AccelAV Study (Accelerometer Sensing for Micra AV)

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Medtronic **Clinical Study Document Approval Form**	
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Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Accelerometer Sensing for Micra AV Abbreviated Name: AccelAV study
Study Product Name	Micra AV Transcatheter Pacing System
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1. Glossary

Term	Definition
A4	Accelerometer signal associated with active ventricular filling (associated with A-wave on echo)
ACC	American College of Cardiology
ACE	Atrial Contraction Excursion
AE	Adverse Event
AF	Atrial Fibrillation
ADE	Adverse Device Effect
ADL	Activities of Daily Living
AP	Anterior-Posterior
AV	Atrioventricular
AVB	Atrioventricular Block
CEC	Clinical Event Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organization
.csv	Comma-Separated Values file
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DMC	Data Monitoring Committee
EC	Ethics Committee
e-CRF	Electronic Case Report Form

Term	Definition
ECG	Electrocardiogram
EDC	Electronic Data Capture
Ethics Board	Term that will be used collectively to reference an Institutional Review Board (IRB), Medical Ethics Committee (MEC), Human Research Ethics Committee (HREC), Research Ethics Board (REB), or Ethics Committee (EC) unless otherwise stated
FAL	Foreseeable Adverse Event List
GCP	Good Clinical Practice
HIPPA	Health Insurance Portability and Accountability Act of 1996
HRS	Heart Rhythm Society
IC	Informed Consent
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDE	investigational Device Exemption
IFU	Instructions For Use
IRB	Institutional Review Board
ISF	Investigator Site File
LVEF	Left Ventricular Ejection Fraction
MATLAB	A multi-paradigm numerical computing environment and proprietary programming language developed by MathWorks, Natick, MA
MEC	Medical Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
MR	Magnetic Resonance
LVOT	Left Ventricular Outflow Tract
PHI	Protected Health Information

Term	Definition
RDC	Remote Data Capture
RV	Right Ventricular
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SID	Subject Identification Number
TAPSE	Tricuspid Annular Plane Systolic Excursion
TPS	Transcatheter Pacing System
US	United States
USB	Universal Serial Bus
VDD pacing mode	Sensing occurs in the atrium and in the ventricle, while pacing is limited to the ventricle. In VDD, pacing is synchronized to atrial sensing. In the absence of atrial activity, VVI pacing behavior is seen. The ventricle is paced synchronously to the atrium up to the programmed maximum tracking rate.
VDI pacing mode	Sensing occurs in the atrium and in the ventricle, while pacing is limited to the ventricle. In VDI, pacing is not synchronized to atrial sensing. The pacing behavior is the same as VVI pacing behavior. The ventricle is asynchronously paced to the atrium at the programmed lower rate.
VTI	Velocity Time Integral
VVI pacing mode	Sensing and pacing occur only in the ventricle.
VVIR pacing mode	Rate adaptive VVI pacing

2. Synopsis

Title	Accelerometer Sensing for Micra AV Abbreviated Name: AccelAV study
Clinical Study Type	Interventional Study
Product Name	Medtronic Micra™ AV Transcatheter Pacing System (Model MC1AVR1)
Sponsor	Medtronic 8200 Coral Sea Street Mounds view, MN 55112 1-800-633-8766
Investigation Purpose	Medtronic is sponsoring the AccelAV Study to characterize chronic AV synchrony in subjects implanted with Micra™ AV device. This study will be conducted upon market approval of the Micra™ AV Transcatheter Pacing System.
Product Status	

Model Number	Component (Manufacturer)	System or Accessory Component	Commercially Available* or Investigational
System Components			
MC1AVR1	Micra™ Implantable Device and Transfemoral Catheter Delivery System	System	Commercially available in applicable geographies
SW044	Micra™ Software Version 1.1 or most current Version	System	Commercially available in applicable geographies
Accessory Components			
MI2355+A	Micra Introducer Sheath (Medtronic)	Accessory	Commercially available in applicable geographies
29901 Series	Standard Medtronic Carelink Programmer	Accessory	Commercially available in applicable geographies
2090 Series	Standard Medtronic Carelink Programmer	Accessory	Commercially available in applicable geographies
9986	2090 Programmer Baseline Operating System Software	Accessory	Commercially available in applicable geographies
SW028	29901 Programmer Baseline Operating System Software	Accessory	Commercially available in applicable geographies

	<table><tr><td rowspan="2">Model ER220 Extended Range Holter Monitor**</td><td>ERX10 Extended Range Tel-B Antenna (Medtronic)</td><td>Accessory</td><td>Investigational</td></tr><tr><td>DR220 Holter (NorthEast Monitoring, Inc)</td><td>Accessory</td><td>Commercially available in applicable geographies</td></tr></table> * Either currently commercially available or will be approved for use in the geographies where the AccelAV study will be conducted prior to subject enrollment. **When permanently attached together, the commercial DR220 Holter and ERX10 Extended Range Tel-B Antenna become ER220 Extended Range Holter Monitor and will be considered investigational.
Primary Objective(s)	Characterize AV synchrony during rest at 1-month post-implant in subjects with persistent 3rd degree atrioventricular block (AVB) and normal sinus node function.
Secondary Objective(s)	1. Characterize the stability of AV synchrony during rest between 1-month and 3-months post-implant in subjects with persistent 3rd degree AVB and normal sinus node function. 2. Characterize the ambulatory AV synchrony at 1-month in subjects with persistent 3rd degree AVB and normal sinus node function. 3. Characterize the change in stroke volume, as measured by left ventricular outflow tract velocity time integral, during Micra AV mediated VDD pacing and VVI pacing in subjects with persistent 3rd degree AVB and normal sinus node function.
[redacted]	[redacted]
Study Design	The Accel AV study is a prospective, single-arm, global, multi-center clinical study to characterize the chronic AV synchrony in subjects implanted with the market released Micra AV (Model MC1AVR1) system. The study is planned to be conducted in the US and Hong Kong. Overall, the study is expected to be conducted at approximately 20 centers and will enroll up to 175 subjects to obtain

	approximately 150 subjects with usable Holter datasets at the 1-month visit to meet the sample size required to evaluate the primary objective of the study. Within 48 hours of implantation of a Micra AV, an echocardiogram will be performed. Subsequently, there are required study visits at 1-month and 3-months post-implant. The expected total study duration (from first subject enrollment to the exit of the last subject) is approximately 12-15 months, representing the time necessary to enroll the target sample size and to complete the 3-month follow-up visit.
Sample Size	A sample size of approximately 150 subjects with usable Holter recordings is required to evaluate the study's objectives. Based on the predicate MARVEL and MARVEL 2 studies it is expected that approximately half, or 75, of these subjects will have a predominant rhythm of persistent 3rd degree AVB and normal sinus node function during the 1-month visit. A sample size of 75 subjects with persistent 3rd degree AVB and normal sinus node function will allow the percentage of AV synchrony during rest to be measured with a precision (distance from point estimate to lower 2-sided 95% CI) of approximately ≤3.5%. Since not all subjects may have usable Holter datasets, up to 175 subjects may be enrolled.
Enrollment Strategy	The intent is to ensure that an adequate number of subjects (approximately 75) contribute to the primary and secondary objectives, specifically subjects with persistent 3rd degree AVB and normal sinus node function. Thus, Medtronic personnel will monitor the number of subjects with a predominant heart rhythm (based on the 1-month Holter monitor) of persistent 3rd degree AVB and communicate this number periodically to study site staff to ensure that an adequate number of subjects with this predominant rhythm are included in the study.
Inclusion Criteria	Inclusion Criteria • Subject will be implanted with a Micra™ (Model MC1AVR1) for an approved indication for use • Subject has history of AV block* • Subject is ≥ 18 years old and as per required local law. • Subject (and/or witness as applicable per local regulations) provides signed and dated authorization and/or consent per institution and local requirements. • Subject is willing and able to comply with the protocol. *This includes subjects with normal sinus node function and persistent 3rd degree AV block and subjects with other forms of AV block.
Exclusion Criteria	Exclusion Criteria

