This document is intended to provide clear, factual, and balanced information that may facilitate detailed understanding of the Micra TPS CED Study when used in accordance with FDA-approved labeling. This document addresses the Micra TPS CED Study specifically, and unless otherwise noted does not apply to the Micra TPS Post-Approval Study (PAS).

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1. Why was the study designed as a claims analysis?

During the public comment period on the National Coverage Determination for Leadless Pacing, CMS received a comment from physician societies (American College of Cardiology (ACC)/Heart Rhythm Society (HRS)/Society for Cardiovascular Angiography and Interventions (SCAI)) encouraging CMS to "develop a robust and minimally burdensome mechanism to capture data without restricting access to leadless pacemaker technology." This statement was made to consider alternatives to the standard method for CED, which is a traditional prospective registry. In the CMS response to that comment, they stated "prospective longitudinal studies using administrative claims data impose the least amount of burden." Because they involve claims analyses only, prospective longitudinal studies use a “big data” approach to research, leveraging a data set that will be created through standard processes without additional effort specifically from providers. The Micra TPS CED Study was designed as such a prospective longitudinal study (the second such study approved by CMS — the first was for a lumbar decompression technology, clinicaltrials.gov identifier NCT03072927).

The Micra TPS CED study involves using only the data that CMS requires as part of their standard billing process, and requires no special data collection responsibility for the provider that is “for research purposes.” Because of the CED status with CMS, there are minor responsibilities for the provider, but these are “for billing purposes” (see “Q14. Medtronic has been providing training to non-research staff — why?”).

The study was designed to be an analysis of the data that would be previously released to CMS, so that any individual provider would not be considered engaged in the research (see Q2 about engagement below).

2. Is my hospital considered to be engaged in research because of this protocol?

This answer is excerpted from the Western Institutional Review Board® (WIRB®) regulatory opinion letter:

This opinion is based on federal regulation 45 CFR 46 and associated guidance. The Office of Human Research Protections (OHRP) has issued guidance entitled “Guidance on Engagement of institutions in Human Subjects Research,” (2008) which describes when an institution is and is not engaged in research. This guidance is available at: http://www.hhs.gov/ohrp/policy/engage08.html.

Institutions would be considered not engaged in an HHS-conducted or -supported nonexempt human subjects research project (and, therefore, would not need to hold an OHRP-approved FWA or certify IRB review and approval to HHS) if the involvement of their employees or agents in that project is limited to one or more of the following:

- Employees or agents will obtain identifiable private information about subjects for research purposes where the employees or agents will release to investigators at another organization identifiable private information about subjects.

Because institutions are only providing private health information about subjects to an investigator at another organization for this research, we would consider those institutions not engaged in research under the HHS regulations. However, WIRB cannot provide a formal regulatory opinion regarding individual institutions without the institution’s agreement to rely on WIRB. Many institutions have internal policies for making these decisions, and WIRB cannot provide an opinion for an institution that does not choose to use WIRB as an IRB.
3. If my hospital is not engaged in research, why do I have to enter the National Clinical Trials (NCT) clinical trial number on the billing forms?

Because of the CED status of leadless pacemakers, an additional piece of information that is required on these claims is the study's NCT number for the Micra TPS CED Study. This number must be included on all claims to assure that Medicare patients are covered for the use of the Micra leadless pacemaker. The inclusion of this number is considered for billing purposes according to standard CMS procedures:

- From the CMS approval letter for the Micra TPS CED Study:
  “To facilitate the Medicare payment process, you should provide your study sites with appropriate billing instructions. These include entering the National Clinical Trial (NCT) identifier from the ClinicalTrials.gov website on Medicare claims along with the other codes and modifiers provided in the NCD claims processing instructions.”

- From the Medicare Claims Processing Manual — Chapter 32 Section 69.5 (Billing Requirements — General):
  “...it is mandatory to report a clinical trial number on claims for items/services provided in clinical trials/studies/registries, or under CED.”

The inclusion of the NCT number does not create a condition for the hospital to consider they are “engaged in research,” because from the perspective of the provider, the inclusion of this number is for billing purposes and not for research purposes. The NCT number for the Micra TPS CED Study is NCT03039712, and can be found at: https://www.clinicaltrials.gov/ct2/show/NCT03039712?term=micra&rank=2.

