China Micra™ Transcatheter Pacing Study

Statistical Analysis Plan (Version 1.0, 11/Dec/2018)

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Medtronic
Statistical Analysis Plan

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Kristie Wallace, Sr. Statistician

2. List of Abbreviations and Definitions of Terms

Table 1: List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
CEC	Clinical Events Committee
CFDA	China Food and Drug Administration
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRT	Cardiac Resynchronization Therapy
CRF	Case Report Form
CSR	Clinical Study Report
EC	Ethics Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
ICD	Implantable Cardioverter Defibrillator
IRB	Institutional Review Board
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
METS	Metabolic Equivalents of Task
M-PREP	Minnesota Pacemaker Response Exercise Protocol
MRI	Magnetic Resonance Imaging
OPC	Objective Performance Criterion
PHD	Pre-Hospital Discharge
PPS	Per Protocol Set
SS	Safety Analysis Set
SAP	Statistical Analysis Plan
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TPS	Transcatheter Pacing System

3. Introduction

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 yea[1]r (Mallela et al. 2004). Pacemakers remain the only known, long term effective treatment for bradycardia[2] (Gilles et al. 2012).

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 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 (TPS) 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, 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 the 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.[3]

In the global human study, 719 patients were implanted from 725 implant attempts.[3] 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.

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.

This Statistical Analysis Plan (SAP) has been designed to document - before any data is analyzed - the rationale for the study design, and the planned analyses, which will be included in the Final Clinical Study Report (CSR), summarizing the primary, secondary, [redacted] However, this SAP does not limit the analyses in reports and/or publications, and additional exploratory analyses of the study data may be conducted as deemed appropriate throughout the study. This SAP is developed in accordance with the China Micra™ Study Clinical Investigation Plan (CIP) version 3 (dated 19 April 2018).

4. Study Objectives

The study will have one primary objective, two secondary objectives [redacted] to characterize the safety and efficacy of the Micra™ Transcatheter Pacing System in human use in China. [redacted]

4.1 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 months post implant.

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

Major complications are those Adverse Events (AEs) 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.

4.2 Secondary Objective

1) To demonstrate the effectiveness of Micra TPS

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 are expected to be stable over time.

2) To summarize all adverse device effect throughout the study

All procedure and/or system-related AEs are collected throughout the duration of this study. AEs will be reported by event term and based on relatedness to procedure/system and event severity.

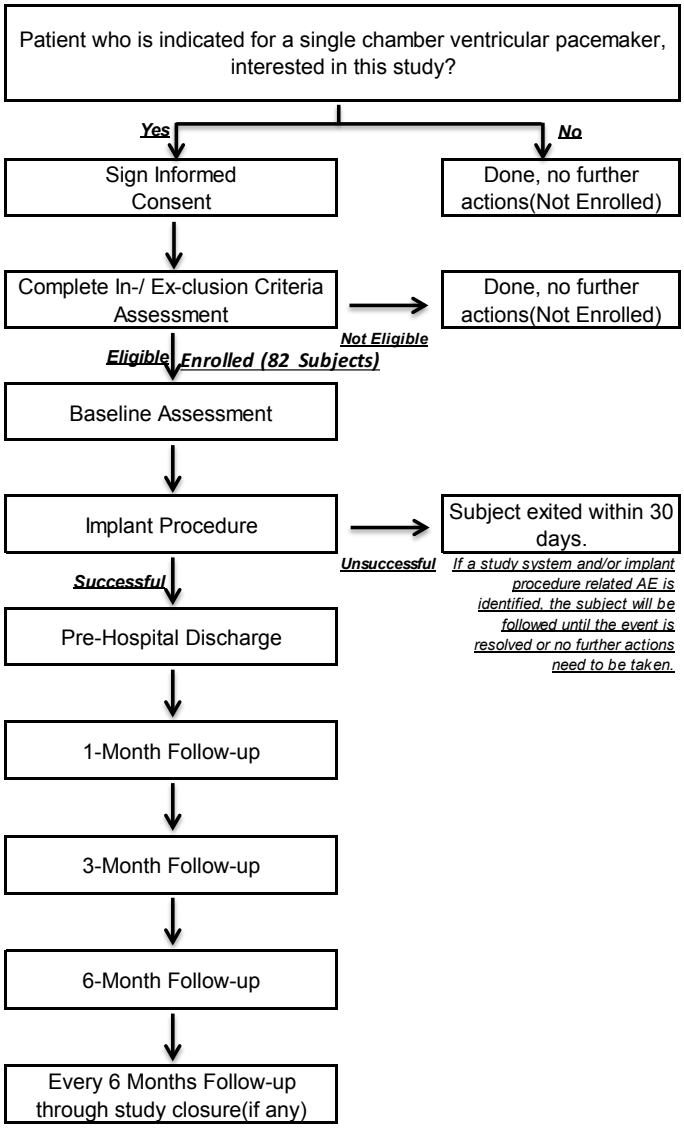
[redacted]

