China Micra™ Transcatheter Pacing Study

Clinical Investigation Plan (Version 3.0 19/Apr/2018)

NCT No.: NCT03624504

Clinical Investigation Plan	
Clinical Investigation Plan/Study Title	China Micra™ Transcatheter Pacing Study
Protocol No.	China Micra
Study Product Name	Micra™ Transcatheter Pacemaker System
Study Product Model/specification	MC1VR01
Category of investigational medical device	Class III
Class III medical devices requiring clinical trial approval	Yes
Similar product in China	No
Sponsor	Medtronic Inc. 710 Medtronic Parkway N.E., Minneapolis, MN 55432, U.S.A
Locol Sponsor(Agent)	Medtronic (Shanghai) Management Co., Ltd. 3rd Floor, No. 180. Rijing Road, China (Shanghai) Pilot Free Trade Zone, 200131, Shanghai, P.R.China
Document Version/Version Date	3.0/19/Apr/2018
Lead Principal Investigator(s)/Lead Study Site	Dr. Shu Zhang, Fuwai Hospital CAMS&PUMC No.167, Beilishi Road, Xicheng District, Beijing, China, 100037
Clinical Trial Institutions and Investigators	Refer to Appendix B-Clinical Trial Institutions and Investigators List

Confidential

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Tiger Ma/Sr.Clinical Research Specialist
2.0	• Revised the sample size • Revised the statistical method related section • Note: all the revised part in this version are based on the comments/suggestions from the statistical department of leading site.	Tiger Ma/Sr.Clinical Research Specialist
3.0	• Revised Micra Software version number • Corrected reporting timeline for suspending or terminating clinical trials, • [redacted] • Add cardiovascular medications collection at baseline • [redacted]	Frank Zhu/Principal Clinical Research Specialist

2. Investigator Statement

Study product Name	Micra™ Transcatheter Pacemaker System
Sponsor	Medtronic Inc.
Locol Sponsor(Agent)	Medtronic (Shanghai) Management Co., Ltd.
Version Number/Date	3.0/ 19/Apr/2018

I agree that:

1. I will conduct this clinical trial in strict compliance with the Declaration of Helsinki, current laws and regulations of China, and the requirements of the protocol;

2. And record all required data accurately on the Case Report Form (CRF) and complete the final report of the clinical trial on time;

3. The investigational medical device will be used only for this clinical trial and the receipt and use of the investigational medical device will be recorded completely and accurately and the records will be retained during the process of the clinical trial;

4. The monitor and verifier authorized or designated by the Sponsor and the regulatory authorities are allowed to conduct monitoring, verification and inspection for the clinical trial;

5. The clinical trial should be conducted in strict compliance with contract/articles of agreement signed by all parties.

I have already read the clinical study protocol, including the above statement and I fully agree all the above requirements. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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3. Glossary

Term	Definition
Addendum	An addition to an existing agreement, contract, protocol or Informed Consent.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. (ISO 14155:2011 section 3.1)
Adverse Event	See definition in the Table 12 for AE.
Audit	Systematic independent examination of activities and documents related to clinical investigation to determine whether these activities were conducted, and the data recorded, analyzed and accurately reported, according to the CIP, standard operating procedures, this International Standard and applicable regulatory requirements.
Case Report Forms (CRFs)	A paper or electronic data collection form, designed to collect information on each subject as required by the Study Protocol / Clinical Investigation Plan.
Charter	Document that describes the committee membership, roles and responsibilities, and processes to be utilized by the committee.
Clinical Data	Any data collected in a clinical study and stored in a study database or related database, including

Term	Definition
	device databases and clinical study records (e.g., subject questionnaires, discharge summaries, save-to-disk and informed consent documents).
Clinical Database	The compilation of data fields that store the data collected for a study.
Clinical Events Committee (CEC)	An independent committee of experts not participating in a clinical study that provides adjudication of study specific endpoints and/or events utilizing study-specific or consensus definitions available in the field.
Clinical Investigation Plan (CIP)	Document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation. Note: The term "protocol" is synonymous with "CIP". However, protocol has many different meanings, some not related to clinical investigation, and these can differ from country to country. Therefore, the term CIP is used in this International Standard.
Clinical Study Report (CSR)	A written description of a study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.
Clinical Study Synopsis	An outline of the general requirements and parameters of the study. The synopsis is used as a tool in developing the protocol as well as providing insight as to what resources may be required to conduct the study.
Close-out Visit (COV)	A final monitoring visit to a site conducted to obtain all required study-related information, and to review ongoing and future study-related investigator responsibilities (e.g., regulatory

Term	Definition
	inspector access, document archival, financial disclosure) per contractual agreements and relevant regulations.
Compliance (in relation to studies)	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
Consent Form	See Informed Consent.
Ethics Committee (EC)	Independent body whose responsibility is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation. Also known as the Institutional Review Board (IRB). Note: For the purposes of this International Standard, "ethics committee" is synonymous with "research ethics committee," "independent ethics committee" or "institutional review board". The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region.
Good Clinical Practice (GCP)	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical studies that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of study subjects are protected.
Implant	A device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. FDA may, in order to protect public health, determine that devices placed in subjects for shorter periods are also "implants" for purposes of this part.
Inclusion/ Exclusion Criteria	The medical or social standards determining whether a person may or may not be allowed to enter a clinical study. These criteria are based on

Term	Definition
	such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. The criteria are not used to reject people personally, but to identify appropriate participants and keep them safe.
Independent	Not involved in the conduct of a clinical investigation, except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest.
Informed Consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Inspection	The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and other resources that are deemed by the authority(ies) to be related to the clinical study and that may be located at the site of the study, at the sponsor's and/or contract research organization's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).
Institution	A person, other than an individual, who engages in the conduct of research on subjects or in the delivery of medical services to individuals as a primary activity or as an adjunct to providing residential or custodial care to humans. The term includes, for example, a hospital, retirement home, confinement facility, academic establishment, and device manufacturer.
Institutional Review Board (IRB)	Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of,

Term	Definition
	biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. Also known as Ethics Committee (EC).
Interim Monitoring Visit (IMV)	A site visit conducted during the execution phase of a clinical study to assure the Investigator's obligations to the study protocol/CIP are being fulfilled and the facilities used in the clinical study continue to be acceptable.
Investigational Device	A device, including a transitional device, which is the object of an investigation.
Investigational Site	Institution or site where the clinical investigation is carried out.
Investigational Product	A product (e.g., Device, Drug, Software) that is being evaluated in a clinical study and; is not approved/cleared, or is different from the approved/cleared form, or is being used for an unapproved or uncleared indication/use.
Investigator	A person responsible for the conduct of the clinical study at the study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Sub-Investigator.
Investigator's Brochure (IB)	A compilation of the clinical and nonclinical data on the study product(s) that is relevant to the study of the study product(s) in human subjects.
Investigator Site File (ISF)	A study-specific file maintained by the Principal Clinical Investigator, which contains all documentation specific to their clinical site. Also called a Site Regulatory Binder.

Term	Definition
Monitoring	Act of overseeing the progress of a clinical investigation and to ensure that it is conducted, recorded, and reported in accordance with the CIP, written procedures and the applicable regulatory requirements.
Monitoring Visit	A visit to a clinical study site by a qualified monitor for the purpose of performing a site qualification visit (SQV), site initiation visit (SIV), interim monitoring visit (IMV) or close out visit (COV) activities.
Protocol	See Clinical Investigation Plan.
Protocol Amendment	A written description of a change(s) to or formal clarification of a protocol.
Publication	A medical or scientific written or electronic summary of research work that is used to educate external audiences, such as HCPs, on the use(s) or benefit(s) of Medtronic products and therapies.
Publication Plan	The specific tasks and deliverables in order to execute on the publications strategy.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	See definition in the Table 12 for SAE.
Site Initiation Visit (SIV)	A site visit designed to document general site readiness, including but not limited to, a review of study procedures and the Investigator's responsibilities with the investigator and site personnel.
Site Initiation	The process of gathering regulatory documents and conducting the activities required to activate a site to enroll subjects in a clinical study. The initiation process begins after the site is selected to

Term	Definition
	participate in the clinical study.
Source Data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the clinical study. Source data are contained in source documents (original records or certified copies).
Source Documents /Documentation	Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).
Sponsor	An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical study.
Study Deviation	An event where the clinical investigator or site personnel did not conduct protocol required procedures according to the study protocol.
Sub-Investigator (Sub-I)	Any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions (e.g., associates, residents, research fellows). See also Investigator.
Subject/Study Subject	An individual who participates in a clinical study either as a recipient of the study product(s) or as a control.

Term	Definition
Suspension (study or site)	A temporary postponement of study activities related to enrollment and distribution of the product. (Possible for the total study or a single site.)
Termination (study or site)	Discontinuance, by sponsor or by withdrawal of EC or CFDA approval, of an investigation before completion.
Termination Letter	A letter terminating an agreement or contract.

4. Synopsis

Title	China Micra™ Transcatheter Pacing Study
Clinical Study Type	Pre-Market Approval
Product Name	Micra™ Transcatheter Pacemaker System
Sponsor	Medtronic Inc. 710 Medtronic Parkway N.E., Minneapolis, MN 55432, U.S.A
Local Sponsor(Agent)	Medtronic (Shanghai) Management Co., Ltd. 3rd Floor, No. 180. Rijing Road, China (Shanghai) Pilot Free Trade Zone, 200131, Shanghai, P.R.China
Investigation Purpose	To confirm the safety and efficacy of the Micra™ Transcatheter Pacing System in human use in China.
Product Status	CE mark was obtained in April 2015; FDA approval was obtained in April 2016. Investigational status in China
Primary Objective(s)	To demonstrate the Micra™ Transcatheter Pacing System (TPS) is safe by estimating the Micra™ TPS implant procedure and/or system related major complications free survival probabilities.
Secondary Objective(s)	1) To demonstrate the effectiveness of Micra™ Transcatheter Pacing System. 2) To summarize all adverse device effect throughout the study
[redacted]	[redacted]
Study Design	The China Micra™ Transcatheter Pacing Study is a prospective, multi-center, single arm human clinical trial utilizing Objective Performance Criterion(OPC) to confirm the safety and efficacy profile of the Micra system for regulatory approval in China. All study sites will be in China. Subjects successfully implanted with the Micra system in all sites will be followed at implant/pre-discharge, 1-month, 3-months, and 6-months, and at 6-month intervals thereafter (if applicable) through study closure. The overall follow-up period of China Micra™ Transcatheter Pacing Study will end when the last enrolled patient has 6 month follow-up.

Sample Size	Based on statistical calculations, the study will enroll 82 subjects in total. (The definition of subject enrolled is that subject signed on the Informed Consent Form and the subject met all the inclusion criteria and none of the exclusion criteria.)All implanted subjects are expected to complete 6 months post implant follow-up visits.
Inclusion/Exclusion Criteria	**Inclusion Criteria** 1) Subjects who have a Class I or II indication for implantation of a single chamber ventricular pacemaker according to ACC/AHA/HRS 2008 guidelines and China guideline 2) Subjects who are willing to participate in study through consent and willing to undergo study specific required procedures with expectancy of geographically stable for follow up duration. 3) Subjects who are at least 18 years of age. **Exclusion Criteria** 1) Subject has an existing or prior pacemaker, ICD or CRT device implant. 2) Subject has unstable angina pectoris or has had an acute myocardial infarction (AMI) in the 30 days prior to eligibility assessment. 3) Subjects with current implantation of neurostimulator or any other chronically implanted device which uses current in the body. Note that a temporary pacing wire is allowed. 4) Subjects with a mechanical tricuspid valve, implanted vena cava filter, or left ventricular assist device (LVAD). 5) Subjects who are morbidly obese and physician believes telemetry communication of ⩽5 inches (12.5 cm) could not be obtained with programmer head. 6) Subjects whose femoral venous anatomy is unable to accommodate a 23 French introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity) in the opinion of the implanter. 7) Subjects who are considered as unable to tolerate an urgent sternotomy 8) Subjects with a known intolerance to Nickel-Titanium (Nitinol) Alloy. 9) Subjects for whom a single dose of 1.0mg dexamethasone acetate may be contraindicated. 10) Subjects with a life expectancy of less than 12-months. 11) Subjects who are currently enrolled or planning to participate in a

	potentially confounding drug or device trial during the course of this study. Co-enrollment in concurrent trials is only allowed when document pre-approval is obtained from the Medtronic study manager. 12) Pregnant women or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth regulation method or abstinence. 13) Subjects with exclusion criteria required by local law (age or other). 14) Subjects with medical condition which precludes patient from participation in the opinion of the Investigator
Study Procedures and Assessments	Subjects successfully implanted with the Micra system in all sites will be followed at implant/pre-discharge, 1-month, 3-months, and 6-months, and at 6-month intervals thereafter (if applicable) through study closure.
Safety Assessments	Adverse Events will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the sites' Ethics Committee.

5. Introduction

5.1. Background

Since their introduction in the 1960s, pacemakers have steadily shrunk in size and grown in sophistication, yet their basic function remains the same. The job of the pacemaker is to provide life-sustaining therapy by sustaining a normal heart rhythm when the heart rhythm gets too slow. Pacemaker treatment for bradycardia is frequently used, with more than 600,000 people worldwide receiving a cardiac pacemaker each year.[1] Pacemakers remain the only known, long term effective treatment for bradycardia.[2]

Conventional pacing systems consist of a pacemaker device containing the electronics and battery typically implanted in a subcutaneous pocket in the chest region, and a lead threaded from the device pocket through veins into the heart, that conducts the pacing therapy to the desired pacing site. Technology advances in electronics miniaturization and battery chemistries have now made it possible for

[1] Mallela et al, Indian Pacing Electrophysiol J. 2004 Oct-Dec; 4(4): 201–212.