4. How do I know if my hospital is enrolled in the CED Study as a site?

As noted above, no hospital is considered to be a research site for this study.

There is a reference to Emory University Hospital in some of the materials, associated with the Micra TPS CED Study, including:

- In the cc list of the WIRB approval letter for protocol version 1.0
- In the “Contacts and Locations” section of the posting for the trial on clinicaltrials.gov

These references simply acknowledge that the primary investigator of the study, Mikhael F. El Chami, is affiliated with this hospital. Emory University Hospital is not considered to be engaged as a provider research site for the same reasons noted in Q3 above.

5. Do I need to approve the study with my hospital’s local institutional review board?

As noted above in Q3, the hospital does not have a direct role in this research, and the entities that do have a role in the research (CMS and Medtronic) have obtained IRB approval through WIRB. Given this, it is Medtronic’s belief that no further IRB approvals are required for this research. Any hospital considering a local IRB approval should carefully review its own policies and procedures in addition to this document to determine whether it is necessary to do so.
6. Why are specific hospitals not listed on the clinicaltrials.gov website?

First, as noted above, individual hospitals are not considered to be engaged in this research. Second, the primary aim of listing investigational sites on this website is to allow transparency to patients who might want to seek out such a site for access to the care that might only be available as part of a clinical trial. Listing sites for the Micra TPS CED Study is not necessary for this purpose since a Medicare patient could be implanted with Micra TPS at any hospital in the United States, and by virtue of that hospital submitting a claim with the clinicaltrials.gov NCT number, would be a part of the study (for more information regarding the requirement to add the NCT number to the claims form, see “Q4. How do I know if my hospital is enrolled in the CED Study as a site?”).

One exception to the listings referenced at clinicaltrials.gov is Emory University. Emory is not listed because the institution is an investigational site in the study; instead it is listed as background information on the physician who is the principal investigator of the trial, Mikhael F. El Chami, M.D.

7. Can hospitals choose between participating in the PAS or the CED Study?

No. Hospitals participating in Micra TPS PAS are part of the Medtronic Product Surveillance Registry network. This is a predetermined network of sites participating in the Product Surveillance Registry (PSR) that was established to meet the product performance and mandated post-approval data requirements across the Medtronic Cardiac Rhythm and Heart Failure business.

All Medicare patients who receive a Micra TPS will be included in the CED Study, regardless of whether they participate in the Micra TPS PAS Study.

8. Which patients are included in this research?

All Medicare beneficiaries implanted with a Micra TPS leadless pacemaker (submitted for reimbursement under Category III CPT® 0387T or the hospital Inpatient ICD-10 PCS, Procedure Coding System 02HK3NZ) on or after the study start date will be included in the study.

9. Are Medicare Advantage patients covered by the CED Study?

Yes. Medicare requires Medicare Advantage (MA) plans to follow CMS’ national coverage decisions. Therefore, Medicare Advantage patients should not be treated differently than standard Medicare patients and all the information in this document applies equally. This requirement is found in the Medicare Managed Care Manual,8 Chapter 4, Section 90.1:

“As discussed in section 10.2 of this chapter, an item or service classified as an original Medicare benefit must be covered by every MA [Medicare Advantage] plan if:

- Its coverage is consistent with general coverage guidelines included in original Medicare regulations, manuals and instructions (unless superseded by written CMS instructions or regulations regarding Part C of the Medicare program);
- It is covered by CMS’ national coverage determinations (see sections 90.3 and 90.4); or
- It is covered by written coverage decisions of local Medicare Administrative Contractors (MACs) with jurisdiction for claims in the geographic area in which services are covered under the MA plan, as described in section 90.2.”

Nevertheless, we are aware that some Medicare Advantage plans do not necessarily understand this requirement and services may be denied. Providers who have concerns in this area should request clarification from these health plans. Any denials should be brought to the attention of Medtronic by sending an email to: rs.healthcareeconomics@medtronic.com. Medtronic does not intend to manage appeals for individual patients, and this email communication is for awareness so Medtronic can consider whether a broader interaction with a particular payer may be of value.
10. How are my patients enrolled in the CED Study?
This study applies to all Medicare patients who receive a Micra TPS device. The Micra TPS device must be used in accordance with FDA-approved labeling (http://manuals.medtronic.com/manuals/main/en_US/home/index). Once implanted, the Micra TPS device is registered with Medtronic, the billing claim is submitted by the provider and the patient is enrolled in the study.