	• Subject currently enrolled or planning to participate in a potentially confounding drug or device trial during the study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic Clinical Research Specialist • Subject implanted with a Micra™ (Model MC1AVR1) on a non-permanent basis (e.g. CIED infection) • Subject is pregnant (if required by local law, women of child-bearing potential must undergo a pregnancy test within seven days prior to Micra™ Model MC1AVR1 implant procedures) • Subject meets any exclusion criteria required by local law (age or other).
Study Procedures and Assessments	After consent and enrollment, the subject will be implanted with a Micra™ (Model MC1AVR1). During implant, data will be collected to characterize the implant procedure. Immediately following implant, a Holter will be placed for approximately 1 hour to record data related to the device's Atrial Sensing Setup process. Within 48 hours of implant, an echocardiogram will be performed in both VDD and VVI modes. At the 1-month and 3-month visits, data, including any reportable adverse events, will be collected, an initial Micra™ Model MC1AVR1 device interrogation will be performed, and a customized Holter monitor will be placed on the subject. The Holter will record surface ECG, EGM, accelerometer signals, and device markers. Following Holter placement at the 1-month and 3-month visit, the subject will rest quietly for approximately 20-minutes to assess AV synchrony during rest. Additionally, at the 1-month visit, the subject will wear the Holter for approximately 24-hours to assess ambulatory AV synchrony performance. The study participation is expected to last 3 months.
Safety Assessments	All Micra AV system (including the Micra AV device, delivery system and software) or procedure related adverse events (AEs) and all cardiovascular related AEs regardless of their severity that occur from the time of enrollment through study exit will be collected and reported to Medtronic starting from the time the Informed Consent Form is signed. Additionally, all deaths will be reported on an AE CRF. Additionally, any device deficiencies related to the Micra™ Model MC1AVR1 transcatheter pacing system will be collected.
Statistics	The primary objective of the study is to characterize the percentage of AV synchrony in subjects with a predominant rhythm of persistent 3rd degree AVB and normal sinus node function during rest at the 1-month study visit. For each ECG detected P-wave, the primary endpoint will be considered met if the Micra AV system delivers a

	pacing spike or senses an intrinsic R-wave within 300 ms of the confirmed P-wave. A logistic regression model utilizing generalized estimating equations to account for within subject correlation in AV synchrony status will be used to estimate the average percentage of AV synchrony in the study population during rest and its two-sided 95% confidence interval. In addition, AV synchrony percentage will also be computed using the methods described above for subjects not included in the primary objective cohort including those with intact AV conduction or other predominant rhythms.

3. Introduction

3.1. Background

The Micra™ Transcatheter Pacing System (TPS), Model MC1VR01, hereafter referred to as Micra VR, was developed to provide pacing entirely within the right ventricle to minimize or eliminate the acute and chronic complications related to the leads and pocket-based generator of traditional transvenous systems.[1] In a cohort of 726 implants with a median follow-up of 16.9 months, Micra VR had a system or procedure major complication rate that was nearly half that observed in studies of traditional transvenous pacing systems[2] and these results have been maintained in real-world settings.[3]

The Micra™ Model MC1AVR1, hereafter referred to as Micra AV, is expected to be approved for use in all the geographies where the AccelAV study will be conducted, specifically: US and Hong Kong. The Micra AV system provides all the functionality of the Micra VR system including VVI(R) pacing. Additionally, the Micra AV system provides a form of VDD pacing that is based on mechanical atrial sensing utilizing the device's 3-axis accelerometer, which provides rate response in the Micra VR.[4] This allows the potential benefits of leadless pacemakers for patients where there is a need to preserve atrioventricular synchrony, such as those with AV block.[5]

The MASS/MASS2 studies collected the intracardiac accelerometer signal from 39 subjects with an implanted Micra VR and intrinsic AV conduction during the study period. These studies showed that four distinct signals, including a signal associated with atrial contraction (designated A4) could be observed.[6] Accelerometer signals from these subjects were used to develop an algorithm to provide AV synchronous pacing. That algorithm was evaluated in the MARVEL study. The MARVEL study demonstrated improved atrioventricular synchronous pacing in humans using Micra VR's intracardiac accelerometer to mechanically detect atrial contraction.[6] Specifically, a total of 64 subjects completed the MARVEL study procedure at 12 centers in 9 countries. The MARVEL study showed that the average AV synchronous pacing percentage was 87.0% (95% CI: 81.8% - 90.9%) across all subjects and 80.0% in

subjects with high-grade AV block. In subjects with high-grade AV block, the AV synchrony was greater than the 37.5% observed during VVI pacing (p<0.001). The MARVEL study also demonstrated that VDD pacing based on mechanical atrial sensing was safe. A sub-study of the MARVEL study, MARVEL-Evolve, re-tested the MARVEL algorithm in patients from one center to compare the accelerometer signals and AV synchrony at two time-points.[7] The mean time between visits was 7.1±0.6 months. MARVEL-Evolve study showed no evidence of a difference in the percentage of AV synchrony during rest between study visits (p=0.740). There was no difference in the A4 amplitude during rest between visit 1 (205.7 mG, 95% CI: 97.9 – 313.6 mG) and visit 2 (207.1 mG, 95% CI: 91.9 – 322.4 mG, p=0.933).

The accelerometer signal is complex and currently is not well understood by clinicians. Therefore, it is desirable to reduce the clinical burden and expertise required to accurately set up the accelerometer detection algorithm. To accomplish this, Medtronic enhanced the MARVEL algorithm to automatically adjust the most often programmed detection parameters. In addition, two mode-switching algorithms were incorporated: 1) a mode-switch to VVI-40 for patients with paroxysmal AV block who often have intact AV conduction and 2) a mode-switch algorithm that switches to VVIR (rate adaptive pacing) if the sensor rate is significantly faster than the VDD pacing rate. The performance of the enhanced algorithm was the focus of the MARVEL 2 study, which showed the safety and ability of mechanical sensing of the atrium to provide atrioventricular synchronous pacing during rest leading to improved cardiac function in subjects with persistent 3rd degree AV block and normal sinus node function.[8] Specifically, among 40 subjects with a predominant rhythm of persistent 3rd degree AV block and normal sinus node function, 38 (95.0%) had >70% AV synchrony during rest compared to 0% during VVI pacing (P<0.001) with average AV synchrony percentage improving from 26.8% during VVI pacing to 89.2% during mechanical sensing based VDD pacing. In these same subjects, stroke volume, as measured by LVOT VTI, increased from 22.7 cm during VVI pacing to 24.5 cm (P=0.002) during VDD pacing as measured by blinded echocardiogram assessment. The MARVEL 2 clinical study was used as pivotal evidence to support market approval of the Micra AV system for expanding the use of transcatheter pacing systems into patients with AV block and normal sinus node function.

