the Evera MRI ICDs are the same as those approved for Evera ICD. Similarly, the Sprint Quattro Secure MRI SureScan Leads Indications for Use are the same as their non-MR Conditional labeled versions. The Indications for Use and MRI Conditions for Use are summarized in Table 1-14 of this submission.

MRI Conditions for Use

The MRI Conditions for Use as stated by the firm on page 1-128 and 1-130 are:

> "A complete SureScan defibrillation system is required for use in the MR environment. A complete SureScan defibrillation system includes an Evera MRI XT DR SureScan device with a SureScan right atrial pacing lead and a SureScan defibrillation lead. Any other combination may result in a hazard to the patient during an MRI scan.
>
> Warning: Do not scan a patient without first programming MRI SureScan to On. Scanning the patient without programming MRI SureScan to On may result in patient harm or damage to the SureScan defibrillation system.
>
> Note: MRI SureScan cannot be programmed to On if the device is recommended for replacement."

On March 31st, 2015 FDA suggested to the firm in an e-mail pertaining to the labeling of the 5076 leads when used in conjunction with the Advisa SR MRI to modify the labeling / conditions of use to the following:

> "A complete SureScan system, which consists of *an approved combination* (see Table X or *visit http://www.mrisurescan.com/)* of a SureScan device with the appropriate number of SureScan leads, is required for use in the MRI environment. Any other combination may result in a hazard to the patient during an MRI scan. The SureScan feature must be programmed to On prior to scanning a patient according to the specified conditions for use."

A similar modification of the labeling / Conditions for Use for the Evera MRI ICD was suggested to the firm via e-mail on May 19th, 2015 impacting multiple pages: 4-50, 4-182, third bulled on page 4-183, 4-220,4-238,4-263, 4-268, 4-277, 4-318, 4-330, 5-8,5-20,5-53, 5-108. In their June 02, 2015 response the firm indicated that it would make changes in all areas indicated except the Patient Manual/Patient ID card. The firm reasoned that only the radiologists and MR technologists are responsible to determine if the patient has an MR conditional system and the additional information in the patient manual would not be meaningful to the patient. The ID card was however modified to include the http://www.mrisurescan.com reference. The rationale and modifications provided by the firm were considered acceptable by the reviewers.

During the review of Module M003 it was noted that the pacemaker IFU required the system to be implanted for at least 6 weeks prior to an MRI. No such requirement was listed for the ICD. Since the force on the ICD is expected to be larger due to the higher content of ferromagnetic materials in the device, one would expect that a similar minimum time should be required for the ICD. Furthermore, the force limit was set to 8 times the device weight and no justification was provided for this limit. It was not clear if the limit would present a risk to the patient immediately after implant. As part of the response to the January 27th, 2015 Module M003 deficiency letter the firm provided rationale for the 8x gravity force limit and provided rationale why this force would even be acceptable immediately after implant. Combining the provided information with the caution "Lead maturation – MRI scans during the lead maturation period have not been prospectively studied by Medtronic and are not recommended" (see page 4-184) addressed the concern.

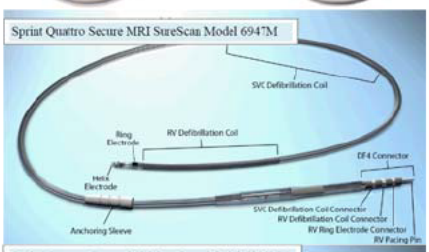
It should be noted that the firm added a requirement for the spatial magnetic field gradient to be less than 20 T/m (2000 Gauss/cm) to the MRI Conditions of Use. The limit is consistent with the note in ASTM F2052–14, stating that the spatial magnetic field gradient accessible to patients in typical 1.5 and 3 T systems is less than 19 T/m.

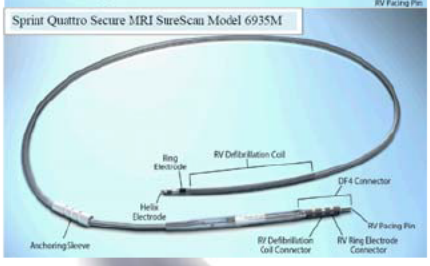
DEVICE DESCRIPTION

The Evera MRI system includes the Evera MRI SureScan single chamber (VR) and dual chamber (DR) Implantable Cardioverter Defibrillators (ICD), the 55 and 62 cm Sprint Quattro Secure MRI SureScan lead models 6935M and 6947M, and programmer software model SW033 supporting the SureScan features. According to the firm, the 55 and 62 cm leads represent approximately (b) of all Sprint Quattro Secure lead implants. The leads have not been modified to attain MRI conditional labeling. The firm intends to utilize market released atrial pace/sense leads to complete the dual chamber ICD system. The firm submitted data for the 5076 and 5086 MRI leads for this purpose.

Table 1-8: Device Models and Brand Names

Device Model	Brand Name
DDMB1D4	Evera MRI™ SureScan™ XT DR
DVMB1D4	Evera MRI™ SureScan™ XT VR
DDMC3D4	Evera MRI™ SureScan™ S DR
DVMC3D4	Evera MRI™ SureScan™ S VR





The firm is only including the DF4 connected ICD devices listed in Table 1-8 for MRI conditional labeling. It should be noted that the S models have the same hardware and mechanical design as the XT models with the exception that they do not have the OptiVol feature. OptiVol measures the fluid buildup around the heart and in the thorax by monitoring the intrathoracic impedance via an IPG to right ventricular impedance measurement.

The IPG changes required to address additional environmental functionality imposed by the MR conditional labeling consists of updates to the hybrid assembly, the firmware, identifying radiopaques in the connector modules, and product labeling (device markings, as well as manual content).

6935M Lead Cross Section

Hybrid Changes

The Evera MRI DR/VR hybrid footprint is identical to Evera DR/VR hybrid. There are minor changes made to replace obsolete parts, and to protect the Telemetry B circuit. These have already been approved for the Evera ICD.

1 (b) (4)

[redacted]

2.

3

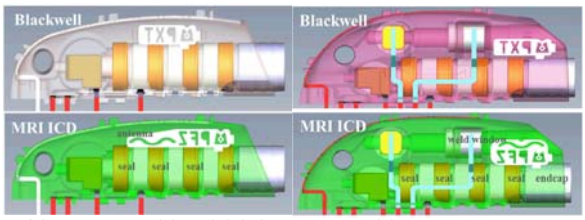
4

5

4 o

Radiopaque Markers

Physical changes to the device mechanics are limited to updated shield graphics, and the addition of a radiopaque indicator (including MRI "squiggle") in the header for device identification as shown for example in the figure to the right (Fig. 1-10 and 1-11 of the submission).



Left images VR models and right images DR models

Device Feature Changes

MRI SureScan

This feature is similar to the SureScan operation present in the released Advisa DR MRI devices (P980035/S334, approved Dec 6, 2013), with considerations added for the ICD and single chamber population. The changes to the Evera MRI from the Advisa DR MRI baseline are the following:

- Ventricular tachyarrhythmia therapy is disabled to prevent tachyarrhythmia therapies or inappropriate detection in the MRI environment.
- Added OVO pacing mode to support single-chamber devices.
- The programmable range for pacing rate was changed from 30ppm-120ppm to 60ppm- 120ppm to reduce the potential for competitive pacing.
- Suspended patient alert notifications while in SureScan to reduce the potential for inaudible alerts, or failed transmissions.