11. Do I need to notify patients that they are going to be included in the study?
No, it is not required for any hospital to provide notification or informed consent to any Medicare patient treated with a Micra TPS device. This is primarily because the hospital is not considered to be engaged in research.

The entities that are engaged in research are CMS and Medtronic. These entities are required to abide by the HIPAA (Health Insurance Portability and Accountability Act) regulations. For access by these entities to the data for research, the central IRB (WIRB) has found that this research meets the requirements for a waiver of consent under 45 CFR 46.116(d). See Q12 for the rationale for this finding.

12. How specifically will patient data be handled?
Access to the CMS data that will be used for this research will be managed by the Research Data Assistance Center (ResDAC). ResDAC is a CMS contractor (Contract Number HHSM-500-2013-00166C) that provides free assistance to academic, government, and nonprofit researchers interested in using Medicare and/or Medicaid data for their research. ResDAC is staffed by a consortium of epidemiologists, public health specialists, health services researchers, biostatisticians, and health informatics specialists from the University of Minnesota.

ResDAC and the CMS Privacy Board will review the Micra TPS CED research study package. Upon approval, a dedicated Medtronic researcher will upload a finder file to CMS on an annual basis, via a secure file transfer system. The file will contain Social Security numbers and implant dates for all Micra TPS implanted patients in a calendar year. The Micra TPS CED Study data set will be available to designated Medtronic personnel via the Virtual Research Data Center (VRDC). The CMS VRDC is a virtual research environment that satisfies all CMS privacy and security requirements. A Medtronic researcher will be required to go through Remote Identity Proofing, including providing personal and credit information prior to obtaining a user ID to access the VRDC. Identity proofing is required for CMS compliance with Federal Information Security Management Act (FISMA) and National Institute of Standards and Technology (NIST) requirements. A Medtronic researcher accessing the VRDC for the Micra TPS CED Study will complete and provide proof of online security training to the CMS VRDC contractor prior to gaining access for analysis. The researcher will not be permitted to share access with another individual. Medtronic will ensure that any non-public data being uploaded into the VRDC environment is not proprietary or restricted by a license agreement or provides approval within the data package request.

13. Medtronic has been providing training to non-research staff — why?
Medtronic has engaged hospitals in a series of webinars to help hospitals better understand the detailed coding considerations when Micra TPS is used. These sessions provide information to help the hospital with a standard process (claims), and are not related to research. Part of this standard billing process is to help the hospital meet CMS requirements for billing for Micra TPS, which includes noting the clinicaltrials.gov NCT number on the claims form (for more information regarding the requirement to add the NCT number to the claims form, see “Q4. How do I know if my hospital is enrolled in the CED Study as a site?”).

Participation in this training is for normal business processes, and the hospital is not considered engaged in research because of this training.
14. Why was a waiver of HIPAA granted?

The HIPAA requirement does not apply at the hospital level. The hospital will treat patients according to their own policies and standard of care, which will likely include releasing patient protected health information (PHI) to CMS for billing purposes. At this point, the data becomes CMS data and is no longer under the hospital’s HIPAA requirements.

The study will be carried out under a waiver of HIPAA authorization with respect to Medtronic and CMS. There are two components to this finding that are addressed in detail below — first that the study cannot be practicably carried out without the waiver, and second that proper measures are taken to minimize the risk of inadvertent access to the PHI.

The study cannot practicably be carried out without a waiver because of the requirement that CMS has that all Medicare patients that receive a Micra TPS leadless pacemaker in the United States be enrolled in the study. Having explicit informed consent would imply site level IRB review of the study at more than a thousand U.S. implanting centers, and seeking consent in tens of thousands of patients. Such a requirement would place a high burden on providers inconsistent with CMS intent and unduly limit access to this FDA-approved medical technology.