The focus of Accelerometer Sensing for Micra AV Study (AccelAV) is to characterize chronic AV synchrony in subjects implanted with the market released Micra AV.

3.2. Purpose

The purpose of the **Accel**erometer Sensing for Micra **AV** Study is to characterize chronic AV synchrony in subjects implanted with the market released Micra AV (Model MC1AVR1).

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective

Characterize AV synchrony during rest at 1-month post-implant in subjects with persistent 3rd degree AVB and normal sinus node function.

4.1.2. Secondary Objectives

4.1.2.1. Secondary Objective #1

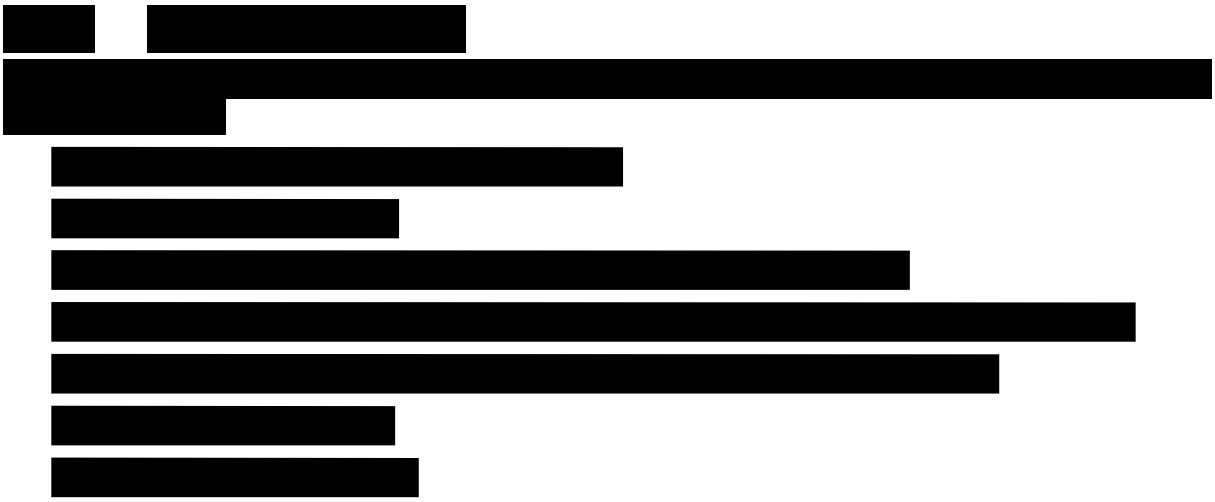
Characterize the stability of AV synchrony during rest between 1-month and 3-months post-implant in subjects with persistent 3rd degree AVB and normal sinus node function.

4.1.2.2. Secondary Objective #2

Characterize the ambulatory AV synchrony at 1-month post-implant in subjects with persistent 3rd degree AVB and normal sinus node function.

4.1.2.3. Secondary Objective #3

Characterize the change in stroke volume, as measured by left ventricular outflow tract velocity time integral, during Micra AV mediated VDD pacing and VVI pacing in subjects with persistent 3rd degree AVB and normal sinus node function.



4.2. Endpoints

AV Synchrony: AV synchrony will be computed on an individual heartbeat basis and is defined as met for paced or sensed ventricular beats that are within 300 ms following an ECG confirmed P-wave. This endpoint will be used for the primary objective (AV synchrony during rest at 1-month post-implant), for the secondary objective #1 (stability of AV synchrony during rest between 1-month and 3-months post-implant) and for the secondary objective #2 (ambulatory AV synchrony at 1-month post-implant).

[redacted]

[redacted]

Micra AV system revision: A Micra AV system revision is defined as an invasive modification (i.e., explant attempt or repositioning attempt) or programming the device off (i.e., programming pacing mode to OOO or Device Off mode) on a permanent basis after an initial successful implant.

LVOT VTI: This endpoint is the left ventricular outflow tract (LVOT) velocity time integral (VTI) as obtained from echocardiogram while the Micra AV is programmed to VDD and VVI pacing. This will be measured by the Echo Core Lab.

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[redacted]

[redacted]

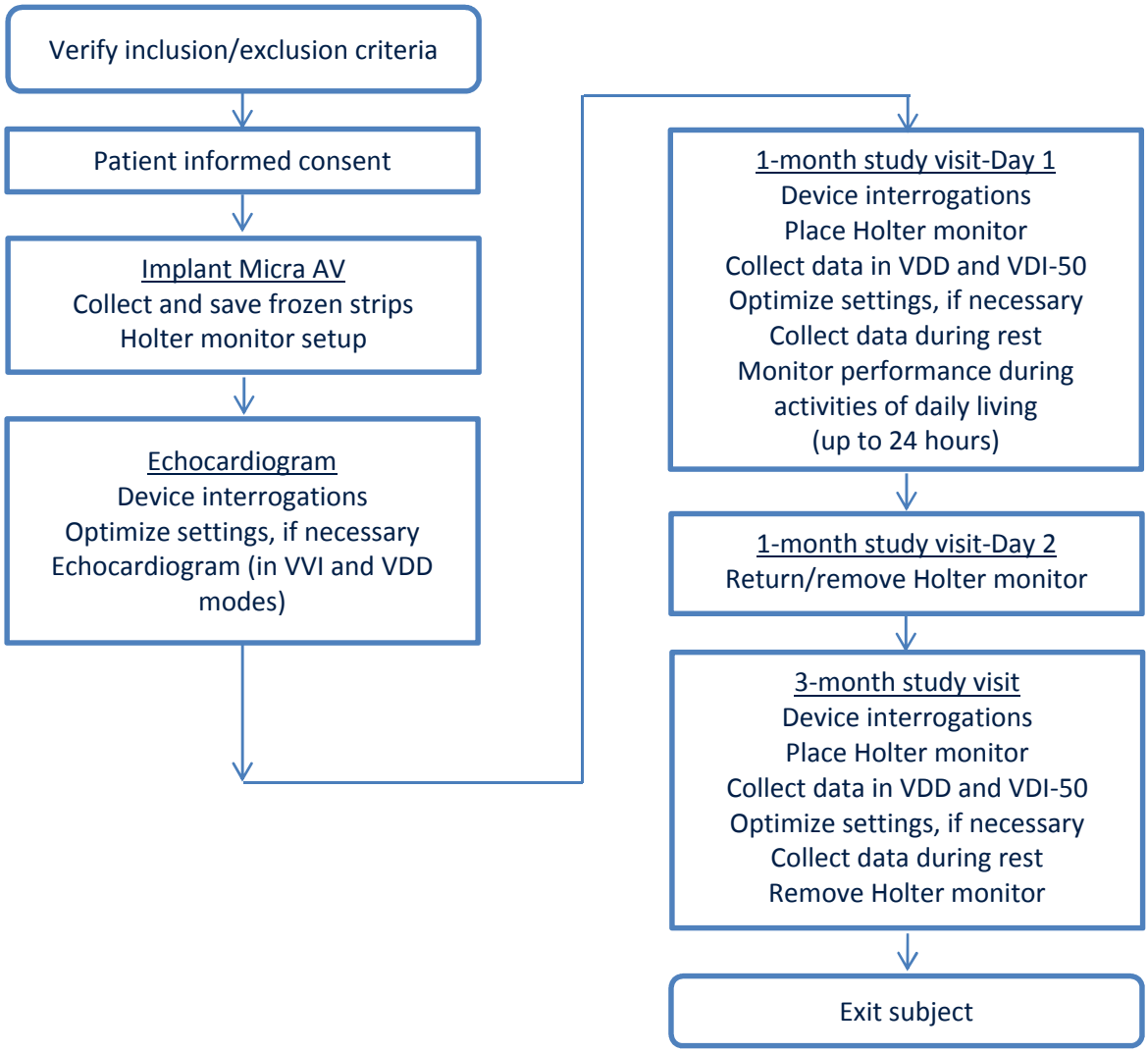
[redacted]