MRI SureScan Timeout

MRI SureScan mode disables tachyarrhythmia detection. A foreseeable misuse case is that the patient leaves medical care without SureScan operation being disabled, which would leave the patient unprotected from lethal arrhythmia until the next follow-up. More than 13,000 MRI study were analyzed, in addition to more than 1,000 scans of Medtronic MRI SureScan devices to determine a timeout duration that would both give high probability of the MRI scan being complete (including prep time) before the timeout occurs, and also short enough to not leave the patient unprotected for an extended duration. As a result, a timeout value of 6 hours was selected. Six hours after SureScan mode is programmed, it will automatically disable and the device will revert back to previous operation.

MRI SureScan Power on Reset (POR) Recovery

The current generation of Medtronic MRI SureScan devices will recover to current SureScan operating mode (enabled vs disabled) if a device reset occurs in which a memory is not corrupted. In the case where memory is corrupted, default values are recovered to replace the corrupted programmed values. The MRI SureScan POR Recovery operation includes the capability for the device to recover the current SureScan values to ensure that the appropriate SureScan operation is always in effect. This is accomplished by reserving a bank of non-volatile memory (EEPROM) which is updated to reflect the appropriate SureScan settings. These settings can then be recovered if a device reset occurs, ensuring that the patient is in the correct SureScan state after the reset.

The hardware (hybrid) changes have already been implemented on the (non-MRI) Evera ICD and are minor. These changes will not impact MRI performance and they could be handled via a 30 Day Notice but are clearly submitted here for approval; this is acceptable to the lead reviewer.

From the review it was not clear what the risks are for a patient that was scheduled to undergo an MRI, i.e., is in the SureScan mode but the time limit of 6 hrs. is exceeded and the device reverts back to the non-MRI settings. Even though the firm argued that this is highly unlikely, it was not clear what happens when it does. This question was communicated to the firm on May 19th, 2015 and was addressed in their June 02 response. The firm pointed to the HP MRI Feature Risk Management Report V4 DSN008847 which was part of Module 002 (pg. 1-299). Even though the module was closed prior to receiving this PMA supplement, the lead reviewer examined the pages indicated by the firm. The firm correctly identified delivery of unintended shocks as one potential result and as a consequence, a Lorentz force acting on the lead. The firm has a design requirement that Lorentz forces are not to dislodge the leads. The firm indicated that a force analysis was performed and the force acting on the lead is not large enough to cause dislodgement. Furthermore, the firm performed a probability analysis and arrived at a probability of ~ 7.9E-8, i.e., 1 in 12 million rate of occurrence. The firm concluded that the benefit outweighed the risk. The lead reviewer agreed with the firm's assessment.

PRECLINICAL/BENCH

Based upon the similarities to previously approved Evera ICD devices, the ability of the devices to meet their specifications in the intended non-MRI environment has been demonstrated through comprehensive device and system level verification, validation bench testing, and complementary animal testing, as well as clinical data to demonstrate product safety and effectiveness. The non-MRI related design qualification, verification, and validation testing activities performed for the Evera ICD system also apply to the Evera MRI ICD system so these requirements have been qualified by equivalence in module M140016/M004. The module was found to be acceptable and was closed on February 25, 2015

Only testing for design requirements associated with MRI exposure have been conducted and were presented in module M140016/M003. The associated testing structure consisted of the activities identified in Figure 1-2 of Module M003 and is consistent with those completed for Evera ICDs and the Advisa DR MRI IPG.

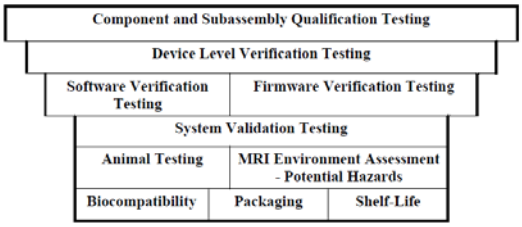


Figure 1-2: Overview of the Non-Clinical activities for the Evera MRI device

The Sprint Quattro Secure and Secure S Lead models have been verified and validated and are market released. The Sprint Quattro Secure MRI SureScan Lead models are the exact same leads but re-labeled for MR Conditional Use. Since the verification and validation testing for these leads have already been reviewed, only system level testing for MR Conditionality was included in M003, which includes animal studies and system validation testing. The review of M003 is presented at the end of this memo since it is the most complex part of the submission.

BIOCOMPATIBILITY/MATERIALS

The biocompatibility of the tissue-contacting materials used in the Evera MRI device has been established through equivalence to the Evera ICDs, presented in P980016/S382, approved in April 2013. The biocompatibility information for Evera MRI ICD was provided in Module M001, found to be acceptable and closed on October 31, 2014. The biocompatibility that was demonstrated for the market released Model 6935M (P920015/S091) and 6947M (P920015/S055) transvenous Sprint Quattro Secure leads during FDA PMA review is unchanged and remains valid. There are no changes to the tissue contacting materials or related manufacturing processes required for exposure of these leads to MRI in the clinical setting. Therefore, no additional biocompatibility information was provided in this PMA.

Reviewers Comment: The rationale regarding the biocompatibility of the device(s) and lead(s) are acceptable.

MANUFACTURING/STERILIZATION/PACKAGING/SHELF LIFE

Sterilization was qualified by equivalence to the Evera ICD as part of the Viva/ Brava/ Evera family of ICDs. The ETO sterilization process for the Evera MRI ICD devices is the same as the approved sterilization process for the Evera ICD. Additionally Evera ICDs and Evera MRI ICDs are manufactured using the same processes at the same manufacturing facilities and are packaged in the same packaging components. The sterilization information of the Evera MRI ICD was provided in Module M001, found acceptable and closed on October 31, 2014.

The firm indicates that the ETO sterilization process, packaging and manufacturing processes that have been qualified for the market released Model 6935M (P920015/S091) and 6947M (P920015/S055) transvenous leads during FDA PMA review are unchanged with this MR Conditional relabeling. There are no changes to the lead design, packaging materials or related manufacturing processes required for

exposure of these leads to MRI in the clinical setting that would require requalification of the sterilization processes for these leads. The firm indicates that no additional information will be provided as the process qualification remains valid.

The Shelf Life of Evera MRI was qualified by equivalence to the Evera ICD as part of the Viva/ Brava/ Evera family of ICDs and was provided in Module M001, found acceptable and closed on October 31, 2014.

The Evera MRI uses the exact same packaging and packaging processes as Evera ICD. The firm provided rationale for application of the package qualification testing to the Evera MRI ICD devices in module M004. The module was found acceptable and was closed on February 25, 2015.

The firm indicates that the assembly processes used to manufacture the Medtronic Evera MRI ICD devices are exactly the same as the approved manufacturing methods used to produce the Medtronic Evera ICD devices. The Manufacturing Section of Module M006 provided an overview of manufacturing facilities, manufacturing flowchart, and manufacturing changes. The module was reviewed in detail. In particular, the manufacturing changes were reviewed and an assessment was made if the changes could impact the MRI conditional labeling. The following changes (Module M006 and Volume 7 of this submission) were reviewed:

Change ID	Description of Change	Type / Approved for Other Products	Comment
(b) (4)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted] as suggested in this 30 day notice.
(b) (4)	[redacted]	[redacted]	[redacted]

	(b) (4) [redacted]		
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	(b) (4) [redacted]	

Reviewer's Comments:
Items **8502, 8625** and **8678** can be approved but warrant a note to the firm. The following should be communicated:

8502: (b) (4) [redacted]

8625:

8678:

The need to review changes with regards to MRI compatibility was discussed with the firm in a telephone conversation on June 16, 2015. During this conversation the firm confirmed that MRI compatibility review is part of the assessment of manufacturing changes and changes in general. The firm confirmed that such a review was part of the above submitted changes, including 8502, 8625 and 8678. The firm also lists the 2014 annual reportable changes in table 7.5. A review of these changes did not raise any concerns. Additionally, the firm listed changes to be included in the next annual reportable changes report in Table 7.6. None of these changes should impact the MRI conditional labeling. It should be noted that a review of table 7.6 does not imply that they are appropriate for inclusion in an annual reportable changes report or should be handled via a different route; it only addresses the impact on MRI conditional labeling.