The following precautions will be taken to minimize risk of inadvertent access to the data:

- The protocol was approved by an Institutional Review Board, including review and approval of the waiver of HIPAA authorization.
- Only the minimum set of data needed to perform the research will be accessed.
- Data will be limited only to those who have a demonstrated need to access, and those who have access will sign a confidentiality agreement.
- Data will be stored only on secure electronic systems, not in paper format.
- PHI will be removed from the data set as early as possible (i.e., once CMS has matched the device registration data to the claims data), and final analyses will be performed on a de-identified data set.
- The de-identified data set will be hosted virtually by CMS and Medtronic does not take physical possession of the data set.

15. Who will have access to the results of the study?

It is the intent of Medtronic to make the results of this study transparent. First and foremost, Medtronic is obligated to report the results to CMS as a condition of coverage with evidence development. This analysis will be driven by the prospectively defined protocol that was approved both by CMS and by WIRB.

Information and results from the Micra TPS CED Study will be made publicly available in the following ways:

- ClinicalTrials.gov, a website listing information on clinical activities conducted worldwide.
- Peer-reviewed manuscripts will include but may not be limited to:
  - A primary manuscript of two-year follow-up based on the complete annual claims data files and quarterly files

To further strengthen the transparency of the results, Medtronic will use the Strengthening and Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies for reporting. STROBE represents a consensus of methodologists, researchers, and journal editors on recommendations for what should be included in an accurate and complete report of an observational study.
16. What is the FDA-approved labeling for Micra TPS?

Micra TPS is currently the only FDA-approved leadless pacing device. The FDA-approved labeling for Micra TPS can be located at http://manuals.medtronic.com/manuals/main/en_US/home/index and is as follows:

The Micra single chamber ventricular system is indicated for the following conditions:

- Symptomatic paroxysmal or permanent high-grade AV block in the presence of atrial fibrillation (AF)
- Symptomatic paroxysmal or permanent high-grade AV block in the absence of AF, as an alternative to dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy
- Symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy

Rate-responsive pacing is indicated to provide increased heart rate appropriate to increasing levels of activity.

Micra TPS is contraindicated for patients who have the following types of medical devices implanted:

- An implanted device that would interfere with the implant of the Micra™ device in the judgment of the implanting physician
- An implanted inferior vena cava filter
- A mechanical tricuspid valve
- An implanted cardiac device providing active cardiac therapy that may interfere with the sensing performance of the Micra device

The device is contraindicated for patients who have the following conditions:

- Femoral venous anatomy unable to accommodate a 7.8 mm (23 Fr) introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity)
- Morbid obesity that prevents the implanted device from obtaining telemetry communication within ≤ 12.5 cm (4.9 in)
- Known intolerance to the following materials: Titanium, titanium nitride, parylene C, primer for parylene C, PEEK, siloxane, nitinol, platinum, iridium, liquid silicone rubber, and silicone medical adhesive or to heparin, or sensitivity to contrast media that cannot be adequately premedicated

Steroid use — Do not use in patients for whom a single dose of 1.0 mg dexamethasone acetate cannot be tolerated.


17. Why did CMS require coverage with evidence development for Micra TPS?

While CMS indicated the evidence for leadless pacemakers is promising, they wanted to collect more data while allowing appropriate patient access. CMS wants data to address the following research questions:

1. What are the peri-procedural and post-procedural complications of leadless pacemakers?
2. What are the long-term outcomes of leadless pacemakers?
3. What are the effects of patient characteristics (age, gender, comorbidities) on the use and health effects of leadless pacemakers?

In addition, CMS outlined six evidentiary gaps in the final NCD for leadless pacemakers:

1. What are the peri-procedural and post-procedural complications, and long-term outcomes of leadless pacemakers?
2. Are leadless pacemakers equivalent or superior to conventional pacemakers in general clinical practice?
3. What are the infection rates, the long-term hemodynamic effects, and the rates of formation of thrombi?
4. What are the patient demographics and effects of patient characteristics (age, gender, comorbidities) on the use and health effects of leadless pacemakers?
5. What are the device-related issues (handling of end of battery life; effects of having multiple leadless pacemakers implanted; rate of device dislodgement; and the possibility of device extractions)?
6. How are operators and facility characteristics related to peri-procedural and post-procedural complications, and long-term outcomes of leadless pacemakers?
18. Whom should I contact for more information about the Micra TPS CED Study?