5. Study Design

The Accel AV study is a prospective, global, multi-center clinical study to characterize the chronic AV synchrony in subjects implanted with the market released Micra AV. The study is planned to be conducted in the US and Hong Kong. Overall, the study is expected to be conducted at approximately 20 centers and will enroll up to 175 subjects to obtain approximately 150 usable Holter datasets at the 1-month follow-up visit to meet the sample size required to evaluate the primary objective of the study. Holter datasets will be considered usable if there are readable telemetry signals as determined by Medtronic personnel experienced in the review of Holter recordings.

There is no minimum number of subjects required to be enrolled at a center. However, to ensure a widespread distribution of data and minimize center bias in study results, the maximum number of enrolled subjects at a single site is 30 (or approximately 20% of the target sample size). Figure 1 displays the AccelAV study flow for all study subjects.

Figure 1. AccelAV Study Flow



5.1. Duration

The expected total study duration (from first subject enrollment to the exit of the last subject) is approximately 12-15 months. This represents the time necessary to enroll the target sample size of at least 150 subjects and to complete a 3-month follow-up.

Subject study visits will include baseline, Micra AV implant, an echocardiogram, 1-month post-implant and 3-months post-implant.

Overall, individual subject study participation is approximately 26-28 hours across all study visits including the overnight hours of the Holter monitor recording at the 1-month study visit. These study visits include:

- Baseline: At baseline, a subject's height, weight, and blood pressure will be measured. In addition, quality of life and patient symptoms questionnaires will be completed. This visit will take approximately 10-15 minutes.
- Implant: At implant, study procedures will consist of confirming programming of the subject's Micra AV device and will take approximately 15-20 minutes in total to collect accelerometer and EGM waveform data, device interrogations, placement of a Holter monitor, and additional programming per physician's discretion.
- Echocardiogram: Within 48 hours of the Micra AV implant, the subject will have an echocardiogram. This will take approximately 30-45 minutes. Prior to the echocardiogram, atrial sensing of the Micra will be assessed and sensing parameters may be optimized. The expected time for this assessment is approximately 30 minutes.
- 1-month follow-up: Approximately 1 hour of in-clinic testing will be performed at the 1-month follow-up. Subsequent to this testing, the subject will wear a Holter monitor for 24 hours to record Micra AV performance during the subject's activities of daily living. The subject will receive an activity log to document activities of daily living described in Ambulatory Holter Monitoring (1-Month Visit Only)
- 3-month follow-up: Approximately 1 hour of in-clinic testing will be performed at the 3-month follow-up. Once this is completed, the subject will be exited from the study.

5.2. Rationale

The acute nature of the MARVEL 2 study was meant to optimize the length of data collected with the limitation that the mechanical sensing algorithm in its downloadable implementation, combined with the study's Holter telemetry requirements, consumed battery energy at an unacceptable rate for longer-term testing. Thus, data collection to assess AV synchrony in MARVEL 2 was limited to less than 5 hours. Therefore, the main focus of the AccelAV study is to characterize chronic AV synchrony in subjects implanted with the market released Micra AV system. The objectives of this study are to characterize, at rest, the percentage and stability of AV synchrony respectively at the subject's 1- and 3-month study visits.

5.3. Minimization of Bias

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

1. Subjects will undergo screening to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment.
2. All centers will use the same version of the clinical investigation plan and standardized case report forms.
3. All investigational center personnel, echocardiogram core lab personnel, and Medtronic personnel will be trained using standardized training materials.
4. An independent echocardiogram core lab will make all echocardiogram measurements. The Echo Core Lab will also be blinded to the study center, subject, and pacing mode (VDD or VVI) when making LVOT VTI measurements.
5. To ensure widespread distribution of the data between study centers, a maximum of 30 subjects may enroll at any single study center.
6. Regular monitoring visits will be conducted for adherence to the CIP and to verify source data.
7. A statistical analysis plan will be developed prior to analyzing data. The plan will further document all pre-specified analyses and analysis methods.
8. An independent CEC will regularly review and adjudicate reported adverse events.

6. Product Description

6.1. General

The study will be conducted using the components described in Table 1 below. Products are listed as Commercially Available or Investigational in applicable geographies. Instructions for use are provided in the respective device manuals; each of the system and accessory components are manufactured by Medtronic with the exception of the DR220 Holter Monitor. Figure 2 depicts the Micra AV System. Refer to the respective manuals for any possible interaction with concurrent medical interventions.