[2] Gilles et al, HRS/ACCF Expert Consensus Statement on Pacemaker Device and Mode Selection, Heart Rhythm Volume 9, Issue 8 , Pages 1344-1365, August 2012

Medtronic to develop a device small enough to implant within the heart while still providing similar battery longevity.

The Micra system leverages both existing and new technologies. The basis for the pacemaker capsule comes from a long history of providing basic bradycardia pacing therapy via transvenous lead based systems. The new technology in the Micra system is made possible due to market advances in miniaturization technologies (high density battery), catheter delivery systems, novel materials (nitinol), and placing the electrodes directly on the pacemaker capsule.

The Micra Transcatheter Pacing System is a miniaturized single chamber pacemaker system that is delivered via catheter through the femoral vein and is implanted directly inside the right ventricle of the heart. The Micra device eliminates the need for a device pocket and insertion of a pacing lead, thereby potentially eliminating complications associated with traditional pacing systems while providing similar pacing benefits.

Extensive pre-clinical testing has been conducted to mitigate risks for potential hazards / risks from a product lifecycle perspective. A summary of pre-clinical testing results is provided in the Investigator Brochure (provided under separate cover), showing acceptable electrical and mechanical performance. The primary supporting body of preclinical testing evidence which demonstrates safety to begin implanting in humans includes the Inc2 GLP animal study, bench testing and modeling.

A comprehensive risk assessment identified all potential hazards / risks associated with the Micra system throughout the product life cycle compared to existing single chamber pacemakers. The comparison found there are many similarities between an existing single chamber pacemaker and Micra system; however, the Micra system reduces or eliminates a number of risks that are primarily attributed to elimination of the need for a device pocket and lead, with the tradeoff of a limited number of new risks introduced by the Micra system. The results of pre-clinical testing demonstrate the probable benefits of the Micra system outweigh potential risks, demonstrating reasonable assurance of safety to proceed with implanting in humans. The findings from pre-clinical testing were confirmed in the global human study.

In the global human study, 719 patients were implanted from 725 implant attempts. The Micra pacemaker performed as expected, and the primary efficacy objective was passed, demonstrating low and stable thresholds from implant to 6 months. The primary safety objective was also met, demonstrating a low rate of major complications. The safety profile of Micra was compared to a historical control comprised of six previous pacing studies. Micra safety appeared to be as good as or better than the historical control. Based on the results from the global human study, CE mark was obtained in April 2015, and FDA approval was obtained in April 2016.

5.2. Purpose

Medtronic (Shanghai) Management Co., Ltd. is sponsoring the China Micra™ Transcatheter Pacing (Micra system) study in China. This study is a prospective, multi-site, single arm human clinical trial utilizing Objective Performance Criterion (OPC) to confirm the safety and efficacy of the Micra™ Transcatheter Pacing System in human use in China. This study is expected to begin as a pre-market study using investigational product in China.

6. Objectives and Endpoints

6.1. Objectives

The analysis for the MICRA study objectives will be conducted when study required minimum sample size is reached. The study will have one primary objective ,two secondary objectives and [redacted] to provide summary statistics on safety and efficacy of the Micra™ Transcatheter Pacing system in human use in China.

6.1.1. Primary Objective

To demonstrate the Micra™ Transcatheter Pacing System (TPS) is safe by estimating the Micra TPS implant procedure and/or system related major complications free survival probability through 6 month post implant.

6.1.2. Secondary Objective

1) To demonstrate the effectiveness of Micra™ Transcatheter Pacing System
2) To summarize all adverse device effect throughout the study

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoint

The study primary endpoint is defined as a subject's first occurrence of a major complication related to the Micra system and/or Micra procedure as determined by the CEC that occurs on or prior to 6-months (183-days) post-implant.

Major complications are those adverse events resulting in:

- Death
- Permanent loss of device function due to mechanical or electrical dysfunction of the device (e.g. pacing function disabled, leaving device abandoned electrically)
- System revision (reposition, replacement, explant)
- Hospitalization
- Prolonged Hospitalization by 48 hours or more

NOTE: Only system or procedure related AEs will be classified as a major complication, minor complication or an observation

In the Micra TPS Global clinical study, a total of 725 subjects underwent Micra TPS implant attempt with 719 subjects successfully implanted with the Micra system. There were a total of 28 system/procedure related major complications (in 25 subjects) reported. The Kaplan-Meier estimate for the freedom from major complications related to Micra system or procedure at 6-months (183 days) post-implant was 96.0% (98.66% CI: 93.3% - 97.6%). Table 1 provides a summary of all reported complications and the 28 major complications that counted against the study primary endpoint.

Table 1: System and/or Procedure Related Complications Observed in the Micra TPS Global clinical sStudy

	No. Events (No. Subjects, %)	
Adverse Event Keyterm	**All Complications**	**Major Complications**
TOTAL EVENTS	**54 (48, 6.62%)**	**28 (25, 3.45%)**
CARDIAC ARRHYTHMIAS	**7 (7, 0.97%)**	**0 (0, 0%)**
ATRIOVENTRICULAR BLOCK COMPLETE	5 (5, 0.69%)	0 (0, 0%)
VENTRICULAR FIBRILLATION	1 (1, 0.14%)	0 (0, 0%)
VENTRICULAR TACHYCARDIA	1 (1, 0.14%)	0 (0, 0%)
EMBOLISM AND THROMBOSIS	**3 (3, 0.41%)**	**2 (2, 0.28%)**
DEEP VEIN THROMBOSIS	2 (2, 0.28%)	1 (1, 0.14%)
PULMONARY EMBOLISM	1 (1, 0.14%)	1 (1, 0.14%)
EVENTS AT GROIN PUNCTURE SITE	**11 (11, 1.52%)**	**5 (5, 0.69%)**
ARTERIAL INJURY	1 (1, 0.14%)	0 (0, 0%)
ARTERIOVENOUS FISTULA	4 (4, 0.55%)	4 (4, 0.55%)
INCISION SITE HAEMATOMA	1 (1, 0.14%)	0 (0, 0%)
INCISION SITE HAEMORRHAGE	2 (2, 0.28%)	0 (0, 0%)
INCISIONAL DRAINAGE	2 (2, 0.28%)	0 (0, 0%)
VASCULAR PSEUDOANEURYSM	1 (1, 0.14%)	1 (1, 0.14%)
TRAUMATIC CARDIAC INJURY	**12 (12, 1.66%)**	**11 (11, 1.52%)**
CARDIAC PERFORATION	3 (3, 0.41%)	3 (3, 0.41%)
PERICARDIAL EFFUSION	9 (9, 1.24%)	8 (8, 1.10%)

	No. Events (No. Subjects, %)	
Adverse Event Keyterm	**All Complications**	**Major Complications**
PACING ISSUES	**2 (2, 0.28%)**	**2 (2, 0.28%)**
DEVICE DISLOCATION	1 (1, 0.14%)	1 (1, 0.14%)
DEVICE PACING ISSUE	1 (1, 0.14%)	1 (1, 0.14%)
OTHER	**19 (19, 2.62%)**	**8 (8, 1.10%)**
ACUTE MYOCARDIAL INFARCTION	1 (1, 0.14%)	1 (1, 0.14%)
CARDIAC FAILURE	3 (3, 0.41%)	3 (3, 0.41%)
HYPOTENSION	3 (3, 0.41%)	0 (0, 0%)
MEDICATION ERROR	2 (2, 0.28%)	0 (0, 0%)
METABOLIC ACIDOSIS	1 (1, 0.14%)	1 (1, 0.14%)
NON-CARDIAC CHEST PAIN	1 (1, 0.14%)	0 (0, 0%)
OSTEOARTHRITIS	1 (1, 0.14%)	0 (0, 0%)
PACEMAKER SYNDROME	1 (1, 0.14%)	1 (1, 0.14%)
PERICARDITIS	1 (1, 0.14%)	0 (0, 0%)
PRESYNCOPE	3 (3, 0.41%)	1 (1, 0.14%)
SYNCOPE	1 (1, 0.14%)	1 (1, 0.14%)
URINARY RETENTION	1 (1, 0.14%)	0 (0, 0%)

[1]Increased pacing capture threshold described as micro-dislodgement by investigator. Chest X-ray showed device was in place.

6.2.2. Sencondary Endpoint

- Secondary Endpoint #1

The effectiveness of the Micra TPS will be characterized by pacing capture thresholds, impedance and sensing amplitudes at implant and all follow-up visits (i.e. 1 month, 3 months and 6 months).

It is expected that majority of the subjects will have pacing capture thresholds $\leqslant$ 2 Volts at all visits. Pacing impedance and sensing amplitude will be stable over time.

- Secondary Endpoint #2

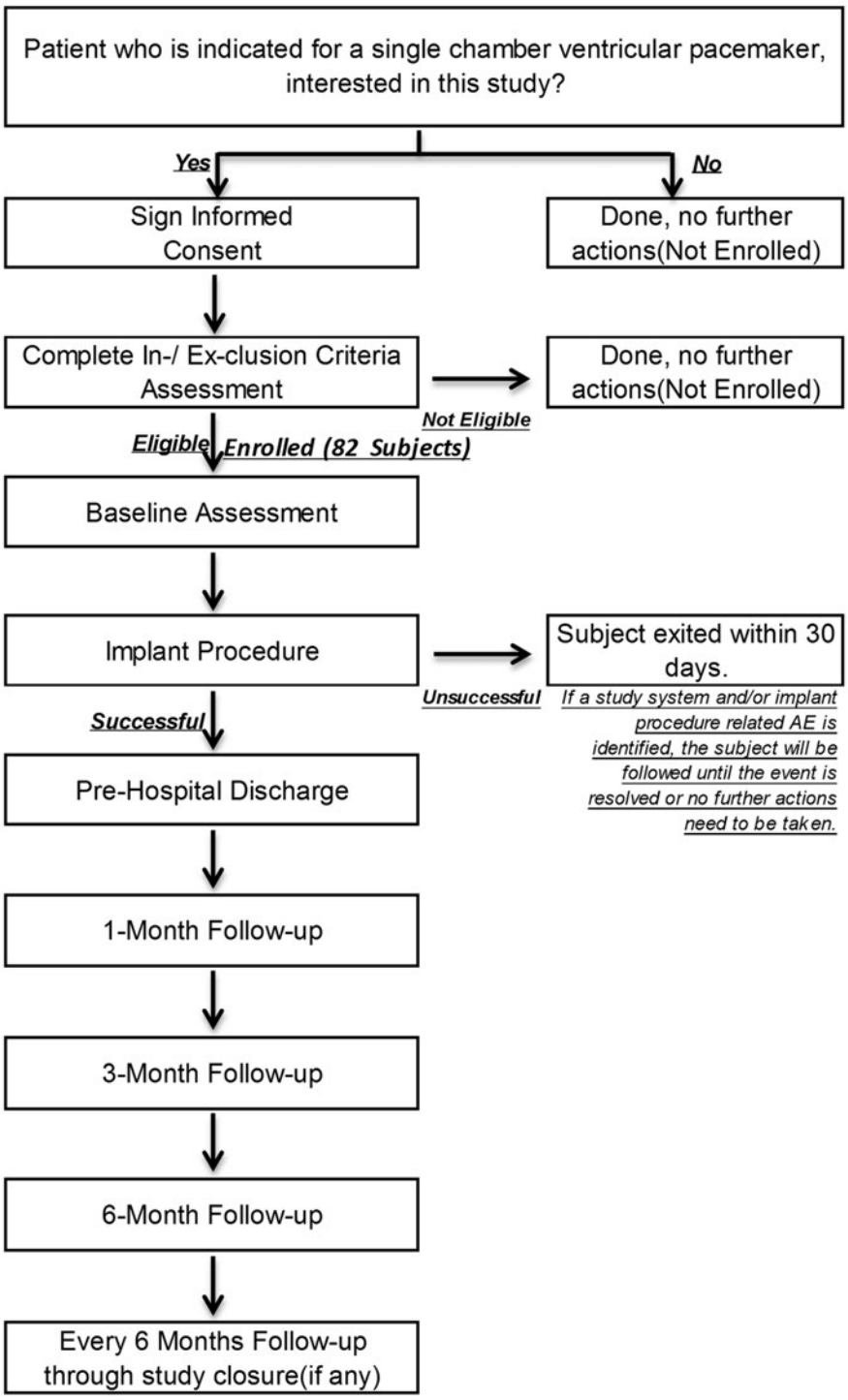
All procedure and/or system related adverse events are collected throughout the duration of this study.

Adverse events will be reported by event term, and based on relatedness to procedure/system and event severity.

7. Study Design

The China Micra™ Transcatheter Pacing Study is a prospective, multi-center, single arm human clinical trial ultizing OPC to confirm the safety and efficacy profile of the Micra system for regulatory approval in China. All study sites will be in China. All study sites and Investigators are listed in Appendix B. Subjects successfully implanted with the Micra system in all sites will be followed at implant/pre-discharge, 1-month, 3-months, and 6-months, and at 6-month intervals thereafter (if applicable) through study closure. The overall follow-up period of China Micra™ Transcatheter Pacing Study will end when the last enrolled patient has 6 month follow-up.

Figure 1: Study Flow Chart



7.1. Duration

The China Micra™ Transcatheter Pacing study will be conducted at 7 sites in China. The study will enroll 82 subjects in total. All subjects with chronically implanted Micra are expected to complete 6 months post implant follow-up visits for the study objective analyses.