Please contact your local Medtronic Regional Economic Manager (REM). If you need to learn who is the REM for your institution, please contact your Medtronic sales representative, or send an email to: rs.healthcareeconomics@medtronic.com.

19. Whom should I contact if a payer continues to deny a prior authorization/predetermination or a Micra implant?

Send an email to: rs.healthcareeconomics@medtronic.com.

RESOURCES

CMS website with the Decision Memo for Leadless Pacing:

CMS website listing approved CED trials for leadless pacing:

CMS website listing notice of privacy practices for original Medicare:

Clinicaltrials.gov website with the Micra CED Study posting:

OHRP Guidance on Engagement of Institutions in Human Subjects Research

Other Attachments:
- WIRB Approval Letters (Version 1.0 (which contains the explicit waiver of consent) and Version 2.0 - Final)
- WIRB Letter with Clarification on Engagement of Institutions in this research
Brief Statement
Micra™ Transcatheter Pacing System VVIR Single Chamber with SureScan™ MRI

Indications
Micra Model MC1 VR01 is indicated for patients with:
- Symptomatic paroxysmal or permanent high grade AV block in the presence of AF
- Symptomatic paroxysmal or permanent high grade AV block in the absence of AF, as an alternative to dual chamber pacing when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy
- Symptomatic bradyarrhythmia-tachyarrhythmia syndrome or sinus node dysfunction (sinus bradycardia/sinus pauses), as an alternative to atrial or dual chamber pacing when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy

Rate-responsive pacing is indicated to provide increased heart rate appropriate to increasing levels of activity.

Contraindications
Micra Model MC1 VR01 is contraindicated for patients who have the following types of medical devices implanted: an implanted device that would interfere with the implant of the Micra device in the judgment of the implanting physician, an implanted inferior vena cava filter, a mechanical tricuspid valve, or an implanted cardiac device providing active cardiac therapy that may interfere with the sensing performance of the Micra device.

The device is contraindicated for patients who have the following conditions: femoral venous anatomy unable to accommodate a 7.8 mm (23 French) introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity), morbid obesity that prevents the implanted device from obtaining telemetry communication within ≤ 12.5 cm (4.9 in), or known intolerance to the materials listed in the Instructions for Use, or to heparin, or sensitivity to contrast media that cannot be adequately premedicated.

Warnings and Precautions
End of Service (EOS) — When the EOS condition is met, the clinician has the option of permanently programming the device to Off and leaving it in the heart, or retrieving the device, provided the device has not yet become encapsulated. Removal of the Micra device after it has become encapsulated may be difficult because of the development of fibrotic tissue. If removal of the device is required, it is recommended that the removal be performed by a clinician who has expertise in the removal of implanted leads.

MRI conditions for use — Before an MRI scan is performed on a patient implanted with the Micra device, the cardiology and radiology professionals involved in this procedure must understand the requirements specific to their tasks as defined in the device manuals.

Rate-responsive mode may not be appropriate for patients who cannot tolerate pacing rates above the programmed Lower Rate. Asynchronous VVIR pacing with sinus rhythm may interfere with the sensing performance of the Micra device.

The use of deactivated Micra devices in situ and an active Micra device, or an active transvenous pacemaker or defibrillator, has not been clinically tested to determine whether EMI or physical interaction is clinically significant. Bench testing supports that implantation of an active Micra device, or an active transvenous pacemaker or defibrillator, next to an inactivated Micra device is unlikely to cause EMI or physical interaction. Post-approval studies are planned to characterize risks of co-implanted, deactivated Micra devices. Currently recommended end of device life care for a Micra device may include the addition of a replacement device with or without explantation of the Micra device, which should be turned off.

Potential Complications
Potential complications include, but are not limited to, toxic/allergic reaction, oversensing, acceleration of tachycardia, myocardial infarction and surgical complications such as cardiac perforation, pericardial effusion, cardiac tamponade, death, device embolization, access site hematoma and AV fistulae, vessel spasm, infection, inflammation, and thrombosis.

See the device manuals for detailed information regarding the implant procedure, indications, contraindications, warnings, precautions, MRI conditions for use, and potential complications/adverse events. For further information, please call Medtronic at 1-800-328-2518 and/or consult the Medtronic website at medtronic.com.

Caution: Federal law (USA) restricts these devices to sale by or on the order of a physician.