Table 1: System component information

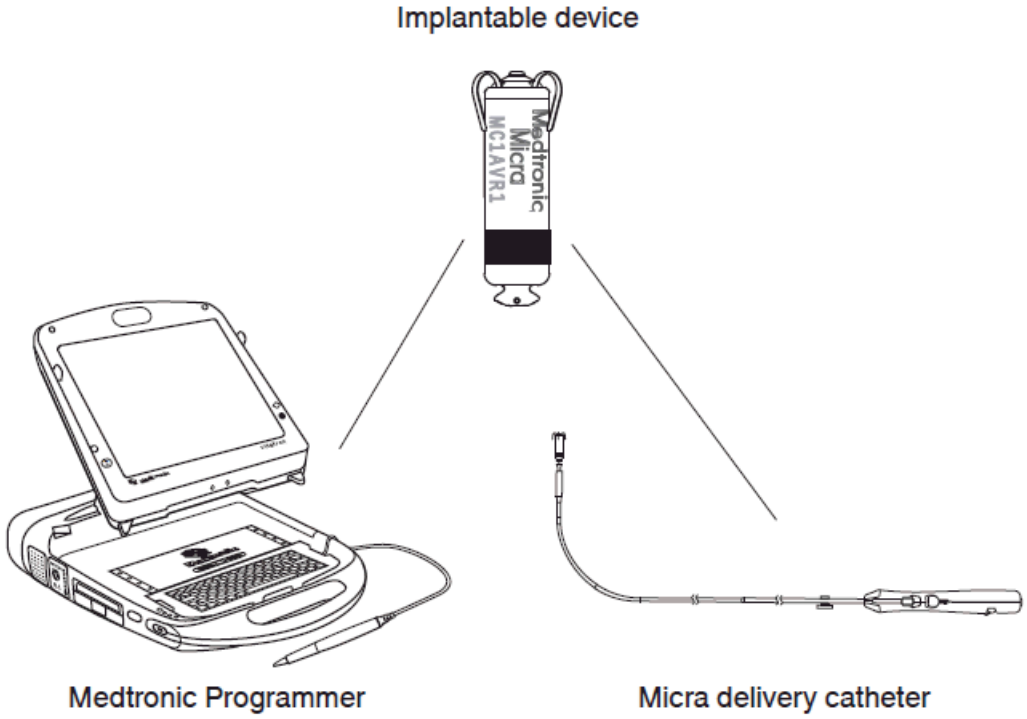
Model Number	Component (Manufacturer)	System or Accessory Component	Commercially Available* or Investigational
System Components			
MC1AVR1	Micra Implantable Device and Transfemoral Catheter Delivery System (Medtronic)	System	Commercially available in applicable geographies

Model Number	Component (Manufacturer)	System or Accessory Component	Commercially Available* or Investigational
SW044	Micra Software Version 1.1 or most current Version (Medtronic)	System	Commercially available in applicable geographies
Accessory Components			
MI2355+A	Micra Introducer Sheath (Medtronic)	Accessory	Commercially available in applicable geographies
29901 Series	Carelink Encore Programmer (Medtronic)	Accessory	Commercially available in applicable geographies
2090 Series	Carelink Programmer (Medtronic)	Accessory	Commercially available in applicable geographies
9986	2090 Programmer Baseline Operating System Software (Medtronic)	Accessory	Commercially available in applicable geographies
SW028	29901 Programmer Encore Baseline Operating System Software (Medtronic)	Accessory	Commercially available in applicable geographies
Model ER220 Extended Range Holter Monitor System ER220**	Model ERX10 Extended Range Tel-B Antenna (Medtronic)	Accessory	Investigational in all geographies
	DR220 Holter (NorthEast Monitoring, Inc.)	Accessory	Commercially available in applicable geographies

* Either currently commercially available or will be approved for use in the geographies where the AccelAV study will be conducted prior to subject enrollment.

**When permanently attached together, the DR220 Holter and ERX10 Extended Range Tel-B Antenna become ER220 Extended Range Holter Monitor and will be considered investigational.

Figure 2 : **Micra AV Transcatheter Pacing 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 AV device are similar to those for the commercially available Micra VR transcatheter pacing system. Detailed descriptions of the system and accessory components are listed in the sections below.

6.1.1. Micra AV Transcatheter Pacing System

The Medtronic Micra AV Model MC1AVR1 MR Conditional dual chamber, transcatheter pacing system with SureScan technology is a programmable cardiac device that monitors and regulates the patient's heart rate by providing rate-responsive bradycardia pacing to the right ventricle and AV synchrony based on the mechanical sensing of atrial activity.

6.1.1.1. Implantable device

The Micra AV Model MC1AVR1 is a dual chamber transcatheter pacing system that provides AV synchronous pacing and bipolar sensing and pacing in the right ventricle. The device has an active

fixation mechanism consisting of 4 electrically inactive tines designed to anchor the device in the cardiac tissue at the implant location in the right ventricle.

6.1.1.2. Device Delivery Catheter System

The Micra AV delivery catheter system consists of the following parts:

A delivery catheter designed to carry, deliver, and position the device for implant in the right ventricle by accessing this chamber through the femoral vein. The delivery catheter has a steerable, flexible shaft with a rigid distal end that contains a device cup to hold the device and a recapture cone to retrieve it. The delivery catheter is compatible with a 7.8 mm (23 Fr) introducer sheath that is 56 cm (22 in) long or longer, such as the Medtronic Micra Introducer.

A handle with controls to navigate the delivery catheter and deploy the device. The handle also provides a tether designed as an aid to test the device fixation and to recapture and reposition the device for proper fixation during the implant procedure.

6.1.1.3. Programmer and Software

The Medtronic programmer and software are used to program the device for implant testing and patient follow-up sessions. The use of a Medtronic programming head is required for communication between the device and the programmer. Programmers from other manufacturers are not compatible with Medtronic devices but will not damage Medtronic devices.

6.1.2. Extended Range Holter Monitor System

A customized investigational Extended Range Holter Monitor System (ER220) will be used to collect data from the Micra AV in all study subjects. The ER220 system uses a market-released Model DR220 Holter Monitor (NorthEast Monitoring, Inc, Maynard, MA) and an investigational accessory cable (Model ERX10) created by Medtronic, Inc. The accessory cable is based on a market-released cable that communicates with the implanted devices via telemetry; it has been modified to extend its range and increase noise rejection to communicate with the Micra device inside the heart.

Each study site will receive Medtronic Extended Range Holter Monitor Systems (ER220, each system consists of a DR220 Holter and ERX10 Extended range Tel-B antenna cable), in order to perform the study procedure on the enrolled subjects. Based on estimated AccelAV enrollment rates for participating sites, it is expected that approximately 2-3 Holter monitors per site need to be provided. The participating site and sponsor will use a Holter disposition log to track this item.

6.2. Dosage Form and Route of Administration

This section is not applicable.

6.3. Manufacturer

The Micra AV system and ancillary components are manufactured by Medtronic except for the commercial DR220 Holter Monitor manufactured by NorthEast Monitoring Inc, Maynard, MA.

6.4. Packaging

Labeling for the commercially available Micra AV systems and ancillary components can be found with each package insert and is provided in English language. Labeling is also found on http://manuals.medtronic.com.

The investigational Holter monitor will be labeled according to the local regulatory requirements. Outside the United States it will state "Exclusively for Clinical Investigations" and in the US it will state "CAUTION: Investigational Device, limited by Federal law (USA) to investigational use."

6.5. Intended Population

Micra Model MC1AVR1 will be used as intended per the Micra™ AV MC1AVR1 Device Manual and inclusion/exclusion criteria as described in section 7.

6.6. Equipment

The maintenance and calibration of the Medtronic Carelink Programmers used for this study will be conducted using standard Medtronic processes and is not part of this clinical study. Sites are responsible for maintaining and calibrating equipment (such as an echo machine and Medtronic Carelink Programmer) used during this study in accordance with established site practice or local regulation. Maintenance and calibration records should be kept and able to be provided upon request by the Sponsor or Regulatory Agency.

6.7. Product Use

Micra Model MC1AVR1 will be used within its approved labeling and inclusion/exclusion criteria as described in section 7.