It is estimated that study enrollment will be completed in 6 months. The estimated participation duration of each subject will be from 6 month to 12 month if the enrollment can be completed within 6 months. The estimatied duration of whole clinical trial will be approximately 1 year including 6 months enrollment and 6 months follow-up.

7.2. Rationale

Extensive pre-clinical testing has been conducted to mitigate risks for potential hazards / risks from a product lifecycle perspective. A summary of pre-clinical testing results is provided in the Investigator Brochure (provided under separate cover), showing acceptable electrical and mechanical performance. The primary supporting body of preclinical testing evidence which demonstrates safety to begin implanting in humans includes the Inc2 GLP animal study, bench testing and modeling.

A comprehensive risk assessment identified all potential hazards / risks associated with the Micra system throughout the product life cycle compared to existing single chamber pacemakers. The comparison found there are many similarities between an existing single chamber pacemaker and Micra system; however, the Micra system reduces or eliminates a number of risks that are primarily attributed to elimination of the need for a device pocket and lead, with the tradeoff of a limited number of new risks introduced by the Micra system. The results of pre-clinical testing demonstrate the probable benefits of the Micra system outweigh potential risks, demonstrating reasonable assurance of safety to proceed with implanting in humans. The findings from pre-clinical testing were confirmed in the global human study.

In the global human study, 719 patients were implanted from 725 implant attempts. The Micra pacemaker performed as expected, and the primary efficacy objective was passed, demonstrating low and stable thresholds from implant to 6 months. The primary safety objective was also met, demonstrating a low rate of major complications. The safety profile of Micra was compared to a historical control comprised of six previous pacing studies. Micra safety appeared to be as good as or better than the historical control. Based on the results from the global human study, CE mark was obtained in April 2015, and FDA approval was obtained in April 2016.

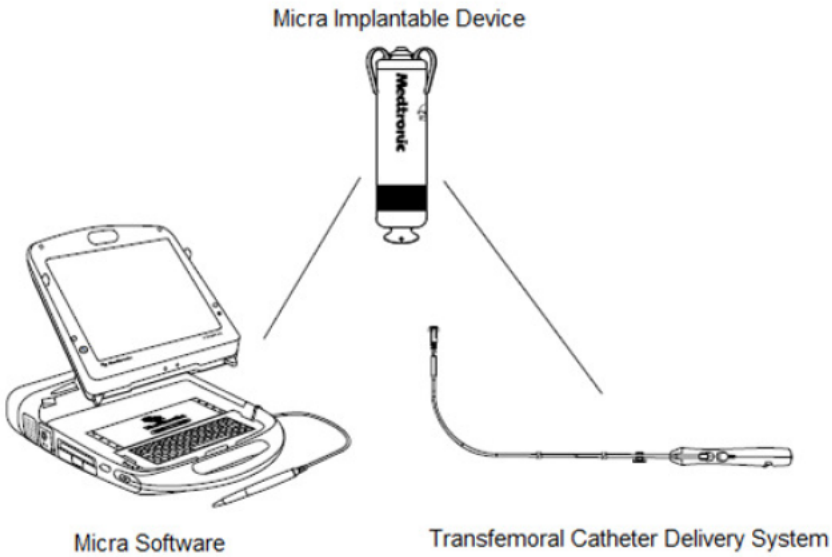
8. Product Description

The study will be conducted using the components described in the table below. Instructions for use are provided in the respective device manuals; each of the system components are manufactured by Medtronic. Refer to the respective manuals for any possible interaction with concurrent medical interventions.

Table 2 : System component information

Model Number	Component	System or Accessory Component	Investigational or Commercially Available at Study Start
System Components			
MC1VR01	Micra™ Implantable Device and Transfemoral Catheter Delivery System	System	Investigational
SW022	Micra Software	System	Investigational
Accessory Components			
MI2355A	Micra™ Introducer Sheath	Accessory	Investigational
2090 Series	Standard Medtronic Programmer	Accessory	Investigational Micra software Model Investigational SW022 is downloaded onto programmer

Figure **2**: Micra System



Instructions for intended use, including indications and contraindications of the components used in this study, as well as medical procedures and information regarding material in contact with tissues or body fluids are provided in their respective manuals. The methods used to diagnose, indicate and treat a patient with the Micra device are similar to those for commercially-available single chamber pacemakers. Detailed descriptions of the system and accessory components are listed in the sections below. And the labeling will be developed according to local requirements

8.1. Micra™ Implantable Device

The Micra™ implantable device is a self-contained, hermetically enclosed, miniaturized single chamber pacemaker. The device is fixated via four electrically inactive nitinol tines, located on the distal end of the device.

Figure 3: Micra™ Implantable Device

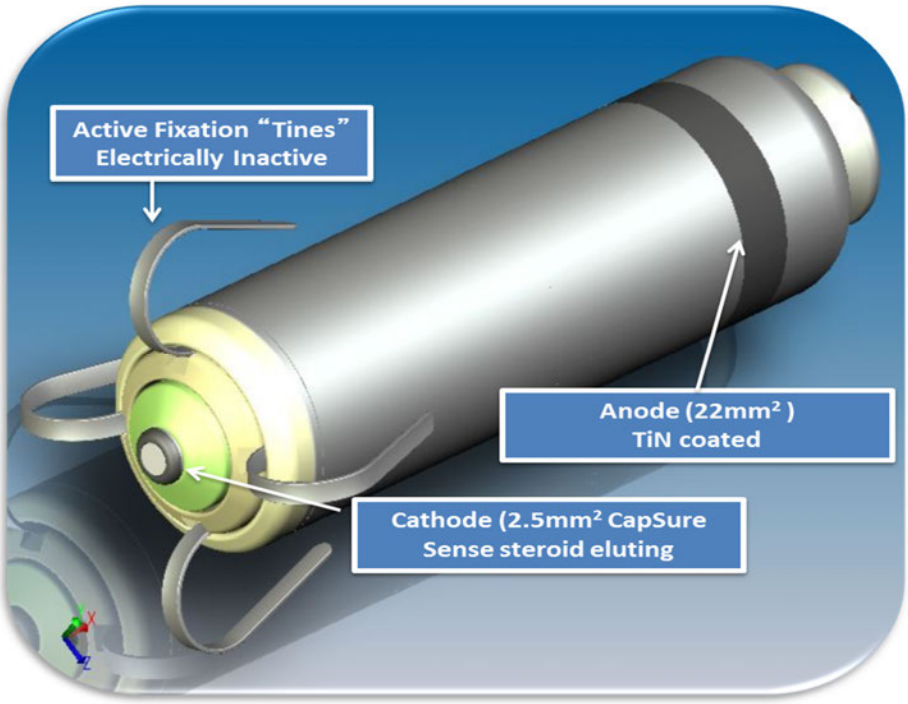


Table 3: Micra™ Implantable Device Specifications

Volume	1.0 cc
Length	25.9 mm
Outer diameter	6.7 mm
Mass	1.75 g

Steroid	Dexamethasone acetate, < 1.0 mg, MCRD release mechanism
Fixation mechanism	Nitinol tines
Battery	Lithium silver vanadium oxide with carbon monofluoride
Nominal pacing cathode	2.5 mm^2, Pt sintered, TiN coated (CapSure Sense)
Minimum pacing anode	22 mm^2, TiN coated
Cathode to anode spacing	18 (+/- 1.5) mm

Despite the differences in size and shape, the Micra device is very similar to standard Medtronic pacemakers in regards to functionality and features. The VVIR pacing therapy delivered by the Micra device is comparable to that delivered by a conventional bradycardia lead such as the Medtronic 4074 in conjunction with a conventional single chamber pacemaker such as the Medtronic Adapta ADSR01. The primary differences in functionality between Micra and standard Medtronic single chamber pacemakers are:

- Rate response: Micra activity sensor is now located within the heart versus the subcutaneous pocket. The device filters cardiac motion during rest from the higher levels of motion occurring during activity. In addition, Micra offers three-axis accelerometer sensor to allow the physician to select an alternate axis to sense activity if the default axis provides suboptimal performance.
- Capture management: Micra expands on Adapta's capture management feature by automatically conducting hourly safety margin confirmation to ensure pacing outputs remain at safe levels while adapting programmed outputs to maximize battery longevity. As battery longevity is also related to pulse durations, the Micra device will be optimized by setting the nominal pulse width duration to chronaxie (0.24ms). The capture management algorithm will run at either 0.24ms (nominal value) or 0.4ms, although other pulse width settings are available.
- End-of-Service (EOS) operation: Micra can be permanently programmed "OFF to OOO mode"(Non-Working Mode) such that the device does not pace or sense. When the battery voltage reaches the EOS condition, the device permanently deactivates pacing and sensing and switches to the device "OFF to OOO mode".

A comparison of Micra to Medtronic's Adapta ADSR01 single chamber pacemaker is provided in Table 4. Micra uses the same electrode design and identical steroid component as the Medtronic Model 4074 pacing lead.

Table 4: Comparison of Micra to Predicate Single Chamber Pacemaker

Attribute	Adapta ADSR01	Micra MC1VR01

Volume (cc)	9.7	1.0 cc
Mass (g)	21.5	1.75
Connector	IS-1	Integrated Pacing Electrode
Battery Chemistry/Capacity	Lithium-iodine, 830 mA-hr	Lithium silver vanadium oxide/carbon monoflouride, 120 mA-hr
Ventricular High Rate Episodes with EGM	Yes	No
Magnet Mode	Yes	No magnet mode*
Prolonged Service Period	3 months	6 months
Rate Response	Single axis accelerometer within subcutaneous pocket	Three individually selectable axes within right ventricle.
Capture Management	Periodic	Periodic, Hourly safety margin confirmation
Threshold Measurement and Tracking	Measure 1/day, Output Max. of 2X threshold or 2.0V	Measure 1/day, Verify 1/hour. Output Threshold + 0.5V
Maximum Pacing Output	7.5V	5. 0V
EOS Behavior	Pace until Battery Depleted	Mode-switch to OOO at EOS
Ability to inactivate device at EOS	No	Yes---with programmer

* The purpose of magnet mode is to allow a clinician to evaluate the sufficiency of the safety margin and the status of the device's battery longevity in the absence of a programmer. This is not necessary in Micra as the device automatically conducts safety margin confirmations on an hourly basis. Device longevity estimates are available via programmer.

Micra device longevity is equal or better than predicate devices at low thresholds but is more sensitive to higher thresholds. It is important to ensure low pacing outputs to optimize Micra longevity. Micra

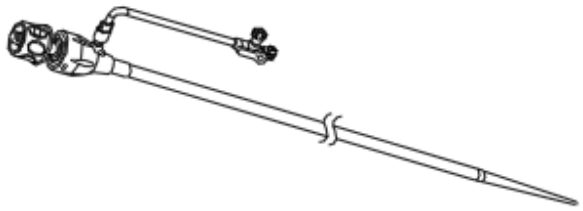
capture management will run an hourly threshold verification test and have a nominal pulse width threshold setting of 0.24ms (chronaxie) to maximize longevity. Micra device longevity is estimated at:

- 7.1 years at a 2.0V output, 60bpm, 100% paced, or
- 9.6 years at 1.5V output, 60bpm, 100% paced

8.2. Micra Introducer

The Micra Introducer is a single-use, disposable, hydrophilic coated sheath that will be used in this study to provide a flexible and hemostatic conduit for the insertion of the Micra device. The introducer system is comprised of 2 components: a dilator which accommodates a 0.035 in (0.89 mm) guide wire, and an introducer sheath. The introducer is comprised of a hydrophilic, coil-reinforced sheath that is attached to a rigid seal housing containing the hemostatic valve assembly. A side port extension with a 3-way valve is permanently attached to the seal housing. A radiopaque marker band is located at the distal tip of the sheath. The Micra introducer also has a suture loop for attaching it to the patient.

Figure 4: Micra Introducer



8.3. Transfemoral Catheter Delivery System

The Micra device is placed via a catheter delivery system through the femoral vein. This delivery approach is similar to other devices which are commonly placed in many geographies today via large caliber catheter systems in the femoral vein, such as:

- Medtronic's Melody transcatheter valve (pulmonic valve), delivered via the 22 French Ensemble delivery system
- Abbott Vascular's MitraClip Delivery System for mitral valve repair, delivered via 24 French Steerable guide catheter

The single use Micra transfemoral catheter delivery system consists of the delivery catheter required to deliver, deploy, and test the Micra device placement. It is constructed of two braided shaft assemblies, one placed inside another and attached to a handle at the proximal end. The distal end of the system can be articulated by activating a button on the handle. The Micra™ device sits inside a cup at the distal end of the catheter and is deployed by activating a button on the handle. The Micra™ device is locked to the delivery system by means of a tether that goes through the proximal end of the device, through the braided shafts to the handle, and can be released (or locked) by means of a button on the handle. The delivery system is used in conjunction with a 23Fr introducer sheath.

Key characteristics of the delivery system include:

- 23Fr delivery system with fixed shape distal curve

- Inner and outer braided shafts attached to handle
- Device Cup to hold device with a recapture cone on the inner shaft
- Tether lock mechanism for Micra device
- Flushing port on handle
- Off-plane distal articulation

8.4. Programmer Software and Medtronic 2090 Programmer

The Micra device communicates with the programmer using the standard Medtronic Model 2090 Programmer. A standard programming head, Model 2067 or Model 2067L, using standard telemetry B is required for communication from the device to the programmer.

Unique SW022 software, needs to be installed on the programmer. This software can be installed on the programmer via an installation kit or through the Medtronic Software Distribution Network (SDN). Using the SDN requires the site and/or Medtronic support to provide the study sponsor with the serial number of the programmer(s) that are planned to be used in the Micra Transcatheter Pacing Study.