FIRMWARE/SOFTWARE

The Evera MRI device use firmware and software (SW033) that is based on the Evera firmware and software (SW016) but with changes to include the SureScan feature set, MRI safety features, and an update to reset values. The firm states that the firmware and software were planned, designed and implemented to be common throughout the Viva/Brava/Evera ICD family. The firm furthermore states that firmware verification testing was executed at the end of the firmware development process to demonstrate that all testable firmware requirements have been correctly implemented.

The software and firmware changes were reviewed according to the "Guidance for Industry and FDA Staff -Guidance for the Content of Premarket Submissions for Software Contained in Medical Device, May 11 2005". The results of the review are summarized in the table below. Green indicates that the

guidance was followed and the reviewer agrees with the firm, yellow indicates some deviation and potential need for additional information and red indicates missing information and a potential deficiency. The table summarizes the review, i.e., a deviation may be either creates by the software or the firmware aspect of the submission.

SOFTWARE DOCUMENTATION	MINOR CONCERN	MODERATE CONCERN	MAJOR CONCERN
Level of Concern	A statement indicating the Level of Concern and a description of the rationale for that level.		
Software Description	A summary overview of the features and software operating environment.		
Device Hazard Analysis	Tabular description of identified hardware and software hazards, including severity assessment and mitigations.		
Software Requirements Specification (SRS)	Summary of functional requirements from SRS.	The complete SRS document.	
Architecture Design Chart	No documentation is necessary in the submission.	Detailed depiction of functional units and software modules. May include state diagrams as well as flow charts.	
Software Design Specification (SDS)	No documentation is necessary in the submission.	Software design specification document.	
Traceability Analysis	Traceability among requirements, specifications, identified hazards and mitigations, and Verification and Validation testing.		
Software Development Environment Description	No documentation is necessary in the submission.	Summary of software life cycle development plan, including a summary of the configuration management and maintenance activities.	Summary of software life cycle development plan. Annotated list of control documents generated during development process. Include the configuration management and maintenance plan documents.
Verification and Validation Documentation	Software functional test plan, pass / fail criteria, and results.	Description of V&V activities at the unit, integration, and system level. System level test protocol, including pass/fail criteria, and tests results.	Description of V&V activities at the unit, integration, and system level. Unit, integration and system level test protocols, including pass/fail criteria, test report, summary, and tests results.
Revision Level History	Revision history log, including release version number and date.		
Unresolved Anomalies (Bugs or Defects)	No documentation is necessary in the submission.	List of remaining software anomalies, annotated with an explanation of the impact on safety or effectiveness, including operator usage and human factors.	

Level of Concern: The firm did not indicate the level of concern for the firmware but did so for the programmer (see page 1-178). Since the firmware is part of a class III implanted device the level of concern for it is "Major" just as it is for the programmer for the class III device. The firm will be reminded to apply the above analysis for all parts of the software but no deficiency is needed.

Software Description: The description of the firmware changes was sparse and scattered throughout the documentation (M140016/M005 as well as this submission). For example, Page 1-126 of module M005 (software / firmware) discussed the changes on a very high level and indicated that the SureScan algorithm for ICD's has been implemented, other MRI related enhancements such as SureScan Power on Reset (POR) survivability, Timeout Counter and increase in VF NID to decrease inappropriate shocks were listed as well. It furthermore stated: Relevant and useful MRI diagnostics have also been added for research purposes. The same statement was essentially repeated on page 1-132 of M005 (HP MRI FW

Development Plan). Both then referred back to the Device Description in Executive Summary. Here table 11 provided are more in depth discussion, in particular on the pages following the table. The discussion itself was sufficient. The programmer software description was found on page 178-185 (M005) and was sufficient.

Device Hazard Analysis: A hazard analysis was performed in Module M002 which was found to be acceptable and was closed on January 15, 2015.

Software Requirement Specifications: Firmware requirement specifications were not provided but are referenced in the firmware development plan. The firm was asked to provide the specifications for the features that have been changed. The software requirement specifications for the programmer software were indicated to be 1867 pages and the firm only provided the cover page and the table of contents. However, a full electronic copy was provided on the submission CD-ROM. The specification was reviewed and found to be acceptable.

Architecture Design Chart: The firmware development plan referenced the architecture as an output but the report verification report did not provide it. The firm was asked to provide documentation for any changes over prior firmware architecture. The firm states that the programmer architecture has not changed.

Software Design Specification (SDS): Software Design specifications were addressed on page 183. Firmware has the same issue as noted above.

Traceability Analysis: A traceability analysis for the software was provided on page 1-184 of Module 005 and appendices. The firmware traceability analysis could not be located.

Software Development Environment Description: Firmware environment description was part of the firmware development plan and was marginally sufficient. The programmer software Development Environment Descriptions was provided on page 1-185.

Revision Level History: Programmer revision history was provided on page 1-185 and is sufficient. Firmware revision history is not clear.

Unresolved Anomalies (Bugs or Defects): The firm indicated 3 software anomalies and assessed the impact starting on page 1-298 (M005). The reviewer agrees with the firm's analysis. No firmware anomalies have been reported or more accurately no discussion has been found in the documentation.

Verification and Validation Documentation: The firm provided verification and validation documentation that is sufficient for the programmer. The firm only provided a summary document for the firmware and was asked to provide documentation similar to what was provided for the software.

In summary, the firm provided sufficient documentation for the programmer software but failed to provide the same level of detail for the firmware. The firm clearly followed the guidance document for the software documentation but not at all for the firmware; making the review of the latter difficult and more importantly resulted in missing documentation needed to fully evaluate the firmware. The firm was asked in the May 19th, 2015 e-mail to provide firmware documentation following the software guidance. The firm provided documentation on June 05, 2015. The provided documentation aligns the information provided in Module M005 with the software guidance document. The firm indicated that some of the documentation, however, was not provided because of the large file size but is available upon request. The lead reviewer did not see the need to request that particular information. All outstanding Software / Firmware questions have been resolved.

SYSTEM VALIDATION TESTING

The firm indicated that System Validation testing was conducted on the system components which included the Evera MRI ICD devices and Sprint Quattro Secure MRI SureScan lead Models 6935M and 6947M, along with programmers, home monitors and application software SW033 using typical and stressing simulated use scenarios covering all functions defined by the project. The firm furthermore indicated that product manual validation which validated the technical statements as written are true and reflect the actual operation of the system was included. System testing consisted of evaluating the compatibility, interaction and functional operation of the system components when used together as a system. Details were provided in M140016/M004. The module was found to be acceptable and was closed on February 25, 2015.

MRI DEVICE LEVEL VERIFICATION / VALIDATION TESTING

Device level design verification testing was performed on the Evera MRI ICD device to ensure specified performance after the device is subjected to various electromagnetic, medical and mechanical environments (representative of those a device and/or patient may encounter) and to verify the device design for implantable use. Testing consisted of device Design Assurance Unit (DAU) mechanical, electrical, and EMC and MRI testing.

Electrical Design Verification Testing (EDVT) was performed on the Evera MRI device configuration to verify the MRI related electrical performance of the devices to specified functional operating parameters defined in the CRM1 Generation 2 Hardware Requirements Specification (HRS). This testing was included in Volume 1 module M140016/M003 and the review of the module and the response to the January 27th deficiency letter are provided at the end of this memo.

Mechanical, EMC and MRI DAU testing for Evera MRI challenges the Evera MRI in and following MRI exposure. This testing was also included in Volume 1 of M140016/M003.