6.8. Product Training Requirements

Product training on the Micra AV system and ancillary components is required prior to the clinical site's first study procedure. Training on the implantation and ongoing system management must be performed by individuals trained in the operation and handling of the system and be in compliance with procedures described in the appropriate technical instructions. Principles of operation of the ER220 Holter Monitor will be provided in the Digital Holter ER220 Instructions.

6.9. Product Receipt and Tracking

Commercially available product will be tracked in a manner consistent with other market-released products. The date when the study participating site receives the investigational ER220 Holter Monitors will be maintained during the clinical investigation. Each received Holter monitor will be traced by the Holter serial number.

6.10. Product Storage

Commercially available product will be stored in a manner consistent with other market-released products. The storage area of ER220 Holter Monitors should be locked and secure with access limited only to approved study trained personnel. The Medtronic Carelink Programmers can be used for commercial use and there are no special storage requirements.

6.11. Product Return

ER220 Holter Monitors will be shipped back to Medtronic Operational Support at 8200 Coral Sea St. NE, RM S1221, Mounds View, MN 55112, USA, at the end of the AccelAV clinical study. Commercially available product related to device explant and return products/procedure will be managed in a manner consistent with other market-released products, as applicable.

6.12. Product Accountability

All products used in the AccelAV study, with exception of the ER220 Holter Monitor, will become commercially available to study participating geographies prior to each site's first enrollment in the study. Product accountability may be required per local laws and regulations. Product accountability will be documented in the electronic Case Report Forms (e-CRFs) which will be maintained in the Electronic Data Capture (EDC) system. The e-CRF will track at a minimum: date of receipt, serial number of the investigational components, location of the investigational components, and date and reason for return.

Device information of the Micra AV system will be collected at implant (e.g., model number, serial number). If there are additional local requirements related to implanted information beyond what is collected by Medtronic on the e-CRF, it is the investigator's responsibility and should be recorded in the subject's medical records, but will not be collected by Medtronic (e.g., national registration card number, identification code linked to names and contact information, log of all subjects enrolled in the clinical study, lot or batch number).

Commercially available product supply will be managed in a manner consistent with other market-released products.

7. Selection of Subjects

7.1. Study Population

The target population will consist of subjects ≥18 years in age, who are being implanted with a Micra AV per approved indications for use.

7.2. Subject Enrollment

Ethics Board and Medtronic approval of this clinical investigation plan, the Informed Consent Form, and any other applicable documents must be obtained prior to enrolling subjects in the study. Medtronic will provide each study center with documentation of study center and investigator readiness; this letter must be received prior to subject enrollment.

When a patient and the principal investigator or authorized designee, as required, have personally signed and dated the Informed Consent Form, the patient is considered a subject enrolled in the study. Subjects must provide informed consent before any study related procedures. The date the subject signed the Informed Consent Form and data protection authorization, as required by local law, must be documented in the subject's medical records.

Subjects will be screened to ensure they meet all inclusion criteria and none of the exclusion criteria prior to study enrollment.

7.3. Inclusion Criteria

- Subject will be implanted with a Micra™ (Model MC1AVR1) for an approved indication for use
- Subject has history of AV block*
- Subject is ≥ 18 years old and as per required local law
- Subject (and/or witness as applicable per local regulations) provides signed and dated authorization and/or consent per institution and local requirements
- Subject is willing and able to comply with the protocol

*This includes subjects with normal sinus node function and persistent 3rd degree AV block and subjects with other forms of AV block.

7.4. Exclusion Criteria

- Subject currently enrolled or planning to participate in a potentially confounding drug or device trial during the study. Co-enrollment in concurrent trials is only allowed when documented pre-approval is obtained from the Medtronic Clinical Research Specialist
- Subject implanted with a Micra™ (Model MC1AVR01) on a non-permanent basis (e.g. CIED infection)
- Subject is pregnant (if required by local law, women of child-bearing potential must undergo a pregnancy test within seven days prior to Micra™ Model MC1AVR01 implant procedures)
- Subject meets any exclusion criteria required by local law (age or other)

7.5. Enrollment Strategy

The intent is to ensure that an adequate number of subjects (approximately 75) contribute to the primary and secondary objectives, specifically subjects with persistent 3rd degree AVB and normal sinus node function. Thus, Medtronic personnel will monitor the number of subjects with a predominant heart rhythm (based on the 1-month Holter monitor) of persistent 3rd degree AVB and communicate this number periodically to study site staff to ensure that an adequate number of subjects with this predominant rhythm are included in the study.

8. Study Procedures

8.1. Schedule of Events

After subject enrollment, study procedures will consist of collecting subject's medical history, physical exam, cardiovascular medications, and device implant information. During the Micra AV implant, additional study-specific data will be collected including: accelerometer and EGM waveforms (either paper strips or electronic form) and device interrogations. Immediately following implant, a Holter will be placed for approximately 1 hour to record data related to the device's Atrial Sensing Setup process.

Within 48 hours of the Micra AV implant, an echocardiogram will be performed. Prior to the echocardiogram, the atrial sensing will be reviewed and optimized, if necessary.

One month after the Micra AV implant, the subject will come into an in-clinic setting for the 1-month post-implant visit. See Table 3: Follow-up Visit Windows. A Holter monitor will be placed on the subject to record accelerometer, EGM, and ECG waveforms and device-specific markers. The atrial sensing will be reviewed and optimized, if necessary. Overall, approximately 30 minutes of data will be collected during the in-clinic visit with approximately 20 minutes collected at rest. The subject will then be given an activity log to be filled out and will wear the Holter monitor for approximately 24 hours. The Holter can be returned in-person or sent back in a pre-addressed package.

Three months after the Micra AV implant, the subject will come back for the final in-clinic 3-month post-implant study visit. See Table 3: Follow-up Visit Windows. A Holter monitor will again be placed on the subject to record accelerometer, EGM, and ECG waveforms and device-specific markers. The atrial sensing will be reviewed and optimized, if necessary. Overall, approximately 30 minutes of data will be collected during the in-clinic visit with approximately 20 minutes collected at rest. Following the in-clinic data collection, the Holter monitor will be removed, and the subject will be exited from the study.

Overall, individual subject study participation is approximately 26-28 hours across all study visits including the overnight Holter monitoring at the 1-month study visit. A summary of the data collected for this study is displayed below in Table 2.

Table 2: AccelAV Data Collection Summary

AccelAV Study Data Collection	Baseline	Micra AV Implant	Echocardiogram	1-month visit	3-month visit
Inclusion/exclusion assessment	X				
Patient informed consent	X				
Demographics and pacing indication	X				
Medical history	X				
Height and weight	X				
12-lead ECG	X				
Blood pressure	X				
Cardiovascular medications	X		X	X	X
Patient symptom checklist	X			X	X
Quality of life questionnaire	X			X	X
Micra AV implant procedure data collection		X			
Accelerometer waveform data collection		X			
Holter monitoring post-implant		X			
X-rays of Micra AV implant location		X			
Echocardiogram			X		
Initial device interrogation			X	X	X
Confirm atrial sensing parameters			X	X	X
In-clinic Holter monitoring				X	X
Ambulatory Holter monitoring				X	
Subject activity log				X	
Final device interrogation		X	X	X	X
Study exit					X
Adverse events	If Occur				
Study deviations					
Device deficiencies					
System modification*					
Unsuccessful implant					
Unscheduled visit					

* If the primary reason for the system modification is pacemaker syndrome then collect the subject's blood pressure and 12-lead ECG prior to the system modification procedure.