In China, the Micra application software is investigational, and loaded on the Medtronic 2090 programmer, that programmer will be labeled to indicate that it contains investigational software. The Micra application software that was installed with investigational status will continue to be considered investigational when used to support the investigational Micra devices.

8.5. Investigational Product Receipt/Tracking/Storage/Accountability

Device and Software Disposition logs will be provided to the site and will be used for tracking of all investigational products.

These logs must be maintained at each investigational site to ensure traceability via assigned lot or serial numbers. It is the responsibility of the investigator to correctly handle, store, and track the investigational products. Disposition of investigational product will be reported when any of these investigational products are received, opened, implanted, explanted, disposed of or returned to Medtronic and will be sent to Medtronic each time it is updated.

Investigational product will be distributed to a site only when Medtronic has received all required documentation, has notified the site of site activation and the site has been authorized to enroll in the study. Distribution of the investigational product to study sites during the clinical study will be managed by Medtronic. Investigational product can only be ordered by Medtronic personnel. Investigational product must be stored in a secure location at the site. Investigational products will be used only in the study according to the CIP.

8.6. Investigational Product Return

All explanted product should be returned to Medtronic for analysis when permissible by local laws and regulations. If the products are explanted but not returned, a justification is required to be reported on the appropriate case report form(s) or disposition log(s). To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel. All unused investigational product must be returned to Medtronic upon study closure at the site, The Investigational Product Disposition Log must be updated with the final device disposition.

8.7. Product Training Requirements

All implanters in the study will be experienced in the implant of pacemaker systems and receive standardized training for the implant of the Micra system. Prior to performing the implant procedure, it is important that all implaters read and understand the Instructions for Use that accompanies the device. They must also undergo documented training by Medtronic. A summary of the implant procedure steps is provided in Appendix D.

9. Selection of Subjects

9.1. Study Population

China Micra™ Transcatheter Pacing study will be conducted in China, thus, the study population to be enrolled in the study will be only from Chinese patient.

9.2. Subject Enrollment

- Ethics Committee approval of the China Micra™ Transcatheter Pacing Study Clinical Investigation Plan and Informed Consent Form must be obtained prior to enrolling patients in the study.
- Subjects are considered enrolled in the study upon signing the informed consent and meet all of the inclusion and none of the exclusion criteria. Informed consent must be obtained prior to performing any study-related procedures. Subjects will be assessed to ensure that they meet all of the inclusion and none of the exclusion criteria

9.3. Inclusion Criteria

Table 5: Inclusion Criteria

INCLUSION Criteria	
Criteria	**Rationale**
Subjects who have a Class I or II indication for implantation of a single chamber ventricular pacemaker according to ACC/AHA/HRS 2008 guidelines and China guideline[3,4]	Study will be evaluated in the standard patient population that is actually indicated for the device under evaluation.
Subjects who are willing to participate in study through consent and willing to undergo study specific required procedures with expectancy of geographically stable for follow up duration.	Ensure ascertainment of data required for clinical evaluation.
Subjects who are at least 18 years of age.	Ensure age is appropriate to provide informed consent.

9.4. Exclusion Criteria

Table 6: Exclusion Criteria

EXCLUSION Criteria	
Criteria	**Rationale**
Subject has an existing or prior pacemaker, ICD or CRT device implant.	Avoid possible confounding factors (i.e. complications due to device change-outs).
Subject has unstable angina pectoris or has had an acute myocardial infarction (AMI) in the 30 days prior to eligibility assessment.	Avoid possible confounding factors (i.e. environment more susceptible to complications due to pre-existing conditions).

[3] Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 Guidelines for Device-based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). 2008.

[4] Europace 2006 8. 746-837 doi:10.1093/europace/eul108

Subjects with current implantation of neurostimulator or any other *chronically* implanted device which uses current in the body. Note that a *temporary* pacing wire is allowed.	Necessary to avoid any possible electrical interference with Micra device.
Subjects with a mechanical tricuspid valve, implanted vena cava filter, or left ventricular assist device (LVAD).	Necessary to avoid electrical or mechanical interference when placing Micra device.
Subjects who are morbidly obese and physician believes telemetry communication of ≤5 inches (12.5 cm) could not be obtained with programmer head.	Necessary to ensure ability to communicate with programmer.
Subjects whose femoral venous anatomy is unable to accommodate a 23 French introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity) in the opinion of the implanter.	Necessary to place Micra introducer sheath.
Subjects who are considered as unable to tolerate an urgent sternotomy	Necessary in case of emergency where urgent vascular surgery would be required
Subjects with a known intolerance to Nickel-Titanium (Nitinol) Alloy.	Necessary since Micra tines are comprised of Nitinol material.
Subjects for whom a single dose of 1.0mg dexamethasone acetate may be contraindicated.	Necessary due to steroid material on Micra electrode (standard exclusion for all pacing studies with steroid on the electrode).
Subjects with a life expectancy of less than 12-months.	Standard exclusion criteria to ensure study cohort is expected to survive to the time of endpoint evaluation.
Subjects who are currently enrolled or planning to participate in a potentially confounding drug or device trial during the course of this study. Co-enrollment in concurrent trials is only allowed when document pre-approval is obtained from the Medtronic study manager.	Standard exclusion criteria to avoid confounding procedural requirements due to multiple experimental studies.
Pregnant women or breastfeeding women, or women of	Pregnant women are excluded to avoid harm

child bearing potential and who are not on a reliable form of birth regulation method or abstinence.	to the fetus caused by fluoroscopy requirements.
Subjects with exclusion criteria required by local law (age or other).	Standard exclusion criteria to comply with any additional local requirements which may apply.
Subjects with medical condition which precludes patient from participation in the opinion of the Investigator	Standard exclusion criteria to apply medical discretion in subject selection.

9.5. Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Below are methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will be screened to confirm eligibility for enrollment with protocol pre-defined inclusion/exclusion criteria (see Table 5 and Table 6)
- Demographics and medical history will be collected at baseline in order to assess possible characteristics that may influence endpoints
- Data collection requirements and study procedures will be standardized across all study sites
- All study sites will follow the same version(s) of the CIP and CRFs.
- The maximum enrollment number from a single site should not exceed 50% of the total study size
- All study site and Medtronic personnel will be trained using standardized training materials
- Regular monitoring visits will be conducted to verify adherence to the Clinical Investigation Plan and source data
- An independent CEC will be utilized to regularly review and adjudicate reported adverse events
- All implanters in the study will be experienced in the implant of pacemaker systems and receive standardized training for the implant of the Micra system
- Final analysis of the study objectives will be carried out as pre-specified in this protocol. The analysis cohort is defined in the statistical method section (see Section 14 for details)

10. Study Procedures

10.1. Schedule of Events

10.1.1. Enrollment

Enrollment of a subject is complete once the potential patient has signed an Informed Consent and passed the screening assessment. All subjects are required to be enrolled prior to the implant procedure/exposure to the investigational product. Once consent has been obtained and the screening assessment has been passed, the individual is considered as enrolled in the study. It is recommended that consent be obtained no earlier than 30 days prior to procedure. Informed consent must be obtained prior to performing any study related procedures.

10.1.1.1. Screening

Consented patients will be considered as screen failure and will be exluded from all study analyses if the subject is deemed to be not suitable for undergoing Micra implant procedure based on study defined inclusion/exclusion criteria.

10.1.2. Baseline

The enrollment and baseline visit can occur at the same time. Information collected at baseline will include the date the consent was signed, verification of eligibility, demographics and medical history,in addition, cardiovascular medications will be collected at baseline. Centers are to report study enrollments as soon as possible upon patient consent into the study database. Per CFDA requirement for pre-market studies, the sponsor will provide the investigational device free-of-charge to the study institution. This will be outlined in the clinical trial agreement.

10.1.3. Procedure/Pre Hospital Discharge

Information collected at implant will include data from the day of the implant procedure and device testing including:

- Device information e.g. model, serial number, etc.
- Name of implanting physician
- General relevant procedure information: e.g. placement methods & location, technique
- Electrical measurements (pacing threshold, lead impedance, and sensing amplitude) submit device data e.g. uploads or transmissions. Report if measurements can't be reported due subject condition (i.e. heart block, atrial fibrillation, etc.)
- Anticoagulation Strategies
- Implant Tools
- Fixation confirmation method

10.1.3.1. Unsuccessful Implant Detail

If a Micra device is not successfully implanted, subjects will be exited from the study within 30-days post the date of implant procedure unless a study system and/or implant procedure related Adverse Event (AE) is identified. If a study system and/or implant procedure related AE is identified, the subject will be followed until the event is resolved or no further actions need to be taken.

10.1.4. Subject Follow-up

All subjects enrolled in the Micra Study will be prospectively followed from implant, 1 month, 3 months and 6 months, and at 6-month intervals thereafter through study closure. Subjects must be seen in-office for all follow-up visits. The study visits window is showing in Table 7.

Table 7: Study Visits Window

Visit	Visit Window
Implant	within 30 days after baseline
Pre-hospital discharge	within 7 days after implant
1-month	23 to 45 days after implant
3-month	77 to 105 days after implant
6-month	183 to 204 days after implant
12-month*	351 to 380 days after implant

**optional visit*

Information collected at post implant follow-up visits may include but is not limited to:

- Subject Status
  - Event assessment: confirmation of any new reportable Adverse Events/updates to previously reported Adverse Events
- Device Status:
  - Electrical measurements including pacing capture thresholds, impedance and sensing amplitude.
  - Assess device performance status through review of the device testing and interrogation. Confirm if there is any new reportable adverse device effect and/or treatment had been applied.
  - Adverse Events and update any unresolved previously reported events.

10.1.5. System Modification

A system modification will be reported if the Micra device requires an invasive procedure after the initial successful implant (e.g. explant, replacement, repositioning) or the Micra system is permanently electrically abandoned (i.e. programmed to OOO). If a new Micra device is implanted, this will be reported on a system modification eCRF as well as a new Implant procedure eCRF.

Following chronic placement of the Micra device, if an introducer sheath is introduced into the body to reposition, explant or replace the Micra system, this is considered a repeat intervention, which must be documented on a Micra System Modification eCRF(e.g. explant, repositioning or replacement).

If a system modification requires explant of the entire Micra Study System, a complete system explant without replacement of any Study System components, the subject will be exited from the study. Subjects should not be exited from the study until all procedure, device related adverse events have been resolved or no further actions will be taken.

Information collected for a system modification procedure may include but is not limited to:

- General relevant modification procedure information (reason for modification, investigator, location of procedure, duration, access technique, etc.)
- Device information (model serial numbers, etc.)
- Electrical measurements
- Adverse Events assessment

Return any explanted Medtronic product to Medtronic for analysis and update the device disposition log for explanted investigational product. If the product(s) are explanted but not returned, a justification is required to be reported.

10.1.6. Electrical Measurement Requirements

Table 8 provides requirements meant to facilitate consistency in collection and reporting of electrical measurements.

Table 8: Electrical Measurement Requirements

	Implant	Pre-Discharge	Follow up
Impedance Measurement	x	x	x
R-Wave Measurement • *If ventricular pacing is occurring on 1st measurement attempt, program to VVI 40*	x	x	x
Capture Management Threshold Test @ 0.24ms	x	x	x
Auto Decrement Threshold Test @ 0.24ms	x	x	x

10.2. Subject Consent

Informed consent is defined as legally effective, documented confirmation of a subject's (or their legally authorized representative or guardian) voluntary agreement to participate in the study. The Patient Informed Consent Form (ICF) is signed only after all relevant information regarding all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study has been provided to the subject. Subject consent will be obtained in accordance with local law and regulations. The ICF must be approved by the sponsor and the site's EC. The documents referenced must be maintained in such a way as to assure control of the document (i.e. version and/or date) such that the version(s) approved by the EC are clear with a documented change history for all revisions. The

principal investigator or his/her authorized designee will conduct the informed consent process. Refer to Appendix E: Informed Consent Templates.

The process for obtaining informed consent shall:

- Avoid any coercion of, or undue influence of subjects to participate
- Not waive or appear to waive subject's legal rights
- Provide documents to the subject in a language s/he is able to read and understand
- Use language that is non-technical and understandable to the subject or legal representative
- Provide ample time for the subject to consider participation
- Include a dated signature of the subject or legal representative acknowledging their participation in the study is voluntary. Include personally dated signatures of the principal investigator or an authorized designee responsible for conducting the informed consent process.
- The informed consent shall be documented before any procedure specific to the clinical investigation is applied to the subject.

In the event that the subject can't read or write, a witnessed (impartial third party) consent form and authorization/data protection will be allowed (as determine by local law), provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the appropriate consent form and authorization.

The signed ICF and the authorization must be filed at the site. A copy of the ICF must be provided to the subject. The original signed ICF and the authorization or other privacy language where required by law must be retained and made available for review by site monitors, auditors, or inspectors.

The consent process should be documented at each site in source documents which may include Medical charts, progress notes of medical history sheets, etc. Any changes to a previously approved Informed Consent Form throughout the course of the study must be approved by Medtronic and then by the Ethics Committee reviewing the application before being used to consent a prospective study subject. The document(s) must be controlled (i.e. versioned and/or dated, per local law) to ensure it is clear which version(s) were approved by the Ethics Committee. All important new information should be provided to new and existing subjects throughout the study, and if relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

10.3. Assessment of Safety

Timely, accurate, and complete reporting and analysis of safety information is crucial for the protection of subjects, clinicians, and the sponsor. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established Standard Operating Procedures (SOPs) to ensure compliance with global regulatory safety reporting requirements. Study activities are conducted in accordance with these SOPs.

Procedure and device related adverse events are collected throughout the duration of this study, starting from the time of signing the CF through study closure. Adverse Events are to be reported upon site awareness using an event form, capturing date of the event; date site became aware of the event, diagnosis of the event, actions taken, assessment of seriousness, relatedness and outcome.