All design verification was done by similarity to Evera ICDs and were include in M140016/ M004.

MRI Interactions with the Implanted ICD and Lead System

Note that all page references are with respect to M140016/ M003 unless otherwise noted. The potential MRI environment hazards/risks inferred from ISO TS 10974 "Assessment of the Safety of Magnetic Resonance Imaging for Patients with an Active Implantable Medical Device", and the possible clinical

Table 1-13: Summary of MRI Hazards for Evera MRI System

Hazard	Field Interaction	Mechanism and Source of Hazard	Potential Clinical Impact
Lead Heating	Radiofrequency	The conductive device lead acts as an antenna, picking up radiofrequency energy. A portion of this energy is dissipated as heat in the cardiac tissue near the electrodes.	Tissue heating near the electrode may result in thermal cardiac tissue damage and affect pacing therapies, VT/VF detection or efficacy of defibrillation therapies.
Unintended Cardiac Stimulation	Gradient Radiofrequency	The gradient and radiofrequency fields will induce voltages along the leads that will be applied to the device lead electrodes. If these voltage pulses are large enough, they may directly stimulate the heart.	Cardiac stimulation may lead to a single or intermittent stimulation or a sustained tachycardia.
Vibration	Static Gradient	Gradient magnetic field induces electrical currents in the conductive surfaces of device components. Interaction of these currents with the static magnetic field causes the component to vibrate.	Device malfunction may affect pacing therapy.
Device Interactions	Static Gradient Radiofrequency	The static, gradient, and radiofrequency fields may adversely impact the electrical operation of the device system if its operation is not protected from the effects of those fields. The coupling mechanism can either be from the radiated field or conducted through the lead-device interface.	Potential device malfunction or failure due to component damage, modification of functional circuits (i.e., transformer core saturation) or noise induced on the system leading to oversensing or inhibition affecting pacing operations.
Force and Torque	Static	The static magnetic field will act on any ferromagnetic material in a device or lead, producing a translation or rotation force on the device or lead.	Device or lead movement may lead to patient discomfort or affect therapy.
Case Heating	Gradient Radiofrequency	Electrical currents on the conductive surface of the device case are dissipated as heat.	Tissue heating near the device case may lead to patient discomfort or tissue damage.

impact associated with each hazard is presented in Table 1-13. The subsequent sections provide additional detail on each hazard, including requirements definition and test results. The firm provided complete details in the referenced reports.

In addition to the hazards listed in Table 1-13, the effect of the Evera MRI system's impact on image artifact was also assessed and is discussed in Volume I of M003.

Lead Heating (Impact on PCT)

The firm provided information with regards to tissue heating near the lead electrodes for all submitted leads (Sprint Quattro Secure 6935M and 6947M, 5076 and 5086 MRI leads) and summarized the results on pages 1-129 (tip heating, 6935M and 6947M), 1-132 (shock coil, 6935M and 6947M) and 1-134 (tip heating, 5076 and 5086). The firm indicated on page 1-128 that all lead heating modeling was conducted assuming a single lead system incorporating the appropriate (b) (4) [redacted] (Q130785, G140039). The firm also stated on page 1-133 that the (b) (4) [redacted] The firm concluded that for this reason, the test results of the 5076 and 5086 lead obtained with the Advisa MRI device should apply to the Evera MRI ICD.

Reviewers Comments

(b) (4) [redacted]

(b) (4)

[redacted]

(b) (4)

[redacted]

Heating of the shock coil sections of the defibrillation leads was reported on page 1-132 of Module M003 and is less than 3 C in the 99th percentile case. The firm estimated these temperature rises for the no-perfused case and substantially smaller increases are expected when the coil is exposed to the actual blood flow. The firm then references a FDA approved Swan-Ganz thermodilution cather. Here the temperature increase is 7 C, in the blood flow. Clearly, the shock coils are well below this value and the reviewer has no concern with a 3C increase.

Unintended Cardiac Stimulation (UCS)

The gradient and radiofrequency (RF) fields produced by MRI scanners induce voltages along cardiac leads that will be applied to the device lead electrodes. If these MRI-induced voltage pulses are large enough, they may directly stimulate the heart. The voltage induced along the lead will be from both the gradient magnetic field and the RF field. The gradient magnetic field has the potential to stimulate the heart directly due to its low frequency content, whereas the RF field can only cause stimulation if the voltage is rectified, converting the high frequency voltage to a low frequency voltage, by the device electronics.

Gradient Induced UCS

(b) (4) [redacted]

Although the risk of unintended cardiac stimulation is considered low and acceptable for the Evera MRI system, gradient induced sub-threshold pulses will occur during MRI scans. However, gradient induced sub-threshold pulses (which will not elicit a cardiac depolarization) do not present additional risk for ICD patients because the physiology of cardiac tissue at the lead-tissue interface is not different between pacemaker and ICD patients.

Reviewers Comment

The material presented by the firm was sufficient and the model of determining the induced voltage appeared to be very robust. The firm indicated a (b) [redacted] charge limit, however, it was not clear where this limit came from. The cited report did not contain the limit and the firm was asked provide rationale for the limit. The firm provided the rational in the response to FDA's January 27th 2015 deficiency letter. The response was sufficient to address the deficiency.

RF Induced UCS

The Evera MRI ICD Device Requirement Document stated that less than (b) (4) of rectified voltage shall be present on the electrode port to the device case, when exposed to an RF signal. Test conditions reflected considerations for all compatible right atrial (5076 and 5086MRI) and right ventricular leads (6935M and 6947M). The result of the test was less than (b) [redacted] of rectified voltage was measured which meets the requirement. The firm pointed to

Evera MRI DR/VR ICD Electrical Design Verification Test Report V3 - DSN011432

for details. The firm indicated that the (b) (4) requirement was derived from animal studies as part of the development of Revo MRI that measured the minimum pacing capture threshold for rectified pulses. The firm stated that the physiologic mechanism for stimulation, and therefore pacing capture threshold, is no different between the ICD and pacemaker patient and therefore the (b) (4) requirement was unchanged for Evera MRI. The firm indicated that the test was executed by directly injecting RF power into the device under test via an injection network that allows for the ability to deliver high frequency RF power and to measure any potential low frequency rectified pulses.

Reviewer's Comments

The firm stated that a (b) (4) limit was derived from animal studies conducted as part of the Revo MRI system. The firm also stated that there is no difference between the ICD and pacemaker patients as far as tip stimulation threshold is concerned. The firm used data shown on page 1-342 to substantiate this claim for the "dc" level thresholds and extended the conclusion to the RF rectified voltage. The data shown substantiate the claim.

The firm also stated that the RF power for the test is injected directly into the device. The firm did not provided a clear definition of the experimental set up nor a level for the injected power. The firm was asked to provide both in order to fully assess the validity of the test. The firm provided both the experimental set-up and power levels in the reply to FDA's deficiency letter. The response was sufficient to address the concerns.

MRI Induced Force

An MRI scanner's static magnetic field exerts translational force on implanted medical device systems containing ferromagnetic components. Excessive movement could result in patient discomfort or cause device damage. (b) (4) which met the requirement. The firm referred to (b) (4)

Reviewer's Comments

The firm indicated on page 1-138 that the Evera MRI device requirements allow an induced force that shall not exceed eight times the device weight. There is no justification given why this is an acceptable limit considering that the ASTM standard ASTM-F2052-06states "For a device to be safe in the MR environment, the magnetically induced deflection force and torque should be less than forces and torques to which the device may safely be exposed if it were not in a large magnetic field, for example, a force less than the weight of the device and a torque less than that produced by normal daily activities (which might include rapidly accelerating vehicles or amusement park rides)." A rationale should be provided for the limit set. The actual measured value was 1.36 Newton or ~2 times the force of gravity. This should not present a problem if the firm can rationalize the 8 times gravity force limit. However, since the firm was also trying to remove the requirement to wait at least 6 weeks after the implant before receiving an MRI the limit would need to be justified taking the new labeling into account or the requirement should remain. The firm provided an acceptable rational in their response to FDA's deficiency letter. The firm cited a paper (Allen, Murray E. et al., "Acceleration perturbations of daily living", Spine 19(11): 1285-1290 (1994)) showing that every day normal activities can result in force exceeding 8 x gravity forces.