8.2. Subject Screening

Pre-screening of potential subjects may be over the telephone or in person (e.g. during a routine clinical care visit) to determine their initial eligibility and interest in the study.

Final screening of potential subjects needs to be performed in person on the day of the baseline visit to confirm the subject meets the inclusion/exclusion criteria.

8.3. Prior and Concomitant Medications

There are no restrictions regarding prior or concomitant medications. All cardiovascular medications prescribed to the subjects at baseline and any changes throughout their participation in the study are to be documented on the case report forms (e-CRFs).

8.4. Subject Consent

Informed Consent (IC) is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining an IC and other privacy language, as required by law, that has been approved by Medtronic and the study center's Ethics Board and signed and personally dated by the subject and by the person who conducted the informed consent discussion, as applicable to local requirements. A subject may only consent after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, each center's Ethics Board will be required to approve the Informed Consent Form (ICF) and other privacy language, as required by law. The document(s) must be controlled (i.e., versioned and dated) to ensure it is clear which version(s) was approved by the Ethics Board. Any adaptation of the sample ICF must be reviewed and approved by Medtronic and the Ethics Board reviewing the application prior to enrolling subjects.

The investigator must notify the subject of any significant new findings about the study that become available during the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, approval may be requested from subjects to confirm their continued participation. ICF templates will be provided under a separate cover.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject (or legally authorized representative). Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize centers to submit subject information to the study sponsor. The IC process must be conducted by the principal investigator or an authorized designee, and the ICF and other privacy language, as required by law, must be given to the subject in a language he or she is able to read and understand. The process of IC must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other center personnel. The IC process shall not waive or appear to waive subject's legal rights. The language

used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the ICF, to inquire about details of the study, and to decide whether to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the clinical study, the ICF must be signed and personally dated by the subject and investigator or authorized designee, as required by the ICF.

If the IC is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write and if allowed by local law the IC process shall be obtained through a supervised oral process. An independent witness (if applicable as per local regulation) must be present during this process. The ICF and any other information must be read aloud and explained to the prospective subject, and whenever possible, either shall sign and personally date the ICF attesting that the information was accurately explained and that ICF was freely given. The source documentation should provide the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents.

A copy of the ICF and other privacy language as required by law, signed and dated if required by local law, must be provided to the subject.

The ICF and other privacy language as required by law must be available for monitoring and auditing. Any Medtronic field personnel who support the study procedure must be able to review the subject's signed and dated ICF and verify its completeness prior to proceeding with the study procedure. In the event the Medtronic Field personnel identify ICF as being incomplete, the study procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

8.5. Randomization and Treatment Assignment

The Accel AV study is not a randomized study. However, to blind the echocardiography (echo) core laboratory to study site, study subject, and pacing mode, a random 5-digit number (echo ID) will be

assigned to label the echo recording medium. This echo ID will allow linking the Echo Core Lab results to an individual study subject and pacing mode.

Additionally, study sites will be randomized to perform the echo while the pacing mode is programmed to VDD mode first followed by VVI mode second or VVI mode first followed by VDD mode. Note that these strategies will blind the Echo Core Lab personnel to study site, subject, and pacing mode. The study worksheets will indicate the programming mode sequence in which the echo images should be acquired.

8.6. Baseline Visit

8.6.1. Demographic and Pacing Indication

The subjects' demographics and pacing indication will be obtained and recorded in an e-CRF.

8.6.2. Medical History

The subjects' medical history will be obtained and recorded in an e-CRF.

8.6.3. Cardiovascular Medications

The cardiovascular medications prescribed to the subjects at baseline and any changes throughout their participation in the study will be recorded in an e-CRF.

8.6.4. Height, Weight, and Blood Pressure

Each subject's height and weight (if not in the subject's medical chart) and blood pressure will be measured and recorded in an e-CRF.

8.6.5. 12-Lead Electrocardiogram

A 12-lead electrocardiogram will be recorded and sent to Medtronic. The recording of this electrocardiogram should be within seven days prior to implant of the Micra.

8.6.6. Patient Symptom Checklist

The subjects will be asked about presence of cardiac-related symptoms from a list of questions with the responses collected and recorded in an e-CRF.

8.6.7. Quality of Life Questionnaire

The subjects' response to the EQ-5D-3L patient questionnaire will be collected and recorded in an e-CRF.

8.7. Micra AV Implant

8.7.1. ECG Setup

Prior to implant, an ECG from the subject will be connected to the Medtronic Carelink Programmer. The ECG may be obtained from an external source (e.g., external defibrillator). If P-waves are not visible on the Medtronic Carelink Programmer, ECG electrodes should be placed or the ECG connections should be repositioned until P-waves are visible.

8.7.2. Accelerometer Waveform Data Collection

At each deployment location and prior to the tether being cut and removed, frozen waveform strips on the Medtronic Carelink Programmer will be collected for up to four (4) accelerometer vectors. Each of the frozen strips will be saved to a PDF file on a USB drive inserted into the Medtronic Carelink Programmer.

After the tether is cut and removed, frozen waveform strips on the Medtronic Carelink Programmer will be collected for up to four (4) accelerometer vectors. Each of the frozen strips will be saved to a PDF file on a USB drive inserted into the Medtronic Carelink Programmer.

The PDF file containing the frozen strips, along with the device interrogation data, should be sent to Medtronic using a secure, electronic transfer.

8.7.3. X-rays of Micra AV Implant Location

After implantation of the Micra AV, an X-ray will be collected so that the implant location of the Micra AV can be determined. At a minimum, the X-rays will be collected in lateral and anterior-posterior (AP) views. A copy of the X-rays will be sent to Medtronic.

8.7.4. Holter Monitoring Post-Implant

The running of the Atrial Sensing Setup in the Micra AV will be postponed until the ER220 Holter Monitor is placed on the study subject. Following the implant, the ER220 Holter Monitor will be placed on the subject per the instructions for use. The ECG electrodes, if previously placed on the subject for connection to the Medtronic Carelink Programmer, may be used for connection to the Holter monitor. Holter telemetry in the Micra AV will be turned on for one hour. Once good Holter telemetry between the Holter monitor and implanted Micra AV device is established, the Atrial Sensing Setup process will be initiated.

Placement of the Holter monitor and initiation of the Atrial Sensing Setup should be performed in the Micra implant room, prior to being transferred to a recovery room, if possible.

8.7.5. Final Device Interrogation

An interrogation of the Micra AV will be performed after the Holter monitoring is completed (final device interrogation) and saved on a USB drive or on a diskette. Device interrogation data (.pdd file) should be sent to Medtronic using a secure, electronic transfer. Missed device interrogations are considered a protocol deviation and must be documented in the protocol deviation e-CRF.

8.7.6. Holter Removal

After approximately one hour, the Holter monitor will be removed from the subject. The data recorded on the SD card in the Holter monitor should be sent (physically or electronically) to Medtronic for evaluation.