5. Investigation Plan

5.1 Study Design

The China Micra™ Transcatheter Pacing Study is a prospective, multi-center, single arm human clinical trial utilizing OPC to confirm the safety and efficacy profile of the Micra TPS for regulatory approval in China. All study sites will be in China. Subjects successfully implanted with the Micra TPS 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 subject has 6 months follow-up.

Figure 1: Study Flow Chart



The China Micra™ Transcatheter Pacing study will be conducted at 7 sites in China. The study will enroll a total of 82 subjects. All subjects with chronically implanted Micra devices 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 months to 12 months if the enrollment can be completed within 6 months. The estimated duration of whole clinical trial will be approximately 1 year including 6 months enrollment and 6 months follow-up.

5.2 Study Population

The China Micra™ Transcatheter Pacing study will be conducted in China. As such, the study population to be enrolled in the study will strictly be Chinese.

Ethics Committee approval of the China Micra™ Transcatheter Pacing Study CIP 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 meeting all 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 the inclusion and none of the exclusion criteria.

5.3 Inclusion Criteria

Table 2: 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[4] and China guideline.[5]	Study will be evaluated in the standard patient population that is 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.

5.4 Exclusion Criteria

Table 3: 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).
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 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 child bearing potential and who are not on a reliable form of birth regulation method or abstinence.	Pregnant women are excluded to avoid harm 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.

5.5 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
- Demographics and medical history will be collected at baseline 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 Case Report Forms (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 CIP and source data

- An independent CEC will be utilized to regularly review and adjudicate reported AEs
- All implanters in the study will be experienced in the implant of pacemaker systems and receive standardized training for the implant of the Micra TPS
- Final analysis of the study objectives will be carried out as pre-specified in this protocol

5.6 Study Procedures

All subjects enrolled in this study will be prospectively followed from implant, pre-hospital discharge, 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 shown in **Table 4**.

Table 4: 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*

Clinical data will be collected at baseline, implant/pre-hospital discharge (PHD), 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 5**.

Table 5: **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
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.

6. Determination of Sample Size

6.1 Total Enrollment Size

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

The study pass/fail criteria are based on statistical hypothesis and final analysis results. The analysis of study primary objective will be 6-month success rate comparing to the pre-specified OPC. If the 95% 2-sided confidence interval (CI) lower bound for the probability of freedom from Micra TPS 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.

The study attrition will include all scenarios that result in enrolled subject not being included in the analysis. The common reasons are due to serious protocol deviations (if it 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 comorbidities, 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%.

6.2 Rationale and Considerations for Sample Size Determination

The study size is determined by the sample size required for the primary objective. Reynolds et al. reported that the Micra TPS and/or procedure related complication free survival probability through 6 months was 96%, (95% CI: 93.3%, 97.6%) in those who underwent Micra TPS implant procedures.[3] 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:

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

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 are no drop-outs.