MRI Induced Torque

An MRI scanner's static magnetic field exerts alignment (torque) force on implanted medical device systems containing ferromagnetic components. Excessive movement could result in patient discomfort. Based on the Evera MRI device requirements, the maximum allowed induced torque shall not exceed the product of the device weight in Newton and the longest overall dimension of the device (L) in meters, (b) (4) Test conditions evaluated the worst-case system configuration with considerations for all compatible right atrial (5076 and 5086MRI) and right ventricular leads (6935M and 6947M). The result of the testing was (b) (4) which meets the requirement. The firm states that the evaluation of torque was consistent with ASTM-F2213-06, "Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment". The magnetic torque is determined by attaching the DUT to a horizontal turntable placed at the iso-center of the bore where

(b) (4) [redacted]

Reviewer's Comments
The firm indicated that it followed ASTM-F2213-06. The suggested pass-fail criterion in the standard is "5.2 If the maximal torque is less than the product of the longest dimension of the medical device and its weight, then the magnetically induced deflection torque is less than the worst case torque on the device due to gravity. For this condition, it is assumed that any risk imposed by the application of the magnetically induced torque is no greater than any risk imposed by normal daily activity in the Earth's gravitational field. This is conservative; it is possible that greater torques would not pose a hazard to the patient." Since the submitted device meets the criterion, no further information is needed.

MRI Induced Vibration
Exhaustive testing using a specialized MRI test system that simulates conditions beyond clinical worst-case with respect to mechanical vibration and for a duration that exceeds the expected lifetime MRI exposure showed no device damage or malfunction. This testing subjected 22 Evera MRI ICD devices each to a minimum of 25 hours total of vibration at the specified frequencies. No MRI induced anomalies or device malfunctions were observed. The firm refers to:

Evera MRI Device DAU MRI Mechanical Design Validation Report V3 - DSN011470

for details.

Reviewer's Comments
The firm provided test frequencies in the Validation Plan, however, did not provide a test set up. Vibration is generally not considered a large risk and the information provided is sufficient. The firm did provide a test set up in their response to FDA's January 27th deficiency letter. The information was reviewed and considered acceptable.

Device (Case) Heating
When a patient with an ICD undergoes an MRI scan, the device will be exposed to two time varying fields, the gradient field and radiofrequency (RF) field. Both of these fields couple energy into or around the device which may lead to heating of the device and surrounding tissue. (b) (4) [redacted]

Reviewer's Comments
Even though the exact test setup is not provided the information and rationale given in the assessment report was detailed and sufficient. There are no questions with regards to the gradient induced case heating.

Image Artifact
Image artifact was assessed in accordance with ASTM F2119-07 and documented in:

Image Distortion on Medtronic SureScan System V5 MDT1968222- R12056

The conclusions of the testing are summarized below:

1. Artifact from the Evera MRI device extends as much as (b) [redacted] beyond the case for spin echo images and as much as (b) (4) [redacted] beyond the case for gradient echo images. Artifact beyond the device is due to the internal ferromagnetic components.
2. Artifact along the length of the Sprint Quattro Secure lead is modest and extends at most (b) (4) [redacted] beyond the lead.

The presence of metallic implants (i.e., IPG or ICD systems) in MRI can cause significant image artifacts, including signal loss, failure of fat suppression, geometric distortion, and bright pile-up artifacts11. Medtronic CRDM's findings are consistent with the experiences of other radiologists and MR technologists.

Reviewer's Comments

The image artifacts created by the device are severe and in fact I believe are underestimated by the firm since it appears the firm used only a visual measurement technique to determine artifacts. Methods utilizing digital comparison of images with and without the device in place tend to give a higher distortion depending on the allowed difference on a pixel by pixel intensity comparison. Image distortion is not a direct risk for a person being scanned; however, it may severely impact the diagnostic value of the scan. Image distortion is not considered a safety concern since the distortion effect is known by the reading Radiologist(s). In addition the firm provides a reminder of this issue on page 7 (4-185) of their MRI Technical Manual. The reminder is sufficient in the opinion of the reviewer.

Device Interactions

During and following static, gradient and RF exposures, the devices were tested to assess whether they were damaged as a result of RF and gradient fields being transmitted to the devices through the leads. Test conditions reflected considerations for all compatible right atrial (5076 and 5086MRI) and right ventricular leads (6935M and 6947M). This testing determined that the devices were not damaged by high static, RF and gradient condition scans per the following reports located in the MRI-Related Device Design Verification and Validation section of Volume 2 for details:

Evera MRI DR/VR ICD Electrical Design Verification Test Report V3 - (b) (4) [redacted]

In addition, Evera MRI ICD's were tested at worst-case exposure settings and positions for the test being conducted. The firm asserted that testing demonstrated the reliability of the Evera MRI system (i.e., pacing rate, pacing amplitude, and pulse width) during and after MRI scans met the required specifications. All tested electrical subsystems (e.g., Telemetry, High Voltage Charging, High Voltage Delivery) were within specification after MRI exposure. Finally, no resets were observed during testing, which demonstrated that the reset rate of occurrence in the MRI environment was well within Medtronic CRDM performance standards and that the data integrity of the Evera ICD system was not compromised. The Evera MRI ICD testing confirmed that the system meets the requirements for the device interactions hazard as summarized in Table 1-17.

The firm asserted that comprehensive analysis and testing demonstrated that the Evera MRI ICD will deliver appropriate therapy during an MRI and that MRI exposure does not compromise subsequent operation, reliability, or longevity. This demonstrated safety and effectiveness in relation to the device interactions hazard of the Evera MRI ICD

Reviewer's Comments

The firm indicated on page1-136 that devices were tested during and following static, gradient and RF exposures to assess if they were damaged as a result of the exposure. The reviewer believes that the test performed and test results were appropriate and acceptable, however, it wasn't quite clear what test set up was used to perform these tests. The reviewer believed that testing was performed using a (b) (4) [redacted]

(b) (4) [redacted]

[redacted],

no information was provided with regards to the positioning in the scanner, instrumentation to measure device output etc. The reviewer believed this information to be necessary to fully evaluate the tests and data presented and the firm was asked to provide the information at least for the MRI related Device

Function Tests. In the response to FDA's January 27th deficiency letter the firm provide a detailed description of the tests performed; confirming the reviewers assumption that many of the test were performed in the (b) (4) [redacted]

Impact of MRI on the Steroid Eluding Drug used in the Pacing and Defibrillation leads
Medtronic conducted a laboratory study comparing the in-vitro elution of the Quattro Secure lead Model 6947 as manufactured and after undergoing simulated MRI thermal stress, similar to what was provided for the 5086MRI lead (in M080013/M005) as part of the Revo MRI system (P090013, approved February 8, 2011). Since the distal tip of the 6935/6935M, 6947/6947M, and 5076 leads are similar, the 6947 lead was used as a representative of all these lead models.

(b) (4) [redacted]

Reviewer's Comment
A biopharm review of the data submitted by Medtronic was provided. According to the consultant reviewer, the data submitted are acceptable and appropriate; the data had been previously submitted for the Advisa submission.