Unavoidable Adverse Events (refer to Section 11.3) need not be reported unless the adverse event worsens or is present outside the stated timeframe

For AEs that require immediate reporting, initial reporting may be done on the CRF completing as much information as possible. The completed AE CRF must be sent to Medtronic as soon as possible.

Adverse Events will be recorded and reported according to local regulatory requirements and are outlined in Table 13. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the sites' Ethics Committee.

10.4. Recording Data

Clinical data will be collected at baseline, implant/pre-hospital discharge, 1-month, 3-month, 6-month post-implant visits and at 6-month intervals thereafter if applicable through study closure. Data will be collected using electronic case report forms (eCRFs) using an electronic data management system for clinical studies. Data will be stored in a secure, password-protected database, which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports will be generated by Medtronic to monitor data quality and study progress. At the end of the study, the data will be frozen and retained indefinitely by Medtronic. Data collection requirements are summarized in Table 9.

Table 9: Summary of Data Collection and Frequency

	Enrollment/Baseline	Procedure/PHD	Follow-up*	Exit
Confirm Eligibility	X			
Consent	X			
Physical Exam, Demographics	X			
Medical History	X			
Procedure Details		X		
Anticoagulation Methods		X		
Device/System Information		X	X	X
Electrical Measurements & Device Interrogations		X	X	
Device Disposition				X
Adverse Events assessment		X	X	X

	Enrollment/Baseline	Procedure/PHD	Follow-up*	Exit
Adverse Events	Upon Occurrence			
System Modification	Upon Occurrence			
Device Deficiency	Upon Occurrence			
Deaths	Upon Occurrence			
Protocol Deviations	Upon Occurrence			

* Follow up includes 1-month, 3-month, 6-month post-implant visits and at 6-month intervals thereafter through study closure if applicable.

10.5. Deviation Handling

A deviation is defined as an event within a study that did not occur according to the CIP or the Clinical Trial Agreement. Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the life or physical well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g., subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction or inability to perform required procedures due to subject illness).

All study deviations must be reported on the Case Report Form regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The description of the deviation and justification must be documented.

Once a deviation has been identified it should be reported to Medtronic as soon as possible. Deviations may be identified through numerous sources, including but not limited to: telephone conversations, site monitoring, subject record, or data review.

It is the site's responsibility to report deviations in compliance with their EC/IRB policies and/or local laws.

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

In the occurrence of a corrupted device interrogation file, Medtronic may request a deviation to document that a readable interrogation file is unavailable. Deviations for missing device interrogation file(s) and missing or incomplete electrical testing at the same visit may be reported on one deviation CRF.

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

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g., amend the CIP, conduct additional training, and terminate the investigation). Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

10.6. Subject Withdrawal or Discontinuation

Every attempt should be made to follow all Micra subjects through study closure.

Upon exiting from the study, no further study data will be collected or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.. In the event of study exit, the investigator should discuss with the subject the plans for future care and treatment. The investigator should explain that the subject will continue to receive standard medical care. Alternative treatment, such as medication options, implant of a commercially available system or follow-up through standard of care procedures instead of study procedures, and medical consequences should also be discussed. The investigator must notify the subject of any significant new findings that may become available during the course of the study, which are pertinent to the safety and well-being of the subject.

Exit

Subjects may be exited from the study for any of the following situations:

- Subject does not meet inclusion/exclusion criteria and was not implanted with investigational device of interest
- No implant attempted
- Implant attempted but was not implanted
- Explant of the investigational device with no planned replacement
- Lost to follow-up
- Subject chooses to withdraw from the study
- Investigator deems withdrawal necessary (medically justified or inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved procedure or device related adverse events are resolved or they are ongoing and no further actions will be taken.

It is recommended to perform a full device interrogation prior to the study exit. A copy of the interrogation files should be sent to Medtronic, with a copy also being maintained at the site.

Lost to Follow-up

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, the requirements set by the governing EC/IRB for subjects lost to follow-up must be followed.

11. Risks and Benefits

11.1. Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. A summary of the risk analysis and risk assessment specific to this study is included in the corresponding Micra IDE study Investigator Brochure or Report of Priors.

Potential risks and side effects associated with a device implant and follow up procedures are documented in the product labeling.

Table 10 provides a listing of potential Micra AEs and is not intended to be a comprehensive listing of all reportable Adverse Events. This listing is provided to facilitate more complete and consistent event reporting.

Table 10: Potential Micra system related Adverse Events included but are not limited to:

air embolism	myocardial damage
aneurysm or pseudoaneurysm	nerve damage
bleeding or hematoma	nerve or extracardiac stimulation
cardiac or vascular trauma	oversensing, undersensing, or loss of pacing therapy
device dislodgment or migration	pacemaker syndrome
device embolization	pain at access site or chest
endocarditis	pericarditis, pericardial effusion, or pericardial rub
fluid accumulation	peripheral ischemia
heart, vessel, or valve tissue damage	reduced device longevity
impaired cardiac function due to device	tissue necrosis such as myocardial infarction
incision site complication	threshold elevation
incision site infection or other infection	thrombus which may result in embolism, such as DVT, PE, or CVA
induction or acceleration of arrhythmias	toxic/allergic reactions
ineffective rate response	venous occlusion

11.2. Potential Benefits

The potential benefits of the Micra implantable device are consistent with the bradycardia therapy provided by similar currently approved single chamber pacemakers. Patients experiencing untreated bradycardia may get an inadequate supply of oxygen to their brain or other organs. This may result in debilitating symptoms, including syncope, weakness, fatigue, shortness of breath, chest pains, and confusion or memory problems. Pacemakers remain the only known, long term effective treatment for bradycardia.[5.]

In addition to the standard benefits which apply to all pacemakers for bradycarida, there may be additional benefits specific to the Micra system due to its design. With no device pocket, risk of infection, vascular complications and device pocket complications (hematoma, erosion, pain) may be reduced or eliminated. Pacing leads are currently regarded as the weakest link in the implanted system as they can lead to lead failure and system reliability issues lead fracture and lead insulation defects. There is no similar technology available to deliver pacing therapy without a lead. Therefore, possible additional benefits specific to the Micra system include:

- Avoid certain complications associated with traditional pacemakers due to Micra design:
    - Subclavian access complications (pneumothorax, occlusion)
    - Pocket complications (Hematoma, Erosion, infections)
    - Lead complications (dislodgement, fracture, infections, connection errors, interaction with vasculature & heart structures, extraction complications)
- Satisfy patient preferences:
    - Cosmetic appeal (lack of pocket)
    - Minimally invasive approach
    - Avoid pain and discomfort associated with pocket
- Efficiency:
    - Faster procedural time
- Increased Access to Brady Therapy
    - More patients have access to pacing therapy since Micra implant isn't limited by number of available specialists in emerging markets

The information gained from this study could result in the improved management of patients with the Micra system. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

It is possible that the Micra Transcatheter Pacing System may offer no benefit.

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[5] Lancet 2004; 364: 1701–19

11.3. Risk-Benefit Rationale

Initial study results from the global human study indicate the device is safe and effective for the intended use. Any potential risks associated with study participation are further minimized by selecting qualified investigators and study training. In addition, investigators will be actively involved in the implantation and follow-up of the subjects implanted with the investigational device/system. During the course of the study, risks will be continuously monitored, assessed and documented by the investigators. It is the investigator's decision to assess whether or not to continue the study at the respective site, should safety-related concerns arise.

Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the investigational device which is the subject of the study. After implantation, subjects enrolled in a study are followed at regular intervals to monitor subject and device status. At each required follow-up, the device will be interrogated to verify appropriate function and to evaluate pacing, sensing, and defibrillation characteristics (as appropriate) and to assess any adverse events.

Medtronic has further minimized the possibility of risks by: performing required laboratory and pre-clinical testing prior to conducting human clinical studies, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

Unavoidable Adverse Event Related to the Implant Procedure: An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration including but not limited to:

Table 11: Unavoidable Adverse Events

Event Description	Time Frame (hrs) from end of Procedure
Anesthesia related nausea / vomiting	24 hrs
Low-grade fever (<100ºF or < 37.8ºC)	48 hrs
Pocket site / incisional pain	72 hrs
Mild to moderate bruising / ecchymosis	168 hrs (7 days)
Sleep problems (insomnia)	72 hrs
Back pain related to laying on the table	72 hrs

12. Adverse Event Assessments

12.1. Definitions/Classifications

Note: if the definition indicates "device", it refers to any medical device. This might be the device under investigation or any market released component of a system.

Table 12: Adverse Event Definitions

Event Type	Definition[6]
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons , whether or not related to the investigational medical device. *NOTE 1: This definition includes events related to the investigational medical device or the comparator.* *NOTE 2: This definition includes events related to the procedures involved.* *NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.* (ISO 14155:2011 section 3.2)
	The medical events with disadvantages occurred during the clinical trials, no matter whether they are related to investigational medical devices or not. (CFDA Order No.25 Article 93)
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. *NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.* (ISO **14155:**2011 section 3.37)
	Any untoward medical occurrence during the clinical trial: results in death or serious deterioration in health; life-threatening diseases or injuries; causing

[6] International Standard ISO 14155:2011(E). Clinical investigation of medical devices for human subjects – Good Clinical Practice.

Event Type	Definition[6]
	permanent damage to the body structure or function; requires hospitalization or prolongation of hospitalization; requires medical operations or intervention for preventing from persistent or significant disability/incapacity; results in fetal distress, fetal death, or congenital anomaly/birth defect. (CFDA Order No.25 Article 93)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. *NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.* *NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.* (ISO 14155:2011 section 3.1)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011 section 3.36)
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. *NOTE: Anticipated serious adverse device effect (ASADE) is an effect, which by its nature, incidence, severity or outcome has been identified in the risk analysis report.* (ISO 14155:2011 section 3.42)
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.* (ISO 14155:2011 section 3.15)
	Any unreasonable risk caused by a medical device in normal use during clinical trial that may endanger human health or life safety, such as label error, quality issues, malfunction and etc. (CFDA Order No.25 Article 93)

12.1.1. Relatedness

Procedure-Related: An event that is directly related to the implantation or modification procedure of a device/system.

System-Related: An Adverse Event that results from the presence or performance (intended or otherwise) of the device (e.g. Micra device, delivery catheter, or software).

Micra Implantable Device Related: An adverse event that results from the presence or performance (intended or otherwise) of the Micra device

Delivery Catheter Related: An adverse event that results from the presence or performance (intended or otherwise) of the delivery catheter

Software Related: An adverse event that results from the performance (intended or otherwise) of the Micra software

Accessory / Tool Related

Programmer Related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer

Introducer Related An adverse event that results from the presence or performance of the introducer

Implant Tool Related: An adverse event that results from the presence or performance of the implant tool (excluding delivery catheter and introducer)

Extraction Tool Related An adverse event that results from the presence or performance of the extraction tool

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

Hospitalization: An overnight hospital admission, where admission date and discharge date are different

An unsuccessful implant is not considered an adverse event; however any adverse events occurring during an unsuccessful implant attempt (e.g. dissection, perforation) must be recorded and classified.

12.1.2. Complication

Complication: An adverse event that results in death, involves any termination of significant device function or requires an invasive intervention.

Non-invasive when applied to a diagnostic device or procedure, means one that does not by design or intention:

- Penetrate or pierce the skin mucous membranes of the body, the ocular cavity or the urethra, or
  - Penetrate: to pass, extend, pierce, or diffuse into or through something; to enter overcoming resistance; to gain entrance to
  - Pierce: to force a way into or through something
- Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os.

Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive.

Major Complication:

A complication which results in:

- Death

- Permanent loss of device function due to mechanical or electrical dysfunction of the device (i.e. pacing function disabled, leaving device abandoned electrically)
- System revision (explant, reposition, replacement)
- Hospitalization
- Prolonged Hospitalization by 48 hours or more

NOTE: Only system or procedure related AEs will be classified as a major complication, minor complication or an observation

Minor Complication: Any adverse event classified as a complication that is not a major complication (e.g. event classified as a complication solely based on intravenous drug administration)

Observation: Any adverse event that is not a complication.

12.1.3. Subject Death

All subject deaths must be reported by the investigator to Medtronic as soon as possible after the investigator first learns of the death. Document the adverse event that led to the subject death on an Adverse Event form. Further supporting evidence that is not originally provided by the site may be requested by Medtronic to aid in the adjudication of the death.

In the event of a subject death, the implanted system should be explanted and returned to Medtronic for analysis whenever possible. Prior to explant, the system should be interrogated and a full summary interrogation performed (save-to-media) when possible. If the system is not interrogated, an explanation must be documented. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated. In summary, the following data will be collected:

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

12.1.3.1. Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The

Investigator shall classify each subject death per the following definitions:

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

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

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

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

Unknown: A death in which there is no clinical evidence to support:

- A direct relatedness to the system component or
- A probable cause relatedness to the system component or
- No relatedness to the system component

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

12.2. Reporting of Adverse Events and Device Deficiency

Adverse Events will be recorded and reported according to local regulatory requirements and are outlined in Table 13. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the sites' Ethics Committee. Investigators are required to evaluate and document all AEs and Device Deficiencies (per the definitions in Table 12) observed in study subjects from the time they enrolled(signed the ICF) until they are no longer participating in the study. AEs should be followed until one of these criteria is met:

- Until the AE resolves
- Until no further action can be taken for an ongoing AE
- Until the subject exits the trial, or
- Until trial closure

NOTE: In the case of permanent impairment, continue to follow the event until it stabilizes and the overall clinical outcome has been ascertained.