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THE FOLLOWING WERE APPROVED

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BOARD ACTION DATE: 02/06/2017
PANEL: 5

STUDY APPROVAL EXPIRES: 02/06/2018
STUDY NUM: 1172233
WIRB PRO NUM: 20170198
ONLINE TRACKING: 11-1878360
INVEST NUM: 219218
WO NUM: 1-992522-1
CONTINUING REVIEW: Annually
SITE STATUS REPORTING: Annually

SPONSOR: Medtronic
PROTOCOL NUM: None
AMD. PRO. NUM: 
TITLE:
Longitudinal Coverage with Evidence Development Study on Micra TM Leadless Pacemakers (The Micra CED Study)

APPROVAL INCLUDES:
Investigator
Protocol (01-26-2017) Version 1.0
Financial Disclosure Form (01-20-2017) El-Chami

WIRB APPROVAL IS GRANTED SUBJECT TO:
The Board found that this research meets the requirements for a waiver of consent under 45 CFR 46.116(d).

WIRB HAS APPROVED THE FOLLOWING LOCATIONS TO BE USED IN THE RESEARCH:
Medtronic, 710 Medtronic Parkway NE, Minneapolis, Minnesota 55432

If the PI has an obligation to use another IRB for any site listed above and has not submitted a written statement from the other IRB acknowledging WIRB’s review of this research, please contact WIRB's Client Services department.

ALL WIRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

1. Conduct the research in accordance with the protocol, applicable laws and regulations, and the principles of research ethics as set forth in the Belmont Report.

2. Although a participant is not obliged to give his or her reasons for withdrawing prematurely from the clinical trial, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the participant’s rights.
3. Unless consent has been waived, conduct the informed consent process without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate. (Due to the unique circumstances of research conducted at international sites outside the United States and Canada, when there is a local IRB and WIRB approved materials are reviewed by the local IRB and translated into the local language, the following requirements regarding consent forms bearing the WIRB "APPROVED" stamp and regarding certification of translations are not applicable.)
   a. Use only the most current consent form bearing the WIRB "APPROVED" stamp.
   b. Provide non-English speaking subjects with a certified translation of the approved consent form in the subject's first language. The translation must be approved by WIRB unless other arrangements have been made and approved by WIRB.
   c. Obtain pre-approval from WIRB for use of recruitment materials and other materials provided to subjects.

4. Enrollment of limited readers and non-readers: unless consent has been waived or the protocol excludes enrollment of limited readers or non-readers, involve an impartial witness in the consent process when enrolling limited or non-readers and document the participation of the impartial witness using the designated signature lines on the WIRB-approved consent form. In the absence of designated signature lines, download the WIRB standard impartial witness form from www.wirb.com.

5. Enrollment of pregnant partners that do not have the capacity to consent for themselves and require consent be provided by a legally authorized representative: unless the protocol excludes the enrollment of pregnant partners that do not have capacity to consent for themselves, obtain consent from the pregnant partners legally authorized representative and document consent using the pregnant partner legally authorized representative signature lines on the WIRB-approved consent form. In the absence of designated signature lines, download the WIRB standard legally authorized pregnant partner form from www.wirb.com.

6. Obtain pre-approval from WIRB for changes in research.

7. Obtain pre-approval from WIRB for planned deviations and changes in research activity as follows:
   - If the research is federally funded, conducted under an FWA, or is a clinical investigation of a drug or biologic, then all planned protocol deviations must be submitted to WIRB for review and approval prior to implementation except where necessary to eliminate apparent immediate hazards to the human subjects [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7].
   - However, if the research is a clinical investigation of a device and the research is not federally funded and not conducted under an FWA, then only planned protocol deviations that may adversely affect the rights, safety or welfare of subjects or the integrity of the research data should be submitted to WIRB for review and approval prior to implementation except where necessary to eliminate apparent immediate hazards to the human subjects [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7].

The reason for these different requirements regarding planned protocol deviations is that the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) drug and biologic divisions have adopted the regulatory interpretation that every planned protocol deviation is a change in research that needs prior IRB review and approval before implementation; however, the FDA device division operates under a distinct regulation (See 21 CFR 812.150(a)(4).

Deviations necessary to eliminate apparent immediate hazards to the human subjects should be reported within 10 days.