6.3 Sample Size Requirement for Each Study Center

The study will be conducted concurrently in multiple study sites. In principle, the number of enrollments 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 relatively balanced, and for any center, the maximum enrollment number should not exceed 50% of the total study size.

6.4 Significant Level and Statistical Power

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

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized by a STROBE flow diagram, similar to the study flow diagram shown in **Figure 1**, but providing additional details on subject follow-up and attrition.

7.1.2 Clinical Investigation Plan (CIP) Deviations

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 CRF 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 Ethics Committee (EC)/Institutional Review Board (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 endpoint analysis). However, prior approval from Medtronic is required for such situations. (Example may include: unable to complete atrial threshold testing due to chronic atrial fibrillation (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.

Deviations from the CIP will be summarized in the clinical study report by coded category. The number of deviations per category, and the number and percentage of subjects with a deviation in each category will be reported.

7.1.3 Analysis Sets

The analysis sets for this study are defined as follows. Further detail regarding the analysis sets can be found in Section 7.1.4.

Full Analysis Set (FAS): This is a dataset defined as 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 primary endpoint 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 and PPS. The electrical parameters (secondary objective #1) will be analyzed on the FAS and PPS. The safety assessment (secondary objective #2), and all baseline demographic summary will be performed on the FAS. [redacted] The baseline demographic summary, secondary objectives, [redacted] will be performed with available data from the database.

7.1.4 Pre-specified Protocol Deviations and Flow Chart of Analysis Population Set Determination

The following pre-specified protocol deviation items will be checked according to the principle of statistical analysis by SAS programming. These items may be a little bit different from the protocol deviations reported by clinical operation which are collected by CRF.

（1）Withdrawal of informed consent: Subjects obtain registration number, but do not end up using the study device. These are subjects who have had no exposure to the study device (i.e., no Successful or Unsuccessful Implant form is completed).

（2）Violation of inclusion and exclusion criteria: Subjects do not meet the inclusion criteria set in the protocol or meet the exclusion criteria set in the protocol, and this protocol deviation may severely affect the results of primary endpoint. Whether protocol deviation severely affect the results of primary effective endpoints shall be judged together by sponsor, investigators and statistician through discussion at a final data review meeting prior to final database lock.

（3）Lost to follow-up : Subjects are unable to obtain the primary endpoint (i.e. the primary endpoint is identified as true missing). If a subject has a primary endpoint failure, and later is lost to follow-up (prior to 183 days), the subject will still be included in the primary endpoint analysis. This criterion will only be used for the primary endpoint.

（4）Out of time window: The difference between the 6-month follow-up date after operation and operation date of subjects is less than 183 days and this may severely affect the results of primary endpoint. Whether protocol deviation severely affects the results of primary endpoint will be judged together by sponsor, investigators and statistician by discussion at the final data review meeting prior to final database lock. If a subject has a primary endpoint failure, and later has the 6 month visit too early (prior to 183 days), the subject will still be included in the primary endpoint analysis.

（5）Application of Non-study devices: The device implanted for subject is not the study device specified in study protocol or the subject ended up receiving no device at all. If a subject has a primary endpoint failure during the unsuccessful implant attempt, the subject will still be included in the primary endpoint analysis.