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

Table 13: Adverse Event Reports

For the following events, reporting requirements are: • **Serious Adverse Events (SAE)**
Investigators shall immediately adopt appropriate therapeutic measures for subjects, and simultaneously report to the management department of medical device clinical trials in clinical trial institutions in written form. Management department of medical device clinical trials shall report to

Medtronic	Immediately
local food and drug regulatory authority and health and family planning competent authority of the province, autonomous region and municipality directly under the central government where the clinical trial institution locates	Within 24 hours
Ethics Committee	Within 24 hours
For the following events, reporting requirements are: • **All other AEs** • **All other Device Deficiencies**	
Investigators shall record all the adverse events and device deficiencies occurred during the clinical trials. Investigators shall analyze the reasons for the events with the sponsor and document the analysis result in written report, including the comments of continuing. suspending or terminating trials, which shall be reported to the Ethics Committee through management department of medical device clinical trials in clinical trial institutions for review	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
Ethics Committee	Per EC's requirements
For the following events, reporting requirements are: • **Serious Adverse Events (SAE)** • **DD with SAE potential**	
Sponsor submits to:	
The food and drug regulatory authorities and health and family planning competent authorities at the same level filed	Within 5 working days upon being informed
Other clinical trial institutions and investigators participating in the trial	Within 5 working days upon being informed
Ethics Committee	Timely report to Ethics Committee of the clinical trial institution through management department of medical device clinical trials

12.3. Documentation and Reporting of Device Deficiencies

Device Deficiency information will be collected throughout the study and reported to Medtronic. Device Deficiencies that led to an AE are reported on the AE eCRF. Device Deficiencies that did not lead to an AE should be reported on a Device Deficiency eCRF (one for each Device Deficiency).

All Device Deficiencies, regardless if it led to an AE, must be reported. Information reported on the Device Deficiency Form shall include a description of the deficiency, the date of onset, actions taken as a result of the deficiency, the outcome of the event, and the date the deficiency was first noticed by the investigator.

Device deficiencies that did not lead to an adverse event but might have led to an SAE if a) a suitable action had not been taken, or b) an intervention had not been made, or c) circumstances had been less fortunate, should be reported to Medtronic as soon as possible. Initial reporting may be done by phone, fax, e-mail, or on the eCRF completing as much information as is available. The original fully completed Device Deficiency eCRF must be submitted to Medtronic as soon as possible.

Initial reporting of AE/DD may be done by phone, fax, e-mail, or on the eCRF completing as much information as is available. The original fully completed AE eCRF must be submitted to Medtronic as soon as possible. Investigators should contact their Medtronic clinical research specialist or site monitor if they have any questions regarding reportable AE/DD. Medtronic will provide and maintain a listing of current contact details for each site.

13. Data Review Committees

13.1. Clinical Events Committee (CEC) Review

As requested by the sponsor, an independent CEC will review and adjudicate at a minimum all procedure, system, and MRI related adverse events and deaths.

The CEC will consist at least 3 non-Medtronic employed physicians that are not participating investigators for the China Micra™ Transcatheter Pacing Study, including a CEC chairperson. At least three CEC members must adjudicate, at a minimum, all deaths and SAEs related to any component of the system under investigation.

For adverse events and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification. The CEC is responsible for reviewing the Investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters.

If the CEC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the case report form documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to ethic committees and regulatory authorities, if required.

14. Statistical Design and Methods

14.1. Primary Objective

To demonstrate the MICRA TPS is safe by estimating the MICRA TPS implant procedure and/or system related major complications free survival probability through 6 month post implant.

14.1.1. Statistical Design, Methods and Anlysis Procedures

14.1.1.1. Hypothesis

The primary endpoint is Micra system and/or procedure related major compliations through 6 months post implant. The corresponding statistical hypothsis for this study (ultizing single arm OPC design) is:

$$\begin{aligned} &H_0 : S_T \le S_0 \\ &H_1 : S_T > S_0 \end{aligned};$$

Where S_T is the expected value of the probability of a subject free from Micra system and/or procedure related major complications through 6 months post implant; S_0 is the OPC .The objective will be considered met if the lower bound of the two-sided 95% confidence interval lower bound for the estimate is greater thangreat then 83%.

14.1.1.2. Statistical Analysis Method

- Baseline Patient Demographics

  Summary Statistics will be obtained: frequency and percentage will be reported for categorical data; mean, standard deviation, minimum, maximum, median, the 1st and 3rd quartiles will be reported.

- Analysis of the Primary Objective:

  All subjects who undergoes an Micra implant procedure will be included in the analysis. The Kaplan-Meier survival analysis will be used to estimate the probability of a subject free from Micra system and/or procedure related relate major complications. The log-log transformation will be used to calculate calculation the confidence limits.

  Definitions:

  - Endpoint event for the survival analysis is Micra system and/or procedure related major complications (see 6.2.1)
    - The CEC will finally final determine if the adverse event is related to Micra system and/or procedure; and if the adverse event is a major complication
  - Censoring occurs in subjects who does not experience any Micra system and/or procedure related major complications
  - Follow-up time: from the date of Micra implant procedure to
    - the onset date of a Micra system and/or procedure related major complication, or

- study termination date (e.g. subject exit, die, or study closure, etc.), or
- the date of Micra deactivation due to any reason that is not related to the Micra system or procedure (e.g. device system upgrade, the subject's other comorbidities, etc) , or
- the last follow-up date, if none of the above occurs.

- Analyses of the Secondary Objectives

  The secondary objectives will be analyzed using descriptive statistics. The Statistical Analysis Plan will provide additional details.

- Safety Evaluation

  All information associated with each adverse event, including event decription, severity, and relatedness to the system, etc., will be reported. In addition, event rate will be summazied. The 2-sided 95% Confidence Intervals will be calculated using the Exact Binomial method.

- The statistical analysis of the primary objective will be 2-sided, using 0.05 significance level. The statsitical analysis software package SAS will be used to conduct these analysis.

14.1.1.3. Statistical Anlysis Procedures

The statistical analysis will follow the requirements documented in the ICH E9, as well as the relevant requirements in the Biostatistic Guidelines for Clinical Trials issued by the Chinese Food and Drug Administration (CFDA). At the same time, all statistical analysis procedures will strictly comply to the standard operating procedures (SOP) of the Medical Reseach & Biomedtric Center, National Center for Cardiovascular Diseases.

14.1.2. Sample Size Calculation

14.1.2.1. Total Enrollment Size

The study will require a enrollment size of 82. The study size is calculated based on statistical hypothesis, assumed expected performance, and projected attrition.

14.1.2.2. Rationale and Considerations for Sample Size Determination

The study size is determined by the sample size required for the primary objective. It is reported in the NEngl J2015[7] that the Micra system and/or procedure related relate complication free survival probability through 6 months was 96%, (95% CI: 93.3%, 97.6%) in those who underwent Micra system implant

[7]Dwight Reynolds, Gabor Z. Duray , etc..A Leadless Intracardiac TranscatheterPacing System. N Engl JMed 2015;NEJMoa1511643:1-9.

procedures. Therefore, we conservatively assume that the expected performance (or, "Success Rate" in later text) in the study population will be 94%. The OPC is set as 83% (the same performance threshold in the FDA approved global study) .The sample size calculation assumes the statistical analysis will be carried out on 0.05 significance level, 2-sided, 80% power and 10% study attrition. The minimum sample size requirement is 82. The sample size formula is displayed as following:

$$n = \frac{\left[Z_{1-\alpha/2}\sqrt{p_0(1-p_0)} + Z_{1-\beta}\sqrt{p_T(1-p_T)}\right]^2}{(p_T - p_0)^2} \quad ;$$

Where p_T is the expected success rate, p_0 is the OPC value, Z value is under normal distribution, α is the type I error (or significance level, 0.05 is used) and β is the type II error (0.2 is used to ensure 80% power).

The sample size calculation employed a formula based on the binomial distribution of the asymptotic normality method because the success rate estimate given by the Kaplan-Meier method is consistent with the actual observed success rate if there is no drop-outs.

14.1.2.3. Sample Size Requirement for Each Study Center

The study will be conducted concurrently in multiple clinical study sites. In principle, the number of enrollment at study sites will be evenly distributed to ensure adequate representativeness of each site. The actual number per center may fluctuate based on actual progress. The study will try to ensure the enrollment size at each center is relative balanced, and for a particular center, the maximum enrollment number should not exceed 50% of the total study size.

14.1.3. Significant Level and Statistical Power

For this study, the statistical significance level is set at 0.05 (two-sided), and the statsitical power is specified at 80%.

14.1.4. Projected Attrition

The study attrition will include all scenarios that results in enrolled subject not being included in the analysis.The common reasons are due to serious protocol deviations (if affects performance evaluation). Other scenarios may include: Micra implant was not carried out or not successful, follow-up visit not completed per study requirement, or subject withdrawal of consent due to other cormorbidities, etc. All these scenarios may constitute subject drop-outs. At the same time, it is assumed that follow-up compliance will be high in pacemaker population. The study attrition is assumed to be 10%

14.1.5. Pass/Fail Criteria

The study pass/fail criteria is based on statistical hypothesis and final analysis results.The analysis of study primary objectives will be 6-month success rate comparing to the pre-specified OPC. If the 95% 2-sided confidence interval lower bound for the probability of free from Micra system and/or procedure related major complication is greater than 83%， the study will be considered yielding a positive result, demonstrating the success rate is higher than expected values, i.e. study objective will be met.

14.1.6. Stopping Rule

No interim analysis is planned for this study. Therefore there is no stopping rule defined. The analysis will be conducted after data collection is completed, verified and locked.

14.1.7. Anlaysis Data Set, handling of missing data, non-compliance, error or non-reasonable data entry.

Statistical analysis procedures (procedures) will strictly compy to SOP of the Medical Reseach & Biomedtric Center, National Center for Cardiovascular Diseases. Please refer to other relevant documents for additional details.

Data entry error or non-reasonable values will be cleaned befored data analysis. In the event of subject exit or withdrawal of consent, the subject will still be included in the final statistical analysis. The specific reasons for subject exit or withdrawal will be provided in detail in the statistical report. If no data can be collected from a subject during post-implant follow-up, additional sensitivity analysis may be performed.

This study will use the survival analysis method for the primary objective. Scenarios for censoring are previously defined. The Worst Case Scenario Analysis will only be performed if it is identified as a true missing (e.g. permanent missing of adverse event related data, and subsequently resulting in non-conclusive CEC review) or if the cause of death is unknown. The sensitivity analysis may count such missing data as failures.

14.1.8. Deviation from Pre-specified Analysis Plan

The statistical analysis plan will be finalized by the sponsor and the primary investigator before the data is locked for analysis. The analysis plan may be modified to consider actual scenarios observed during the study phase before its being final approved. In principle, no major analysis methods or definition of analysis sets should be changed. All versions will be recorded.

14.1.9. Criteria and Rationale for Selection of Subjects for Analysis

Statistical analysis sets should be clearly defined prior to the time when analysis is carried out. The analysis sets for this study are defined as follows:

Full Analysis Set (FAS): This is a dataset defined per Intention-To-Treat principle, it refers to the set of all subjects who participates in the study and is exposed to the investigational device. In the event when data can't be collected from certain subjects, censoring or additional analysis may be applied..

Per Protocol Set (PPS): A subset of study subjects who complies to study protocol (The subject who has a violation related to study inclusion/exclusion criterion will be excluded from the PPS).

Safety Analysis Set (SS): The same definition as FAS should be used. Therefore, no additional definition is provided here.

The primary objective analysis will be performed on the FAS; all baseline demographic data and secondary objectives will be based on the FAS or PPS, and the safety assessment will be performed on the FAS. The electrical parameters will be analzyed on PPS.

14.1.10. Justification for Exclusion of Special Information from the Analysis (if applicable)

Not applicable.

14.2. Secondary Objectives

14.2.1. Secondary Objectives #1

Objective: To demonstrate the effectiveness of MICRA Transcatheter Pacing System

Cohort definition and analysis method

All subjects with a successful Micra system implanted will be included in this analysis.

Pacing capture thresholds, impedance and sensing amplitudes will be summarized for implant and follow-up visits. Mean, standard deviation, and 2-sided 95% confidence interval, as well as minimum, median and maximum values will be presented for each measurement at each visit.

Since Micra utilizes different battery technology, the system nominally paces at a shorter pulse duration (0.24ms vs 0.4ms in traditional pacemakers). It is expected that majority of the subjects will have pacing capture thresholds ≤ 2 Volts at all visits.

14.2.2. Secondary Objectives #2

Objective: To summarize all adverse device effect throughout the study

Cohort definition and analysis method

All subjects who undergo a MICRA implant procedure will include in this analysis. All reportable events will reviewed by the event adjudication committee for relatedness to MICRA system and/or implant procedure. Frequency of each event diagnosis and severity (major complication, minor complication vs observation) will be summarized. Event rates will be reported for this patient cohort. Two-sided confidence intervals will be computed using the Exact binomial method.

[redacted]

14.4. Handling of Missing Data

Study subject disposition will be reported. Subjects visits will be tabulated, and compliance to study protocol required visit schedule will be summarized. Protocol deviation will be required for all missed visits and/or incomplete or incorrect data collection. The main analysis of the study primary objective will be based on available data and missing data will not be imputed. However additional sensitivity analysis will be done to assess the potential impact of missing data.

14.5. Reporting of procedure deviations from the original statistical plan

Any deviations from original statistical plan and the rationale will be described in the study report.