ANIMAL STUDIES
Multiple canine studies were conducted to characterize the lead heating and VF detection performance of the Quattro Secure Lead distal design test lead with the Evera MRI ICD. One canine study investigated the chronic effects of RF induced lead heating on VF detection (S3126). A second canine study investigated the effects of multiple RF exposures on VF Detection (S3134). Details of these studies are included in Volume 1 of M140016/M003. Lastly, a GLP canine study was conducted to confirm the performance of the Evera MRI system, including the SureScan feature (see S3127-Evera MRI System Confirmatory Canine Study Report). The firm stated that the results of the study confirmed that the system operated safely and as expected before, during, and following MRI scans. Details of the study are included in Volume 2 of M140016/M003.

Reviewer's Comments
A review of the animal studies was provided a veterinarian consult. According to the consult the effect of cumulative RF energy delivery and the ability to detect VF and deliver a shock in a timely manner is addressed with the new GLP preclinical study, S3127, found in this submission. Results of GLP S3127 were promising but the pathology report raised a few safety concerns, the consult reviewer requested additional information based on the following concerns:

1. (b) (4) [redacted]

(b) (4)

[redacted]

(b) (4) [redacted]

[redacted]

CLINICAL DATA

The Evera MRI clinical study (IDE# G140039) was a prospective randomized controlled, non-blinded, multi-center worldwide investigational study. The purpose of the Evera MRI System clinical study was to confirm safety and effectiveness in the clinical MRI (Magnetic Resonance Imaging) environment when subjects receive MRI scans up to 2W/kg whole body Specific Absorption Rate (SAR) without positioning restrictions (MRI scans may occur anywhere on the body).

The Evera MRI System study was conducted at centers located in Europe, Saudi Arabia, India, Chile, Hong Kong, Canada, and the United States (US). Enrollment is now complete with the pre-specified 275 subjects.

Following 2:1 randomization ratio, approximately 183 subjects were planned to be randomized to the MRI group to undergo an MRI scan and approximately 92 subjects were planned to be randomized to the control group to not undergo an MRI scan. This was Medtronic's fourth clinical investigation of an MR conditional system and began enrollment outside of the United States (OUS) in April 2014 (National Clinical Trial # 2117414). Importantly, the Evera MRI Clinical study was built upon the foundation established by the EnRhythm MRI and Advisa MRI study designs (appropriate safety and effectiveness endpoints) and incorporates changes recommended by the FDA review team as results of pre-IDE and pre-submission discussions.

The Evera MRI study was conducted at 42 centers located in the United States (25), Canada (3), Europe (10), Middle East (1), India (1), Hong Kong (1) and Latin America (1). The multisite design was used to help ensure a representative sample of the population as well as a reasonable enrollment period.

This clinical trial included single chamber (VR) and dual chamber (DR) Evera MRI device models, as well as both the 6935M and 6947M lead models under the same protocol, resulting in four possible configurations. The Model 5076 pace/sense lead was placed in the atrium when an Evera MRI DR ICD was implanted.

In order to ensure a widespread distribution of data, and to minimize bias in the Evera MRI study results, the maximum number of subjects enrolled at a single site was 28 subjects (approximately 10% of the total subjects enrolled). There was no minimum number of enrollments required at any site.

The study sample size called for 275 subjects to be enrolled. Subjects were enrolled into the study prior to implant at the baseline visit. Following a successful implant of a complete Evera MRI system, consisting of an Evera MRI ICD, Model 5076 RA lead (if applicable), and Model 6935M or 6947M RV lead, subjects were randomized in a 2:1 fashion to the MRI group or Control group.

Following randomization, all subjects were followed in the office at 2 months, 9-12 weeks (MRI/waiting period), 1 week post-MRI/waiting period and 1 month post-MRI/waiting period. At the MRI/waiting period visit, subjects in the MRI group received a series of MRI scans, including scans of the brain, cervical spine and thoracic region. Subjects in the Control group were required to come in for a "waiting period visit"; these subjects did not undergo an MRI scan but rather had an approximately 1 hour waiting period. The 1-

month post-MRI/waiting period visit was calculated from the time point from when the MRI/waiting period visit occurred.

The primary endpoints of the study, MRI-related events, ventricular pacing capture threshold (PCT) changes, and ventricular sensing amplitude changes were assessed after the last subject completed their one-month post-MRI/waiting visit.

All primary and secondary objectives were met. No unanticipated adverse events or new risks were identified during the course of the trial.

A total of 34 VT/VF episodes occurred after MRI in 24 subjects. No impact to detection or therapy delivery was noted in any episode. There was not an increased proportion of episodes with more than 4 intervals ≥ 300 msec, more than 1 interval ≥ 600 msec, or > 10 second detection delay post-MRI relative to pre-MRI. As demonstrated by this data, there is no evidence that an MRI affects the ability to sense and detect VT/VF.

The trial was sized based on an FDA request dating to the first MRI PM trials that approximately 150-200 subjects were exposed to MRI as a compromise between the low sample sizes needed to power most of the endpoints (note that 275 subjects were needed according to power calculations for the ventricular sensing endpoint) and the size of the trial were it powered to show any effect from MRI no matter that it were small and perhaps less than clinically important (for instance minor changes in QRS sensed amplitude that are detectable but never result in under sensing during sinus rhythm).

Of the 275 enrolled subjects, 263 subjects were successfully implanted with a complete Evera MRI system and randomized in the study. The 12 subjects who either had no implant attempted (11) or were not implanted with a complete Evera MRI system (1) were either exited or withdrawn from the study.

A total of 175 successfully implanted subjects were randomized to the MRI group and 88 were randomized to the Control group. Of the 175 subjects randomized to the MRI group, 162 subjects had a MRI/waiting period visit, and 156 subjects underwent a scheduled MRI scan.

A total of 232 subjects have completed the one-month post-MRI/waiting period follow-up (151 MRI group, 81 Control group).

In addition to the 275 subjects enrolled in the study, there has been 1 compassionate use subject implanted with the Evera MRI system who was not included in the analyses of this report (IDE G140039/S006). A second Compassionate Use was requested and approved by FDA (G140039/S010) in October 2014 but the patient developed other issues and the implant was postponed.

There were 11 subjects who had 12 clinically indicated scans. Clinically indicated scans were allowed in any enrolled subject. No significant change in PCT or sensing was seen after any clinically indicated scans.

Clinical Reviewer's Comments

The key function of the ICD, sensing, detection and timely treatment of VT and VF appears preserved over MR exposure with the proposed Evera MRI ICD device under the prescribed MR Conditions of Use. That said, the IDE was designed to provide this key demonstration of continued good sensing after MR exposure in the least burdensome, minimum number of VF inductions or accumulated spontaneous VF episodes. This question has been adequately addressed for approval but should be followed by more substantial study, that is, in a larger cohort in the post-approval period. FDA can work with the firm to devise an appropriate sample size and least burdensome manner of accumulating post-approval experience of induced or spontaneous VF events among Evera MRI ICD patients with prior MRI exposure (*note from lead reviewer: the Post Approval Study Protocol is the outcome of this discussion.*). The firm should update the results reporting in the clinical manual and IDE report as it becomes complete (*note from the lead reviewer: Language in the approval letter requires the firm to update labeling once results from the PAS are available.*

The proposed clinician manual summarizing the design, conduct and results from the IDE study do not appear to provide information about the VF induction testing. The firm should add this important testing to the summary manual. The firm should also verify that the experience in the IDE with multiple and clinically indicated MRI scans is included and that the firm states the findings and limitations of these important types of IDE findings (*Note from the lead reviewer: The VF testing and multiple MRI exposure experience being part of the clinical summary data was discussed during a follow up call to FDA's May 16th, 2015 e-mail. The firm pointed out that page 4-233 points to the location of clinical trial and study*

results: www.medtronic.com/manuals. Even though the link requires selection of the appropriate IPG/lead, it is relatively easy to follow. The lead reviewer considers the issue addressed, however, will ensure during the review of the final labeling amendment that the link indeed provides the appropriate information.)