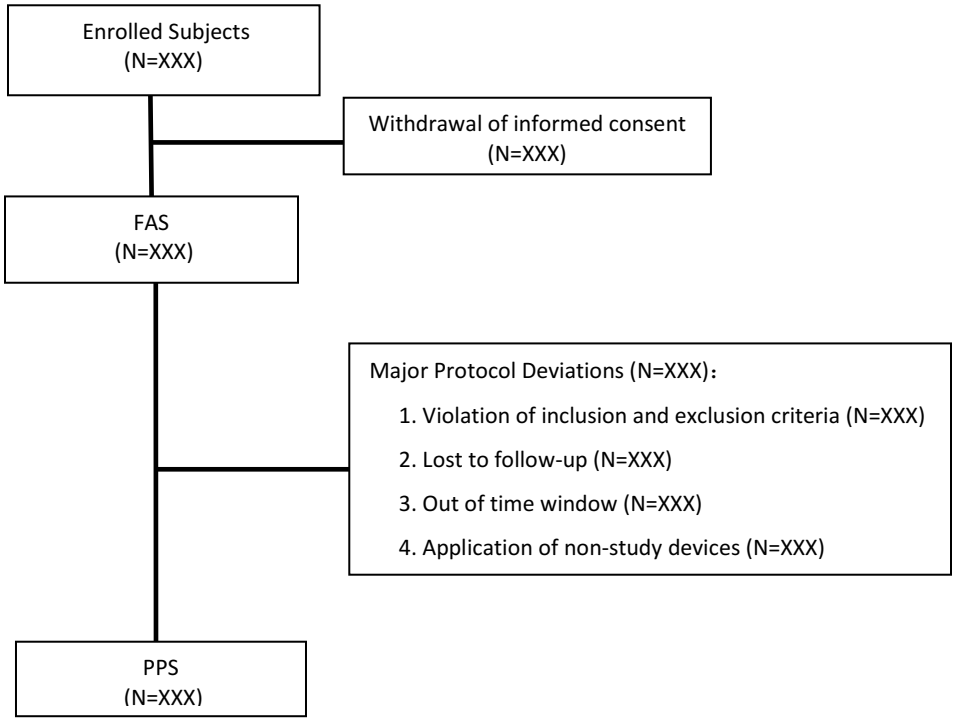
FAS= Number of the enrolled patients – Number of patients who withdraw informed consent;
PPS=FAS – Number of patients who severely violate study protocol;

Number of patients who severely violate study protocol = Number of patients who violate inclusion and exclusion criteria + Lost to follow-up + Number of patients with out of time window + Number of patients with application of Non-study devices

Priority level of severely violating study protocol: Lost to follow-up, application of non-study devices, violation of inclusion and exclusion criteria, out of time window. If subjects meet two or more above severe cases of protocol deviation, they will be classified in accordance with above priority level of protocol deviation.

The serious protocol deviations of subjects will be listed based on actual cases after final data review meeting determination. (For example, if the number of subjects who are out of time window is 0, this item will not be displayed in the table). Additionally, the subjects who were withdrawal of informed consent or serious protocol deviations will be listed, including the center number, registration number, gender, age, deviation type, deviation reason, FAS and PPS.

Figure 2: Flow Chart of Analysis Population Set Determination



7.2 General Methodology

After the study planning phase, the Leading Institution authorized statistician(s) will take responsibilities for statistical activities relevant to statistical analyses that will be used for China Food and Drug Administration (CFDA) submissions. All statistical analyses for the clinical study

report will be carried out and validated by the Leading Institution authorized statistician(s). The Medtronic statistician or designee will continue to be involved in the activities for quality control and provide consultation to study execution (as per Medtronic Guidelines for Statistical Activities Related to Medtronic-Sponsored Pre-Market Human Clinical Studies in China, version 2.0). The Medtronic statistician or designee will be responsible for all publication related statistical activities.

7.3 Center Pooling

The study will enroll 82 subjects from 7 investigational sites in China. The maximum enrollment number from a single site should not exceed 50% of the total enrollment size. Centers will be pooled for all analyses of study objectives.

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

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

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

Study subject disposition will be reported. Subjects visits will be tabulated, and compliance to study protocol required visit schedule will be summarized. Protocol deviations 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 analyses will be done to assess the potential impact of missing data. Refer to section 7.9.1.4 for further details.

7.5 Adjustments for Multiple Comparisons

No adjustments are planned for multiple comparisons.

7.6 Demographic and Other Baseline Characteristics

Baseline characteristics and relevant medical history will be collected on eCRFs for all enrolled subjects. Baseline characteristics will be summarized for all enrolled subjects. Baseline variables to be summarized include, but are not limited to: age, sex, race, height, weight, left ventricular ejection fraction (LVEF), pacing indication, arrhythmia history, medical and surgical history, and baseline cardiovascular medications.