8. Report the following information items to the IRB within 5 days:
   a. New or increased risk
   b. Protocol deviation that harmed a subject or placed subject at risk of harm
   c. Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject
   d. Audit, inspection, or inquiry by a federal agency
   e. Written reports of federal agencies (e.g., FDA Form 483)
   f. Allegation of Noncompliance or Finding of Noncompliance
   g. Breach of confidentiality
   h. Unresolved subject complaint
   i. Suspension or premature termination by the sponsor, investigator, or institution
   j. Incarceration of a subject in a research study not approved to involve prisoners
   k. Adverse events or IND safety reports that require a change to the protocol or consent
   l. State medical board actions
   m. Unanticipated adverse device effect
   n. Information where the sponsor requires prompt reporting to the IRB

Information not listed above does not require prompt reporting to WIRB.

Please go to www.wirb.com for complete definitions and forms for reporting.
9. Provide reports to WIRB concerning the progress of the research, when requested.

10. Ensure that prior to performing study-related duties, each member of the research study team has had training in the protection of human subjects appropriate to the processes required in the approved protocol.

   **Federal regulations require that WIRB conduct continuing review of approved research.** You will receive Continuing Review Report forms from WIRB. These reports must be returned even though your study may not have started.

**DISTRIBUTION OF COPIES:**

**Contact, Company**

Susan Nabhan, Medtronic
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NOTIFICATION TO SPONSOR/CRO OF BOARD ACTION

BOARD ACTION DATE: 03/08/2017
WIRB PROTOCOL NUMBER: 20170198
WORK ORDER NUMBER: 1-999478-1

PANEL: 5
APPROVAL EXPIRES: 02/06/2018
CONTINUING REVIEW: Annually

SPONSOR: Medtronic
PROTOCOL NUM: Micra CED
AMD. PRO. NUM: 
TITLE: Longitudinal Coverage with Evidence Development Study on Micra TM Leadless Pacemakers (The Micra CED Study)

APPROVAL INCLUDES:
Revised Protocol (03-03-2017) Version 2.0

THE BOARD DIRECTED THE FOLLOWING INFORMATION BE PLACED ON THE WIRB CERTIFICATE OF APPROVAL DOCUMENT FOR ANY INVESTIGATOR APPROVED BY WIRB TO CONDUCT THIS RESEARCH:

ALL WIRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

1. Conduct the research in accordance with the protocol, applicable laws and regulations, and the principles of research ethics as set forth in the Belmont Report.

2. Although a participant is not obliged to give his or her reasons for withdrawing prematurely from the clinical trial, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the participant’s rights.

3. Unless consent has been waived, conduct the informed consent process without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate. (Due to the unique circumstances of research conducted at international sites outside the United States and Canada, when there is a local IRB and WIRB approved materials are reviewed by the local IRB and translated into the local language, the following requirements regarding consent forms bearing the WIRB approval stamp and regarding certification of translations are not applicable.)
   a. Use only the most current consent form bearing the WIRB "APPROVED" stamp.
   b. Provide non-English speaking subjects with a certified translation of the approved consent form in the subject's first language. The translation must be approved by WIRB unless other arrangements have been made and approved by WIRB.
   c. Obtain pre-approval from WIRB for use of recruitment materials and other materials provided to subjects.

4. Enrollment of limited readers and non-readers: unless consent has been waived or the protocol excludes enrollment of limited readers or non-readers, involve an impartial witness in the consent process when enrolling limited or non-readers and document the participation of the impartial witness using the designated signature lines on the WIRB-approved consent form. In the absence of designated signature lines, download the WIRB standard impartial witness form from www.wirb.com.

5. Enrollment of pregnant partners that do not have the capacity to consent for themselves and require consent be provided by a legally authorized representative: unless the protocol excludes the enrollment of pregnant partners that do not have capacity to consent for themselves, obtain consent from the pregnant partners legally authorized representative and document consent using the pregnant partner legally authorized representative signature lines on the WIRB-approved consent form. In the absence of designated signature lines, download the WIRB standard legally authorized pregnant partner form from www.wirb.com.

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789
This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB), OHRP/FDA parent organization number IORG 0000432, IRB registration number IRB00000533. WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) REGULATIONS, AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.
6. Obtain pre-approval from WIRB for changes in research.