The clinical reviewer found that the submission provided a reasonable assurance of safety and effectiveness of the system in the MR environment under the recommended MR Conditions of Use; the Conditions of Use are appropriate and the Instructions for Use and Labeling are adequate and appropriate.

Statistical Reviewer's Comments

According to the protocol, the Evera MRI study was considered "an investigational trial in the US and Canada, and an interventional post-market study in other participating geographies" (Section 2.1, Page 2-312). It was noticed that the clinical data for this PMA supplement included subjects from countries other than the US and Canada. The firm should be asked why it is justifiable to pool data from pre-market study and post-market study.

It was noticed that the firm conducted some post hoc analyses to study device safety and effectiveness. The firm should be advised that results of any post hoc analyses cannot be used in the device labeling.

It is noticed that when explaining the tipping point analysis for the primary effectiveness objective for ventricular pacing capture threshold (Page 2-71), the firm referred to the example as a "worst case analysis". FDA does not consider the analysis as presented a worst case analysis and any reference any references to this analysis should not use this wording.

The statistical reviewer concluded that the study met all three primary safety and effectiveness endpoints. It also appears that all four secondary endpoints have been met.

Note from the lead reviewer: The concerns regarding the use of post hoc analyses and use of "worst case" was communicated in a May 16th e-mail and follow up phone call. The firm acknowledged the concerns and indicated that appropriate wording would be used. The lead reviewer considers the concerns addressed appropriately).

Lead Reviewer's Comments

The lead reviewer noticed in the review of M140016/M003 several reports of pocket warming (preliminary clinical data, confirmed in the final study report). The reviewer believes that the number of warming reports will increase over the reports received for the pacemaker SureScan systems. The reason for this increase is twofold: (1) the device area is substantially larger and power deposition on the device increases as the square of the Surface area (page 28, ISO 10974-2012(E)). (2) The onset of pain / discomfort with respect to temperature increases as a function of device area (R. Defrin et. al. , "Sensory determinants of thermal pain", Brain (2002), 125, 501-510); again, ICDs have a larger surface area than their pacemaker counterparts. The firm was asked to add a note to the MRI Technical Manual in the M140016/M003 deficiency letter and has done so for the PMA submission.

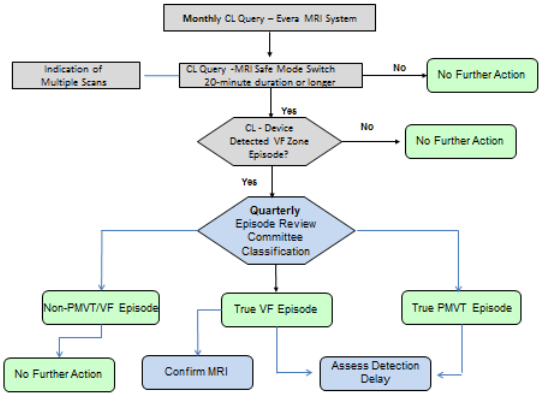
PANEL

An internal meeting was held on May 01, 2015 to discuss the need for a Panel Meeting. Even though the Evera MRI ICD system will be the first ICD to receive MR Conditional Labeling, the team concluded that the technical and clinical questions with regards to the use of ICDs in the MRI system environment are very similar to those encountered for pacemaker systems. Given the experience the field (Clinicians, Industry and FDA) has gained over the past 5 years since the first MR Conditional Labeling was granted for the Revo pacemaker system and the emergence of a standardized test approach based to a large extend on the ISO/TS 10974:2012(E) Technical Specification the team concluded that no Advisory Panel input would be required to arrive at a safety / efficacy decision for Evera MRI ICD.

POST APPROVAL STUDY

The initial PAS protocol was discussed in the May 01, 2015 meeting and again in a meeting on May 29th, 2015. It was determined that lead reliability studies are not required since the leads have a long history. However, the team felt that the total number of true VF incidents studied post MRI exposure was too low and would require some additional data. Feedback was provided verbally to the firm after the May 01 and

May 29th meeting. Based on feedback from FDA, the firm has created the final PAS study protocol; e-mailed to FDA on July 27, 2015.



Study Methodology

Evera MRI systems enrolled in the Medtronic CareLink® Network (CL) will be used to prospectively assess spontaneous Ventricular Fibrillation (VF) episode detection following MRI exposure. It is estimated that the annual incidence of patients who experience at least one true spontaneous VF episode is 1% or less. Therefore, the likelihood of achieving a meaningful number of true VF episodes in patients following an MRI scan is very low. Given this low incidence rate, CL offers the only possible data source with the volume of Evera MRI systems to potentially identify a correlation between VF detection delays and MR exposure.

Due to the expected low incidence rate of VF episodes, the point estimate for the study design was based on the combined Polymorphic VT (PMVT)/VF episode rate. An MRI is considered to have been performed if the device MRI-compatible mode (SureScan mode) has been enabled and remains in the MRI-compatible mode for at least 20 minutes, which has been correlated with an occurrence of an MRI scan in pacemaker patients.

Monthly review of Evera MRI CL transmissions will be completed. All post MRI spontaneous episodes detected by the device in the VF zone will be reviewed by an Episode Review Committee (ERC) approximately quarterly. The ERC is a committee comprised of external independent experts with applicable technical and clinical backgrounds. The ERC will differentiate VF from PMVT episodes during the adjudication process and classify the episode as true VF or PMVT or a non-PMVT/VF episode. The arrhythmia detection delay will be assessed by the ERC for all identified VF and or PMVT episodes. Analysis of detection delays will be completed for VF only episodes, as well as combined PMVT/VF episodes in MRI exposed systems, utilizing the device episode log and the recorded EGM data.

Enrollment and Duration

The study population is sourced from all patients implanted with an Evera MRI system, followed in the Medtronic CL network with de-identified data accessibility. The overall surveillance scope and duration are dependent on a number of variables including:

- Number of implants of the Evera MRI System.
- Number of Evera MRI System implants that enroll in CL.
- Number of CL enrolled patients who regularly transmit device data.
- Annual MRI rate and the prevalence of true VF episodes.

The following assumptions were used to define the surveillance scope and duration:

- An estimated 65% of US ICD implants currently enroll in CL and approximately 60% of those patients regularly transmit device data.
- Applying CL use/transmission rate to the current estimated US sales projections for the Evera MRI system, an estimated 10,979 Evera MRI patients will be actively monitored in CL within three years of product approval.
- Annual MRI scan rate of 9%, an estimated 1,699 patients will have at least one MRI scan within approximately 4 years post product approval.
- Annual true VF/PMVT episode rate of approximately 2%, based on episode adjudication data collected in Medtronic PainFree SST and Shockless studies.

Per the above assumptions, a statistical simulation indicates that approximately 10 to 49 patients will have 10 to 98 true VF/PMVT detected episodes, following an MRI, within approximately 5 years of product

approval. The primary objective will be analyzed and reported when 25 patients with a true VF episode following MR exposure have been identified or 5 years post-approval, whichever comes first.

Primary Objectives

To characterize the proportion of episodes with ≥ 5 seconds VF detection delay in the Evera MRI system following MRI exposure.

Endpoint Justification

No VF/PMVT detection delays of ≥ 5 seconds were observed in the Evera MRI IDE study. A previous Medtronic study estimated a 0.08% detection delay rate in non-MRI patients based on a cohort of 1177 induced VF episodes. Therefore, the probability of observing at least one VF/PMVT episode with ≥ 5 seconds detection delay in the study cohort of 25 patients with VF episodes is 2%.