15. Ethics

15.1. Statement(s) of Compliance

- This study is a pre-market clinical trial for product registration. The study will be conducted in accordance with the laws and regulations of China, including any future applicable laws and regulations in China.
- To protect the rights and welfare of patients, this clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki (2013), the Clinical Trial Agreement (CTA) and

Clinical Investigation Plan, the laws and regulations of China including Good Clinical Practice for Medical Devices (CFDA Order No. 25), Announcement of CFDA on Filing of Medical Device Clinical Trial (2015, No.87) and also including applicable data protection laws. Sites will also comply with any additional ethics committee requirements applicable. This study conforms to the Notice of Requirement of Examine and Approve of Clinical Trial for Medical Device Class Ⅲ from CFDA (No. 14, 2014) and requirement for Clinical Trial Approval (CTA) will be applicable.

- The principles of the Declaration of Helsinki have been implemented through the patient informed consent (IC) process, Ethics Committee approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.
- The clinical trial filing will be completed prior to conduct of this study per the requirement of the Announcement of CFDA on Filing of the Medical Device Clinical Trial (2015, No. 87).
- Approval of the CIP or CIP amendments is required from the following groups prior to any study procedures at a study site: Medtronic, principal investigators and Ethics Committee. Similarly, approval of subsequent revisions to the CIP is required at each study center from the above mentioned groups prior to implementation of the revised CIP at that center.
- Sponsor should be responsible for filing the study to Shanghai Municipal Food and Drug Administration after Ethics Committee approval of the current version of the CIP and fully executed Clinical Trial Agreement.
- All products will be labelled as per local regulations in China and products requiring investigational labelling will be labelled investigational as per local regulatory requirements.
- All participating study sites and investigators should make all the study data and study related records and including source data/records available for the monitoring, audits work from sponsor and inspection from EC and/or Regulatory body per their requirements to ensure the quality of the clinical trial.
- The sponsor shall avoid improper influence on, or inducement to, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the China Micra™ Transcatheter Pacing study.
- Sponsor representatives may provide support as required for the study, including technical support at site. Sponsor representatives may provide technical support as required for the study under supervision of the Principal Investigator, including:
  1) Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities.
  2) Technical support will be provided during implant and/or during follow-up visits.
  3) Technical support will be under the supervision of a study investigator, but no data entry on the eCRF shall be performed by Medtronic personnel or their representatives at sites.
  4) Technical support to conduct device interrogations.

16. Study Administration

16.1. Monitoring

Medtronic monitors the regulatory and reporting compliance of clinical studies to ensure the overall integrity and quality of the data through a combination of the following actions:

- Automated data logic checks
- Statistical analysis to identify data trends or anomalies
- Statistical analysis to identify sites that are outliers relative to other participants
- Source verification using available in-house data e.g. data transmission
- Regulatory and reporting compliance trends
- Interim on-site clinical monitoring visits
- Site Audits

It is the responsibility of Medtronic to ensure proper monitoring of this study per regulations. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring activities to ensure this study is conducted in accordance with the protocol, Clinical Trial Agreement, and applicable regulatory and local requirements.

Medtronic (or delegates) must be allowed access to the subjects' case histories when conducting onsite interim monitoring visits (clinic and hospital records, and other source data/documentation) upon request as per the Informed Consent Form, Research Authorization (where applicable) and Clinical Trial Agreement.

Site Monitoring Visits

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

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

Further details of monitoring and a list of data which can be recorded directly in the CRF will be given in the study specific monitoring plan. The Monitoring Plan will be provided under a separate cover.

16.2. Data Management

Data will be collected using an electronic data management system. Data reporting will be completed and submitted by the clinician or authorized staff. All data will be stored in a secure, password-protected database.

Medtronic will review site reported data to monitor data quality, data discrepancies will be created as required and forwarded to the site for resolution. Study management reports may be generated by Medtronic to monitor data quality and study progress Site personnel are responsible for the timely submission of data and the resolution of discrepancies.

Reported data elements should be supported in the subject's case history. Any time the database reported data are the only record, it should be appropriately documented. In these cases, an alternate method of source documentation is highly recommended.

For products capable of transmitting data, device data uploads/transmissions will be collected for Medtronic products only. This data will be obtained directly from the submitted device file (i.e. transmission, etc.) therefore, additional source verification will not be required.

Medtronic or regulatory authority may audit the site to evaluate the conduct of this study. The Investigator(s)/institution(s) shall allow study-related monitoring, audits, EC/IRB review, and regulatory inspection(s) by providing direct access to study source data/documents, and regulatory documents.

Leading site will be accountable for data management and analysis about the data from each clinical research institution in a centralized manner according to local regulations and study requirements. Medtronic will oversee all data management functions and provide support if necessary.

16.3. Confidentiality

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

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

Medtronic or regulatory authority may audit the site to evaluate the conduct of this study. The Investigator(s)/institution(s) shall allow study-related monitoring, audits, EC/IRB review, and regulatory inspection(s) by providing direct access to study source data/documents, and regulatory documents.

16.4. CIP Amendments

Approval of the CIP or CIP amendments is required from the following groups prior to any study procedures at a study site: Medtronic, principal investigators, geography-specific regulatory authorities (if regulatory approval is required) and an independent Ethics Board. Similarly, approval of subsequent revisions to the CIP is required at each study center from the above mentioned groups prior to implementation of the revised CIP at that center.

16.5. Record Retention

16.5.1. Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of these records, with the exception of case history records and case report forms, should be kept in the

Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs may be maintained and signed electronically within the electronic data capture system during the study. Clinical trial institutions shall keep the clinical trial data for at least ten years after the completion of clinical trials.

- All correspondence between the EC, sponsor, monitor, CFDA/regulatory authority and or the investigator that pertains this study
- Subject identification and enrollment log, and subject screening log, where required per local law Subject's case history
  - Informed Consent
  - Observations of AEs/ADEs/DDs
  - Medical history
  - Implant and follow-up data
  - Documentation of the dates and rationale for any deviation
- All approved versions of the CIP, Informed Consent Form and Investigator Brochure
- Signed and dated Clinical Trial Agreement
- Delegation documentation
- Study training records for site staff
- Any other records that CFDA and local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis
- Current Signed and dated CV of PI (and key study team members if required per local requirements)
- Device accountability records, Shipping records for investigational devices and clinical investigation related documents and materials
- Software disposition logs
- Electronically signed and dated CRFs

16.5.2. Investigator Reports

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

Table 14: Investigator Reports per Medtronic Requirements

Report	Submit to	Description/Constraints

Clinical trial institution and Investigator Initiated Study suspension or termination	CFDA	If it is required to suspend or terminate the trial as the clinical trial institution and investigators found that the risk outweighs the possible benefits or results have been obtained that suffice the judgment of the safety and effectiveness of medical device, the investigators shall inform the subjects, and make sure appropriate treatment and follow-up visits for the subjects, and meanwhile report as required with detailed written explanation for the suspension and termination. Report to the food and drug regulatory authorities of the provinces, autonomous regions and municipalities directly under the central government if necessary. *(GCP for Medical Devices, CFDA order No.25 Article 76)*
Failure to obtain informed consent	Sponsor and Ethics Committee	Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. *(ISO 14155:2011)*
Safety Report	Clinical Trial Institution Sponsor, Local FDA or Regulatory Authority	For the serious adverse events occurred in clinical trials, investigators shall immediately adopt appropriate therapeutic measures for subjects, and simultaneously report to the management department of medical device clinical trials in clinical trial institutions in written form, and notify the sponsor in written form. Management department of medical device clinical trials shall report to corresponding Ethics Committee as well as local food and drug regulatory authority and health and family planning competent authority of the province, autonomous region and municipality directly under the central government where the clinical trial institution locates in written form within 24 hours. In case of death of subjects, the investigators and clinical trial institutions should provide all the required additional information to the Ethics Committee and the sponsor. *(GCP for Medical Devices, CFDA order No.25 Article 71)*

Final report	CFDA, Sponsor, and Clinical Trial Institution	Upon completion of multi-center clinical trials, investigators of all clinical trial institutions shall issue brief summary of clinical trials, respectively, and submit it to coordinating investigator together with Case Report Form upon review as required for coordinating investigator to summarize and complete summary report. *(GCP for Medical Devices, CFDA order No.25 Article 29（7）)* Investigators should, in accordance with the design requirements of the clinical trial protocol, verify and validate the safety and effectiveness of investigational medical devices, and complete the Clinical Trial Report. As for multi-center clinical trials, the Clinical Trial Report should contain the Summaries of Clinical Trial of all sub-centers. *(GCP for Medical Devices, CFDA order No.25 Article 83)* The Clinical Trial Report should be signed and dated by the investigators, and submitted to the sponsor after being reviewed, commented, dated and sealed by medical device clinical trial administration department of clinical trials institutions. For multi-center clinical trial, the clinical trial summary of each center should be signed and dated by the investigators of respective center, and submitted to the leading site after being reviewed, dated and sealed by the site's clinical trial administration department. *(GCP for Medical Devices, CFDA order No.25 Article 86)*

16.5.3. Medtronic Records

Medtronic shall maintain the following (but not limited to) accurate, complete, and current records:

- All correspondence which pertains to the studies
- Investigational device tracking documentation
- Signed Clinical Trial Agreements and delegation documentation as well as the signed agreements with third party(if applicable) and FD from PI
- All electronically signed and dated case report forms submitted by investigator, including reports of AEs, ADEs and Device Deficiencies, Subject Deaths
- All approved Informed Consent Forms, and other information provided to the subjects and advertisements, including translations
- Copies of all EC/IRB approval letters and relevant EC/IRB correspondence and EC/IRB voting list/roster
- Names of the institutions in which the Study will be conducted
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Study final reports
- Sample eCRFs
- All versions of the study protocol and IB
- Training records of site personnel and Medtronic personnel involved in the study

- Sample of labelling attached to investigational products
- Any other records required by the CFDA

16.5.4. Medtronic Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below. In addition to the reports listed below, Medtronic shall, upon request of reviewing EC/IRB or CFDA, provide accurate, complete and current information about any aspect of the respective study.

Table 15: Sponsor Reports

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Clinical Trial Institution Invesitgator Ethical Committee Local Regulatory Authority	For deciding to suspend or terminate clinical trials, sponsor shall notify the management department of medical device clinical trials of all clinical trial institutions within 5 days, and state the rational in written form. Management department of medical device clinical trials in clinical trial institutions shall timely notify corresponding investigators and Ethics Committee. The suspended clinical trials shall not be recommenced without the approval of Ethics Committee. Upon the completion of clinical trials, sponsor shall notify local food and drug regulatory authority of the province, autonomous region and municipality directly under the central government where he locates in written form. *(GCP for Medical Devices, CFDA order No.25 Article 46)*
Safety Report	Local FDA or Regulatory Authority Clinical Trial Institution Invesitgator Ethical Committee	For serious adverse events or the device deficiencies possibly resulting in serious adverse events, sponsor shall report to the food and drug regulatory authorities and health and family planning competent authorities at the same level filed within 5 working days upon being informed, simultaneously notify other clinical trial institutions and investigators participating in the trial, and timely report to Ethics Committee of the clinical trial institution through management department of medical device clinical trials. *(GCP for Medical Devices, CFDA order No.25 Article 54)*

Final report	Investigators, CFDA	The Clinical Trial Report should be signed and dated by the investigators, and submitted to the sponsor after being reviewed, commented, dated and sealed by medical device clinical trial administration department of clinical trials institutions. For multi-center clinical trial, the clinical trial summary of each center should be signed and dated by the investigators of respective center, and submitted to the leading site after being reviewed, dated and sealed by the site's clinical trial administration department. *(GCP for Medical Devices, CFDA order No.25 Article 86)* *Sponsor will submit the final report to CFDA after obtaining it from the medical institution.*

Medtronic records and reports will be stored in secure file cabinets at Medtronic during the course of the study. Electronic versions of the reports will be kept on a password-protected document management system. After closure of the study, all records and reports will be archived indefinitely.

16.6. Preliminary Publication Plan

Publications from this study will be handled according to Medtronic Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

The investigators of this study will serve as members of the Publication Committee, in addition to Medtronic representative(s). This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to:

1. manage elements addressed in the publication plan as outlined below,
2. develop the final Publication Plan under separate cover,
3. execute the Publication Plan,
4. oversee the publication of primary, secondary and ancillary study results,
5. review and prioritize publication proposals,
6. provide input on publication content, and
7. determine authorship.

In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

Management of Publications

The Publication Committee reviews, prioritizes, and manages all publications for the study. The publications are those that address analyses of any efficacy and safety objectives, as specified in the Clinical Investigation Plan.

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

Criteria for Determining Authorship

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

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

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

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

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

Transparency

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

- a final report, describing the results of all objectives and analysis, will be distributed to all investigators, Ethics Committees and Competent Authorities of China when required by local law
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- submitting for publication the primary study results
- disclosing conflicts of interest (e.g., financial) of the co-authors of publications
- according to the policies set forth by the corresponding journals and conferences
- making an individual sites study data accessible to the corresponding
- investigator after the completion of the study, if requested

16.7. Suspension or Early Termination

16.7.1. Planned Study Closure

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

16.7.2. Early Termination or Suspension

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

Study-Wide Termination or Suspension

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

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic (circumstances include but are not limited to; interests of the health of the study subjects, continuation of the study cannot serve any scientific purpose, insolvency) or regulatory body (where the study is operating under regulatory body authority)
- Technical issues during the manufacturing process

Investigator/Site Termination or Suspension

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

- Failure to obtain initial IRB approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to eligibility criteria, failure to follow subjects per the scheduled follow-ups)
- Lack of enrollments
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data discrepancies and monitoring findings in a timely manner, etc.)
- IRB suspension
- Fraud or fraudulent misconduct is discovered
- Investigator request (e.g. no longer able to support the study)

16.7.3. Procedures for Suspension or Termination

Medtronic-Initiated

- For deciding to suspend or terminate clinical trials, sponsor shall notify the management department of medical device clinical trials of all clinical trial institutions within 5 days, and state the rationale in written form.
- Management department of medical device clinical trials in clinical trial institutions shall timely notify corresponding investigators and Ethics Committee.
- The suspended clinical trials shall not be recommenced without the approval of Ethics Committee.
- Upon the completion of clinical trials, sponsor shall notify local food and drug regulatory authority of the province, autonomous region and municipality directly under the central government where he locates in written form.
- Upon receipt of notification of suspending or terminating clinical trials from sponsor, investigators shall timely notify subjects and ensure that subjects receive appropriate treatment and follow-up.
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic with the approval of Ethics Committee.
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare.