7. Obtain pre-approval from WIRB for planned deviations and changes in research activity as follows:
   - If the research is federally funded, conducted under an FWA, or is a clinical investigation of a drug or biologic, then all planned protocol deviations must be submitted to WIRB for review and approval prior to implementation except where necessary to eliminate apparent immediate hazards to the human subjects [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7).]
   - However, if the research is a clinical investigation of a device and the research is not federally funded and not conducted under an FWA, then only planned protocol deviations that may adversely affect the rights, safety or welfare of subjects or the integrity of the research data should be submitted to WIRB for review and approval prior to implementation except where necessary to eliminate apparent immediate hazards to the human subjects [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7).]

The reason for these different requirements regarding planned protocol deviations is that the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) drug and biologic divisions have adopted the regulatory interpretation that every planned protocol deviation is a change in research that needs prior IRB review and approval before implementation; however, the FDA device division operates under a distinct regulation (See 21 CFR 812.150(a)(4).

Deviations necessary to eliminate apparent immediate hazards to the human subjects should be reported within 10 days.

8. Report the following information items to the IRB within 5 days:
   a. New or increased risk
   b. Protocol deviation that harmed a subject or placed subject at risk of harm
   c. Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject
   d. Audit, inspection, or inquiry by a federal agency
   e. Written reports of federal agencies (e.g., FDA Form 483)
   f. Allegation of Noncompliance or Finding of Noncompliance
   g. Breach of confidentiality
   h. Unresolved subject complaint
   i. Suspension or premature termination by the sponsor, investigator, or institution
   j. Incarceration of a subject in a research study not approved to involve prisoners
   k. Adverse events or IND safety reports that require a change to the protocol or consent
   l. State medical board actions
   m. Unanticipated adverse device effect
   n. Information where the sponsor requires prompt reporting to the IRB

Information not listed above does not require prompt reporting to WIRB.

Please go to www.wirb.com for complete definitions and forms for reporting.

9. Provide reports to WIRB concerning the progress of the research, when requested.

10. Ensure that prior to performing study-related duties, each member of the research study team has had training in the protection of human subjects appropriate to the processes required in the approved protocol.

    Federal regulations require that WIRB conduct continuing review of approved research. You will receive Continuing Review Report forms from WIRB when the expiration date is approaching.

DISTRIBUTION OF COPIES:
Contact, Company
Susan Nabhan, Medtronic
Lindsay A. Bockstedt, Medtronic
April 13, 2017

To whom it may concern:

SUBJECT: REGULATORY OPINION LETTER—INSTITUTION NOT ENGAGED IN RESEARCH
Protocol Title: Longitudinal Coverage with Evidence Development Study on Micra TM Leadless Pacemakers (The Micra CED Study)

This letter is in response to Medtronic’s request for an opinion letter as to whether an institution would be engaged in research as a result of the institution providing private health information for the above referenced study.

This opinion is based on federal regulation 45 CFR 46 and associated guidance. The Office of Human Research Protections (OHRP) has issued guidance entitled “Guidance on Engagement of institutions in Human Subjects Research,” (2008) which describes when an institution is and is not engaged in research. This guidance is available at http://www.hhs.gov/ohrp/policy/engage08.html

Institutions would be considered not engaged in an HHS-conducted or -supported nonexempt human subjects research project (and, therefore, would not need to hold an OHRP-approved FWA or certify IRB review and approval to HHS) if the involvement of their employees or agents in that project is limited to one or more of the following:

Employees or agents will obtain identifiable private information about subjects for research purposes where the employees or agents will release to investigators at another organization identifiable private information about subjects.

Because institutions are only providing private health information about subjects to an investigator at another organization for this research, we would consider those institutions not engaged in research under the HHS regulations. However, WIRB cannot provide a formal regulatory opinion regarding individual institutions without the institution’s agreement to rely on WIRB. Many institutions have internal policies for making these decisions, and WIRB cannot provide an opinion for an institution that does not choose to use WIRB as an IRB.

If you have any questions, or if we can be of further assistance, please contact Christopher Gennai, CIP, at 360-252-2460, or e-mail CGennai@wirb.com.

CAG
Cc: Reece Holbrook, Medtronic
cc: Protocol File; Company File