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 for continuous data.

7.7 Treatment Characteristics

After enrollment in the China Micra clinical study, at each protocol required follow-up, the investigator must assess for any AEs or medication changes and evaluate the study device to verify study device function.

7.7.1 Implant

Implant information will be collected on eCRFs for all enrolled subjects. For subjects with successful implants, variables to be summarized include, but are not limited to: device location, number of times engaged, anticoagulation, type of anesthesia, closure method, impedance, R-Wave measurement, auto decrement threshold, capture management threshold, and procedure durations (e.g. skin to skin, introducer in/out, etc.). 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 for continuous data.

For subjects with unsuccessful implant attempt, a listing will be compiled to summarize available information, including the reason(s) the implant attempt was unsuccessful.

The Micra implant success rate will be assessed on a per subject basis, calculated as the number of subjects successfully implanted with a Micra TPS divided by the total number of subjects with at least one implant attempt expressed as a percentage.

7.7.2 Pre-Hospital Discharge

Pre-hospital discharge information will be collected on eCRFs for all subjects with Micra implant attempt. Variables to be summarized include but are not limited to: duration of hospital stay,

and electrical data (impedance, R-Wave measurements, auto decrement threshold, and capture management threshold) and activity restrictions for successfully implanted subjects.

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 for continuous data.

7.7.3 System Modification

In the event a system modification occurs, the data will be collected on the eCRFs. A listing will be compiled to summarize the system modification details. Information will include but is not limited to: reason for system modification, device repositioning, outcome of repositioning, extraction information, additional actions and electrical data.

7.8 Interim Analyses

There is no planned formal interim analysis for this study. However, descriptive summaries of the study data may be conducted as deemed appropriate throughout the study. All efforts will be made to ensure such descriptive analyses will not jeopardize the study final report. The final study analysis will be conducted after data collection is completed, verified and locked.

7.9 Evaluation of Objectives

7.9.1 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 months post implant.

7.9.1.1 Hypothesis

The primary endpoint is Micra TPS and/or procedure related major complications through 6 months (183 days) post implant. The corresponding statistical hypothesis for this study (utilizing 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 TPS 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% CI for the estimate is greater than 83%.

7.9.1.2 Statistical Analysis Method

All subjects who undergo 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 TPS and/or procedure related relate major complications. The log-log transformation will be used to calculate the 95% confidence limits.

Definitions:

- Endpoint event for the survival analysis is Micra TPS and/or procedure related major complications, defined as those AEs 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

The CEC will determine if the AE is related to Micra TPS and/or procedure; and if the AE is a major complication. **Note**: Only system or procedure-related AEs will be classified as a major complication, minor complication or an observation. In the event the CEC provides an "Unknown" classification relationship to the Micra TPS and/or procedure, the event will not be considered "Related" for the primary endpoint analysis. Refer to section 7.9.1.4 for additional information.

- Censoring occurs in subjects who do not experience any Micra TPS and/or procedure related major complications

- Follow-up time: from the date of Micra implant procedure to
    - the onset date of a Micra TPS 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 TPS 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.

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

A Kaplan-Meier survival analysis will be conducted to estimate the freedom from AEs classified as major complications that are related to the Micra TPS and/or procedure by the CEC within 6-months (183 days) post-implant. The Kaplan-Meier method is an appropriate method to analyze this endpoint as it enables inclusion of all subjects with an attempted implant. Additionally, the onset date of all Micra related major complications will be known to the nearest calendar day. Day of follow-up for subjects successfully implanted with the Micra TPS will be calculated as the minimum of the days from successful implant to: (1) onset date of a major complication related to the Micra TPS or procedure (if any), (2) study exit date (if exited), (3) death date (if death occurs), (4) 6-month follow-up visit (if completed), (5) last follow-up visit, or (6) 184 days. Subjects without a major chronic complication related to the Micra TPS and/or procedure during the follow-up period will be considered censored in the Kaplan-Meier analysis. Days of follow-up for subject who have only unsuccessful implant attempt(s) without being successfully implanted will be set to zero (0), unless a major complication occurs in which case the days of follow-up will be calculated from the date of unsuccessful implant attempt to the event onset date. The null hypothesis will be rejected in favor of the alternative if the lower boundary of the two-sided 95% CI is greater than 83%.