Sample Size Rationale

A sample size of 25 patients with a true VF episode will produce a 2-sided 95% confidence interval upper bound for the estimate of approximately 20% (i.e. no more than one VF that will have ≥ 5 second detection delay).

Analysis Methods for Primary Objective

The primary objective analysis cohort is defined as Evera MRI system implanted patients with a true VF episode (i.e. as classified by ERC) which has occurred after the patient has experienced at least one MRI scan. All CL transmitted device detected episodes in the VF zone post MRI scan will be reviewed by the ERC for episode classification (true spontaneous VF or PMVT) and identification of clinically relevant detection delays (i.e. ≥ 5 seconds). The proportion of VF episodes with a ≥ 5 second detection delay will be calculated by dividing the number of VF episodes with ≥ 5 second detection delay by total number of true VF episodes reviewed. Two sided 95% confidence interval will be calculated using the exact binomial method.

All qualifying VF and PMVT episodes will be reported. Episode final classification (VF vs. PMVT), detection times and other relevant device parameters will also be reported.

If one or no VF detection delays are identified, the primary objective will be met. If more than one (1) true VF detection delay (≥ 5 seconds) is identified, the following additional analysis will be completed to facilitate interpretation of the episode and the relationship with the MRI exposure:

Comparative analysis

If more than 1 (> 1) VF detection delay of ≥ 5 seconds is identified for the Evera MRI system following MRI exposure, the difference in proportions of VF detection delays (≥ 5 seconds) will be compared between patients implanted with an Evera MRI system with MRI scans versus those without MRI scans.

Comparative analysis method and sample size justification

The comparison group is defined as Evera MRI system implanted patients with a true VF episode (i.e. as classified by ERC) who have not experienced at least one MRI scan. To avoid bias, all VF episodes occurring during the same time frame as those in the MRI group will be consecutively sampled based on episode detection date.

The Fisher's exact test will be used to determine if the proportion of VF detection delays (≥ 5 seconds) is different between the two groups, with a hypothesis of no difference.

Hypothesis:
H0: P (MRI) = P (Control)
Ha: P (MRI) ≠ P (Control)
Where P is the probability of VF detection delay

Stratified analysis

If more than 1 (> 1) VF detection delay ≥ 5 seconds is identified for the Evera MRI system following MRI exposure, the proportion of episodes with VF/PMVT detection delay (≥ 5seconds) will be calculated by the programmed device VF NID at the time of the episode.

Corroborating Clinic Data

Corroborating clinical data will be sought to confirm the occurrence of an MRI, for patients who have experienced at least one true spontaneous VF episode following a 20-minute SureScan mode duration. Medtronic's ability to collect this information is dependent on:

- Approval to access patient identifiable information
- IRB approval to gather clinic data
- Willingness and ability of clinic (identified in CL) to confirm the occurrence of an MRI

Additional corroborating clinical data will be sought in the event a ≥ 5 second VF detection delay is observed, including but not limited to:

- MRI scan information
- Clinical interpretation and actions taken related to the VF episode
- Non-CL device interrogations
- Baseline characteristics
- Procedure data
- Medications
- Adverse device effects

Multiple MRI Scans

Data regarding the number of patients presumed to have had 2 or more scans will be provided. The time stamp of a when a device was last programmed to the MRI compatible mode (i.e. SureScan mode) will be tracked from CL transmission to transmission. Any change in the time stamp of an MR mode safe switch of greater than 20 minutes will indicate the occurrence of an MRI. The estimate of patients receiving multiple MRI scans will include all patients regardless if the patient has experienced a VF episode.

Report and Analysis Schedule

Interim reports will be provided annually, following product approval. The final report including the primary analyses will be provided when 25 patients with a VF episode following MR exposure have been identified or 5-years post-approval whichever comes first.

The interim reports will include details of progress against surveillance assumptions, including the following:

- The number of Evera MRI System patients who are enrolled in CL with the number of associated CL transmissions
- The number of patients with an indicated (20-minute SureScan mode duration) MRI scan completion
- The number of true VF/PMVT episodes
    - ERC episode adjudication results, including episode final classification (VF vs. PMVT), detection times and other relevant device parameters

The final report will include similar information as the interim reports, as well as the primary analysis results.

Study Design Limitations

CL provides the largest Evera MRI patient population available for assessing VF detection delay following MR exposure within a timeframe that minimizes patient risk. However there are limitations:

- In compliance with HIPAA, CL access is limited to de-identified device data; therefore, no patient information will be accessible via CL.
- The de-identified CL data mart is limited to US, Canada, Australia & New Zealand geographies.
- Clinics may be unwilling to provide corroborating clinical data, if needed.
- Assumption of MRI scan occurrence is based on SureScan mode switch that is recorded in the device, with corroborating confirmation of MRI scan sought from clinic.
- The analysis is limited to only CL enrolled patients who also routinely transmit. Note: this is not presumed to introduce bias since there is no known relationship between CL enrollment and the occurrence of VF episodes.
- Only adverse device effect events that are electrically manifested may be identifiable via the device data, actions taken and/or outcomes will not be available in a de-identified data set.

- Global complaints and returned product analysis will be available for Evera MRI products if reported/returned, however, can't be linked to the CL cohort unless corroborating clinical data is obtained.

Reviewer's Comment

OSB has accepted the study protocol dated July 27, 2015 and sign off was given via consult memo on August 12, 2015. A minor correction to the OSB approval language was confirmed via email on August 21, 2015.

The clinical consult expressed overall agreement with the basic approach (draft protocol) in an e-mail dated June 16th, however wanted to make sure that the firm focuses on true VF episodes "I would not recommend analyzing the data were planning to analyze episodes of polymorphic ventricular tachycardia. I simply don't think that analyzing these episodes will be particularly informative since the signals are much larger than ventricular fibrillation signals". The concerns were communicated to the firm in an e-mail dated June 24th, 2015 and a response was received on June 26th, 2015 and reviewed by the team. The clinical consult provided approval via e-mail on the same day. The firm submitted the formalized protocol via an amendment A002 on July 02, 2015. The formalized protocol reflected all the requests made by the clinical consult and was sent out for approval to the team on July 07, 2015. The clinical reviewer inquired if there was a redlined previous version available and indicated that no formal CTS review was required (July 8th email). Since no redlined version was available an informal discussion between the clinical consult and the lead reviewer concluded that the protocol was acceptable. Small changes / clarifications with regards to (1) timeframe of post MRI risk period, (2) the independence of the Episode Review Committee and (3) the need for IRB approval were requested by OSB in an July 24th, 2015 e-mail. The lead reviewer provide preliminary answers to OSB the same day and forwarded the clarification request to the firm on July 27th, 2015 via e-mail. The firm responded the same day to the questions in a similar manner as the lead reviewer had done on the 24th. The firm's responds, including the redlined version (July 27th final PAS protocol) was forwarded to OSB for a final review. Since the changes made only impacted OSB and not the clinical aspects of the protocol no additional formal concurrence was sought from the clinical consult.

MISCELLANEOUS

On May 6th, 2015 the firm notified the lead reviewer that a device failure had occurred post MRI. The device apparently was fully functioning immediately after the MRI but had experienced a reset sometime prior to the 6 month follow up. The device was explanted and examined. Based on the test results the firm asserts that the failure was not MRI related. The lead reviewer agrees.

CONCLUSION

The submission and additional information provided by the firm is sufficient to approve the submission.

OAI Firm & Corporate-wide Warning List was checked on March 18, 2015 and the document was found to be clear. A subsequent check on September 11, 2015 gave the same result.