Clinical Trial Institution and Investigator-Initiated

- If it is required to suspend or terminate the trial as the clinical trial institution and investigators found that the risk outweighs the possible benefits or results have been obtained that suffice the judgment of the safety and effectiveness of medical device, the investigators shall inform the subjects, and make sure appropriate treatment and follow-up visits for the subjects, and meanwhile report as required with detailed written explanation for the suspension and termination.
- Clinical Trial Institution and Investigator shall report to the food and drug regulatory authorities of the provinces, autonomous regions and municipalities directly under the central government if necessary.
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare.

EC/IRB-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with Ethics
- Committee policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)

- Upon receipt of notification of suspending or terminating clinical trials from Ethics Committee, investigators shall timely notify subjects and ensure that subjects receive appropriate treatment and follow-up.

16.8. Clinical Study Report

The Clinical Study Report will be compliant with CFDA 2016 No. 58 Announcement Annex 5 "Template of Clinical Trial Report of Medical Devices"

16.9. Insurance

Medtronic (Shanghai) Management Co., Ltd is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. And as Ethics Committee of local clinical center may have special requirement on the insurance policy or other formal arrangement, it is necessary to provide a Clinical Study insurance statement/certificate to the Ethics Committee for review and obtain favorable opinion.

16.10. Probability analysis of success

The manufactory system of Medtronic has been tested and proven for many years. The quality of the investigational device has been carefully examined and verified before delivery. The investigational device has been commercially available globally, including the Europe and America countries, with a certain number of clinical application or post-marketing follow-up. The basic principles, structure composition and materials etc. comply with the international and domestic standards, or has been carefully examined and verified by Medtronic, and detected qualified by CFDA certificated medical device testing organization. The study design of this study complies with related CFDA instructions and requirements of ethical review, and all potential subjects will be strictly selected according to indications of the investigational device.

16.11. Probability analysis of failure

Although regulatory/ethical/scientific and medical requirements have been fully taken into consideration, the unanticipated risk in clinical application of investigational device could lead to failure of this study. Potential risks could be reduced to the minimum, with well-trained study staff and strict protocol compliance.

16.12. Responsibilities of all parties

Investigator responsibilities will be included in clinical trial agreement and subject responsibilties will be available in Informed Consent Form (ICF). Sponsor will undertake all the responsibilities of the sponsor as required per CFDA regulations.

17. References

1. Mallela et al, Trends in cardiac pacemaker batteries. Indian Pacing Electrophysiol J. 2004 Oct-Dec;

4(4): 201 212.
2. Gilles et al, HRS/ACCF Expert Consensus Statement on Pacemaker Device and Mode Selection, Heart Rhythm Volume 9, Issue 8 , Pages 1344-1365, August 2012
3. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 Guidelines for Device-based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). 2008.
4. Zipes DP et al, ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace 2006 8. 746-837 doi:10.1093/europace/eul108
5. Trohman RG et al, Cardiac pacing: the state of the art. Lancet 2004; 364: 1701 19
6. International Standard ISO 14155:2011(E). Clinical investigation of medical devices for human subjects Good Clinical Practice.

18. Appendices

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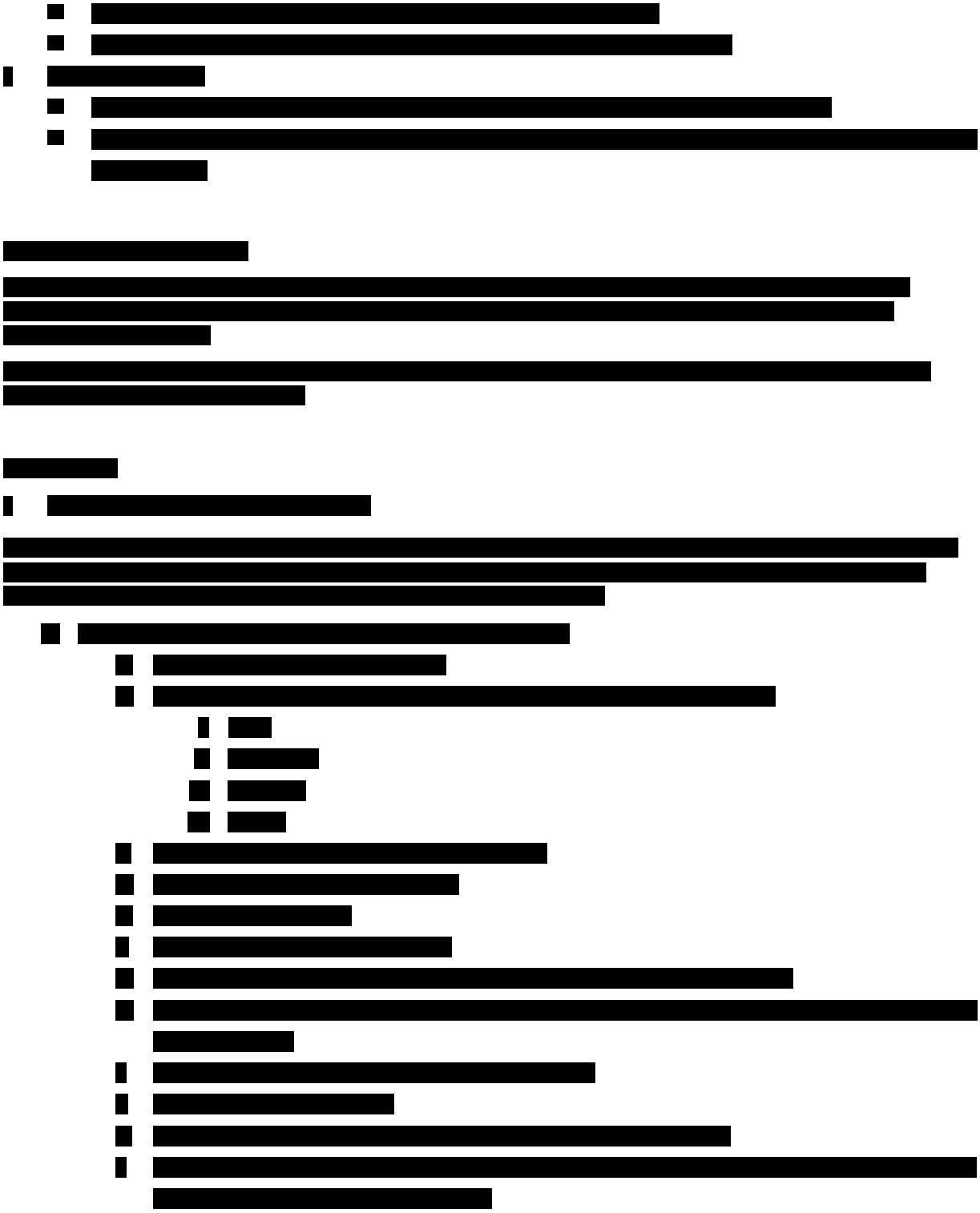

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Appendix B: Clinical Trial Institutions and Investigators List

Table 17: Clinical Trial Institutions and Investigators List

Code of clinical trial institution	Name of clinical trial institution	Investigator	Title	Contact information
30158877	Fuwai Hospital CAMS&PUMC	Dr. Shu Zhang	Professor	No.167, Beilishi Road, Xicheng District, Beijing, China, 100037
30223706	Zhongshan Hospital, Fudan University	Dr. Yangang Su	Professor	No.180, Fenglin Road, Xuhui District, Shanghai, China, 200032
30175608	West China Hospital, Sichuan University	Dr. Xinbin Liu	Professor	No.37 Guo Xue Lane, Chengdu, Sichuan Province, China. 610041
30220711	Jiangsu Provincial People's Hospital	Dr. Kejiang Cao	Professor	No. 300, Guangzhou Road,Nanjing, Jiangsu Province, China.

				210029
30159527	The Second Affiliated Hospital of Zhejiang University School of Medicine	Dr. Jianan Wang	Professor	No.88, Jiefang Road, Shangcheng District, Hangzhou, Zhejiang Province, China, 310009
30158850	Beijing Anzhen Hospital, Capital Medical University	Dr. Yujie Zhou	Professor	No.2, Anzhen Road, Chaoyang District, Beijing, China, 100029
30159320	Ruijin Hospital Shanghai Jiaotong University School of Medicine	Dr. Liqun Wu	Professor	No.197, Ruijin Er Road, Shanghai, China, 200005

Appendix C:

Comments of the Sponsor

Signature (stamp)

Date: MM/DD/YYYY

Comments of the Investigator:

Signature:

Date: MM/DD/YYYY

Comments of medical device clinical trial institution

Signature (stamp)

Date: MM/DD/YYYY

Appendix D: Proposed Implant Procedure Steps

Table 18: Proposed Implant Procedure Steps

	Step	• Description	Tools
1	Pre-Implant Programming	• Clinician or Medtronic personnel places programmer head over the device in the package and the patient data is entered into the programmer.	▪ Model 2090 programmer and programmer head
2	Patient Prep	• Patient receives antibiotics as indicated per standard procedure and best practices to prevent infection • Patient receives conscious sedation or anesthesia if indicated per standard procedures • Patient receives system heparin infusion and/or monitoring of blood work per physician discretion	▪ Betadyne or other standard prep solution ▪ EKG electrodes ▪ Diagnostic monitoring tools (EKG patches, BP cuff, etc) as required

		• Patient's right groin is prepped per standard procedure • Diagnostic monitoring devices (EKG, O_2, Blood pressure, etc.) are placed as required per standard hospital procedure	
3	Venous Access	• Femoral vein is located. (To avoid hitting a femoral artery, implanter can use ultrasound to guide access if preferred.) • Needle with syringe attached are inserted into vein • Guide wire is placed through needle up to heart • Introducer and dilator are flushed • Introducer is wetted to activate hydrophilic coating • Introducer/dilator are placed over the wire up to mid-atrium • Guide wire and dilator are removed • Introducer is aspirated and flushed • A continuous heparinized saline drip is attached to the introducer. • A figure-8 stitch is placed (if preferred)	▪ Introducer set (needle, syringe, guide wire, dilator, and outer sheath) ▪ Fluoroscopy ▪ Suture Optional tools: • SiteRite or other ultrasound • Additional size dilators • Needle and suture
4	Delivery System / Device Prep	• Delivery system is removed from package • Device is retracted into delivery system • Lumen(s) are flushed with saline	▪ Delivery system loaded with implantable Micra device ▪ Saline ▪ Syringe
5	Transvenous delivery of catheter to heart	• Delivery system is inserted into the introducer and advanced to the atrium. • Introducer is retracted down into IVC	▪ Delivery system loaded with implantable Micra device ▪ Fluoroscopy
6	Navigating to the RV apex	• Curve is deflected on the delivery system to cross tricuspid valve • Delivery catheter is advanced to target location in the RV	▪ Delivery system loaded with implantable Micra device ▪ Fluoroscopy
7	Deployment/ fixation of device	• Tether is unlocked • While maintaining forward pressure against the wall of the RV, the device is advanced out of the delivery tool • Delivery system is pulled back from the device	▪ Delivery system loaded with implantable Micra device ▪ Fluoroscopy

8	Fixation Verification	• Tug-test is performed by gently pulling on the tether while observing tines on high magnification cine • Fluoroscopy cine recording obtained per study protocol: during each deployment's tug test to attempt visualization of each of the 4 tines under high magnification cine. Multiple views may be required. Each recording 10 seconds, save recording of tug test for final deployment. • Programming head is placed in sterile cover (if required) and placed over the heart • Acute threshold, R-wave amplitude, and Impedance measurements are taken	▪ Fluoroscopy ▪ Model 2090 Programmer and Programmer Head
9	Reposition capsule (if required)	• Delivery system is advanced back over the device • The device is re-captured back into the delivery system, tether is locked, and system is repositioned in the RV (repeat steps 7 and 8 as required).	▪ Delivery system loaded with implantable Micra device ▪ Fluoroscopy
10	Fixation Test	• Repeat Fixation Verification (step 8)	
11	Removal of Delivery System	• Tether is cut and gently pulled through delivery system while observing device under fluoroscopy to ensure tether removal doesn't compromise fixation • Delivery system removed • Fluoroscopy cine recorded obtained after delivery system removal per study protocol (10 second recording in AP or other view) • Introducer removed	▪ Fluoroscopy
12	Closure	• Pressure is applied at access location • Stitch placed at access site per physician discretion • If Figure of 8 stitch was placed, suture is	▪ Needle and suture Optional Tools ▪ Market approved vascular closure

		tightened	device
13	Final Electrical Testing	• Final device interrogation performed and saved	▪ Model 2090 Programmer and Programmer Head

Appendix E: Informed Consent Templates

Consent form templates will be provided under a separate cover.

Appendix F: Relevant qualification document(s) of the Sponsor/Local Sponsor(Agent)

Relevant qualification document(s) of the Sponsor/Local Sponsor(Agent) will be provided under a separate cover.