The 6-month (183 day) major complication freedom rate will be estimated using the Kaplan-Meier method with the log-log transformation to compute the two-sided CIs, [redacted]

[redacted]

Additionally, a corresponding one-sided p-value comparing the 6-month Micra procedure and/or system major complication freedom rate to 83% will be constructed using the formula:

$$z = \frac{\log\left(-\log\left(S(t)\right)\right) - \log(-\log(0.83))}{\sqrt{\sigma(t)^2 \Big/ \left(S(t) * \log\left(S(t)\right)\right)^2}}$$

Where S(t) is the observed 6-month (183 days) freedom rate and $\sigma^2(t)$ is Greenwood's estimate of the variance of the survival function at time t. The one-sided p-value will then be computed from the standard normal distribution as P(Z<z) [note this is the area of the standard normal distribution less than z since log(-log(S(t))) will be more negative than log(-log(0.83)) if S(t) > 0.83].

[redacted]

[redacted]

7.9.1.3 Determination of Subjects for Analysis

The primary objective will be analyzed using the FAS. All subjects with an attempted implant of the Micra TPS will be included in the analysis.

7.9.1.4 Missing Data for Primary Endpoint

Missing data may occur if a successfully implanted subject discontinues from the study without experiencing a major complication related to the Micra TPS and/or procedure prior to the 6-month visit. Data from such subjects is included in the primary analysis up until their censoring date, but it is unknown if these subjects would experience an event following their censoring date. Should the issue of missing data arise, the reasons for the missing data will be summarized to assess the plausibility that the missing data could change the statistical inference.

The Worst-Case Scenario Analysis will only be performed if it is identified as a true missing (e.g. permanent missing of AE-related data, and subsequently resulting in non-conclusive CEC review). The sensitivity analysis may count such missing data as failures.

A Tipping Point Analysis will only be performed if it is identified as a true missing (e.g. permanent missing of AE-related data, and subsequently resulting in non-conclusive CEC review).

In the event the CEC adjudicates an AE with an "Unknown" classification relationship to the Micra TPS and/or procedure, and the subject has no other failure events within 6 months post implant, a sensitivity analysis will be conducted to consider those subjects as failures at the time of the first "Unknown" classification event.

7.9.2 Secondary Objectives

The secondary objectives will be analyzed using descriptive statistics.

7.9.2.1 Secondary Objective #1

Objective:

To demonstrate the effectiveness of Micra TPS

Cohort definition and analysis method:

All available pacing capture thresholds, pacing impedance and R-wave amplitude data from all successfully implanted subjects from the implant and scheduled follow-up visits will be included in this analysis.

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

[redacted]

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 most of the subjects will have pacing capture thresholds $\leqslant$ 2 volts at all visits.

[redacted]

7.9.2.2 Secondary Objective #2

Objective:

To summarize all adverse device effects throughout the study

Cohort definition and analysis method:

Subjects will be assessed for AEs at all scheduled and unscheduled visits. All procedure related, system related, accessory related, underlying condition or disease related, and serious AEs will be collected on the eCRFs. Safety specialists will ensure that at a minimum all AEs that are potentially system related, potentially procedure-related, and all deaths will be classified by the CEC.

All subjects who undergo a Micra implant procedure will be included in this analysis. All reportable events will be reviewed by the event adjudication committee for relatedness to Micra TPS 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 subject cohort. Two-sided CIs will be computed using the Exact binomial method.

The CEC classification will be used in the analysis. AEs will also be reported separately for subjects with an unsuccessful implant, by relatedness. The number of events and number of subjects with events by MedDRA term will be displayed.

[redacted]

More details surrounding complication definitions can be found in section 7.10.4.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.10 Safety Evaluation

7.10.1 Adverse Events

Subjects will be assessed for AEs at all scheduled and unscheduled visits. All procedure related, system related, accessory related, underlying condition or disease related, and serious AEs will be collected on the eCRFs. Safety specialists will ensure that at a minimum all AEs that are potentially system related, potentially procedure related, and all deaths will be classified by the CEC. Summary tables will be compiled categorizing the AEs with respect to procedure relatedness, system relatedness (including system component), accessory relatedness, underlying condition or disease relatedness, and seriousness. For events classified by the CEC, the CEC classification will be used in the analysis; in cases where only the investigator classifies the event (i.e.., non-system and non-procedure related events), the investigator's classification

will be used. AEs will also be reported separately for subject with an unsuccessful implant, by relatedness. In addition, the number of events and number of subjects with events by MedDRA term will be displayed. A detailed listing of all AEs will also be provided.

All AEs collected during the study will be included in this analysis.

All information associated with each AE, including event description, severity, and relatedness to the system, etc., will be reported. In addition, the event rate will be summarized. The 2-sided 95% CIs will be calculated using the Exact Binomial method.

[redacted]

7.10.2 Deaths

Death information will be collected throughout the trial when the event occurs. Safety specialists will ensure that all deaths will be classified by the CEC. A summary table will be compiled with the death classification, as well as the relatedness to the procedure, system (including specific system component), accessory (including specific accessory or tool), and underlying condition or disease. The CEC classification of relatedness will be used. The number of events and percent of subjects will be provided.

7.10.3 Device Deficiency

In the event a device deficiency occurs, the data will be collected on the eCRFs. A listing will be compiled to summarize the device deficiency details, including description of the deficiency, date of onset, actions taken as a result of the deficiency, and the outcome of the event.

7.10.4 Adverse Event and Death Definitions

7.10.4.1 Relatedness

Procedure-related:

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

System-related:

An AE 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 AE that results from the presence or performance (intended or otherwise) of the Micra device
Delivery Catheter-related: An AE that results from the presence or performance (intended or otherwise) of the delivery catheter
Software-related: An AE that results from the performance (intended or otherwise) of the Micra software

Accessory/Tool-related:

Programmer-related: An AE that results from the presence or performance (intended or otherwise) of the programmer
Introducer-related: An AE that results from the presence or performance of the introducer
Implant tool-related: An AE that results from the presence or performance of the implant tool (excluding delivery catheter and introducer)
Extraction tool-related: An AE that results from the presence or performance of the extraction tool

Note: If an event occurs because 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 AE; however, any AEs occurring during an unsuccessful implant attempt (e.g. dissection, perforation) must be recorded and classified.

7.10.4.2 Complication

Complication:

An AE 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 AE 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 AE that is not a complication.

7.10.4.3 Death Classification

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

7.11 Health Outcomes Analyses

Not applicable for this study.

7.12 Changes to Planned Analysis

This SAP has been developed prior to data being analyzed to further describe the statistical methods and planned analyses of the study data to be included in the clinical study report. Any change to the data analysis methods described in the CIP will require a CIP amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP or SAP, and the justification for making the change, will be described in the clinical study report.

8. Validation Requirements

All statistical analyses for the clinical study report will be carried out and validated by the Leading Institution authorized statistician(s). Levels of validation required for the different

elements of the clinical study report are specified in the table below. In addition, the full clinical study report will be independently validated by Medtronic personnel.

Table 6: Validation Requirement

Validation Level	Definition	Required for
Level I	A peer reviewer independently programs output and then compares the output with that generated by the original author of the program to be validated	All analyses in the CSR pertaining to the primary and secondary objectives of the study
Level II*	A peer reviewer reviews the program, and where appropriate, performs calculations or programming checks to verify the output	All other analyses in the CSR (not pertaining to the primary and secondary objectives of the study)

*Level II validation is the minimum requirement; alternatively, level I validation can be performed if desired since it is more rigorous.

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