8.8. Echocardiogram Assessment

An echocardiogram (echo) will be performed within 48 hours of the Micra AV implant. Prior to the echocardiogram, atrial sensing of the Micra will be assessed and sensing parameters may be optimized.

[redacted].

8.8.1. ECG Setup

To support optimization of Micra AV programming, ECG cables from the Medtronic Carelink Programmer will be connected to the subject. If P-waves are not visible on the Medtronic Carelink Programmer, the ECG connections should be repositioned until P-waves are visible.

8.8.2. Initial Device Interrogation

An interrogation of the Micra will be performed prior to device programming (initial device interrogation) and saved on a USB drive or on a diskette. Device interrogation data (.pdd file) should be sent to Medtronic using a secure, electronic transfer. Missed device interrogations are considered a protocol deviation and must be documented in the protocol deviation e-CRF.

8.8.3. Atrial Sensing Optimization

The atrial sensing and AV synchrony will be evaluated on the Medtronic Carelink Programmer. If necessary, to improve atrial sensing and AV synchrony, the Micra AV parameters will be updated. Changes from the initial device programming will be documented on the e-CRFs.

8.8.4. Echocardiogram

The echocardiogram (echo) should be performed in accordance with the echo views specified by the e-CRF and the AccelAV Study Reference Guide for Cardiac Echocardiogram Data Acquisition (Appendices I). The echo views and measurements that will be collected include, but are not limited to, apical 4-chamber, left atrial volume, LVOT VTI, and mitral flow including E and A wave measurements. A copy of the recording will be sent to the Echo Core Lab for analysis either by mailing the electronic storage medium or through electronic transfer. A copy must be maintained at the center with the subject's records. It is recommended that echo recordings are sent to the Echo Core Lab as soon as possible after obtaining the echocardiogram. The Echo Core Lab will conduct a quality review of all echoes and provide feedback to study centers as needed.

Randomly generated numbers will be assigned to label the echo recording medium and link the Echo Core Lab results to an individual study center and subject as described in section 8.5.

8.8.5. Final Device Interrogation

An interrogation of the Micra AV will be performed after the echo and device programming is completed (final device interrogation) and saved on a USB drive or on a diskette. Device interrogation data (.pdd file) should be sent to Medtronic using a secure, electronic transfer. Missed device interrogations are considered a protocol deviation and must be documented in the protocol deviation e-CRF.

8.9. Follow-up (1- and 3-Month) Visits

8.9.1. Visit Windows

The study subjects will be studied at 1- and 3-months following their Micra AV implant. At this study timepoint, the follow-up study procedures will be performed. The visit windows for the follow-up visits are shown in Table 3. Visits outside the windows are considered a protocol deviation and must be documented in the protocol deviation e-CRF.

Table 3: Follow-up Visit Windows

Visit	Window Start	Target	Window End
1-month	21 days	28 days	42 days

3-month	90 days	90 days	111 days

Note: Day of implant is considered day zero

8.9.2. Patient Symptom Checklist

The subjects will be asked about presence of cardiac-related symptoms from a list of questions with the responses collected and recorded on an e-CRF.

8.9.3. Quality of Life Assessment

The subjects' response to the EQ-5D-3L patient questionnaire will be collected and recorded on an e-CRF.

8.9.4. ECG Setup / Place Holter Monitor

The ER220 Holter Monitor will be placed on the subject per the instructions for use.

In addition to the ECG cables for the Holter monitor, ECG cables from the Medtronic Carelink Programmer will be connected to the subject. If P-waves are not visible on the Medtronic Carelink Programmer, the ECG connections should be repositioned until P-waves are visible.

8.9.5. Initial Device Interrogation

An interrogation of the Micra AV will be performed prior to device programming (initial device interrogation) and saved on a USB drive or on a diskette. Device interrogation data (.pdd file) should be sent to Medtronic using a secure, electronic transfer. Missed device interrogations are considered a protocol deviation and must be documented in the protocol deviation e-CRF.

8.9.6. Data Collection with Initial Micra Parameters

Approximately 5 minutes of data will be collected on the Holter monitor with the initial Micra AV programmed settings. Subsequently, the Micra AV will be programmed to VDI mode and an additional approximately 5 minutes of data will be collected. During this data collection, the subject should remain in a consistent supine or sitting position.

8.9.7. Atrial Sensing Optimization

The atrial sensing and AV synchrony will be evaluated on the Medtronic Carelink Programmer. If necessary, to improve atrial sensing and AV synchrony, the Micra AV parameters will be updated. Changes from the initial device programming will be recorded as source documentation on an e-CRF.

8.9.8. Resting Evaluation

Subsequent to the atrial sensing optimization approximately 20 minutes of Holter data will be collected while the Micra AV is in VDD mode at rest. During this resting period, the subject should remain in a consistent supine or sitting position.

8.9.9. Final Device Interrogation

An interrogation of the Micra AV will be performed after device programming is completed (final device interrogation) and saved on a USB drive or on a diskette. Device interrogation data (.pdd file) should be sent to Medtronic using a secure, electronic transfer. Missed device interrogations are considered a protocol deviation and must be documented in the protocol deviation e-CRF.

8.9.10. Ambulatory Holter Monitoring (1-Month Visit Only)

At the 1-month visit, subjects leave the in-clinic visit and continue Holter monitor recording. During the ambulatory Holter monitoring the subject may leave the study site (e.g., return home) and should go about their activities of daily living (ADL). Each subject will receive a subject activity log and be instructed to document the time of day and a variety of pre-populated ADLs including, but not limited to, “transportation” or “sleep.”

The following day, the subject may return to the study site to return the Holter monitor and subject activity log or send the monitor and log back in a pre-addressed mailing package. The data recorded on the SD card in the Holter monitor should be sent (physically or electronically) to Medtronic for evaluation.

8.9.11. Study Completion (3-Month Visit Only)

At completion of the 3-month visit, the Holter telemetry will be turned off in the Micra AV and the Holter monitor will be removed from the subject. The data recorded on the SD card in the Holter monitor should be sent (physically or electronically) to Medtronic for evaluation. Following study completion, the subject will be exited.

8.10. Unscheduled Follow-up Visits

An unscheduled follow-up visit is defined as any **unplanned** visit by the subject to the investigational study site due to the Micra AV system between protocol required visits. Routine visits such as wound checks or other planned visits are not considered unscheduled visits and are not collected. Emergency department visits are not considered unscheduled visits, however if the emergency department visit is associated with an adverse event, the adverse event should be recorded on the e-CRFs.

If an unscheduled visit occurs:

1. Document any adverse events and device deficiencies on their associated e-CRFs
2. Where possible complete an initial and final device interrogation and save on a USB drive or diskette. Device interrogation data (.pdd file) should be sent to Medtronic using a secure, electronic transfer.

8.11. System Modification

A system modification will be reported in the event the Micra AV requires an invasive modification (e.g. explant, replacement, repositioning, device) or is programmed off (OOO or Device Off) on a permanent basis after an initial successful implant.

For each system modification, the investigator should indicate whether the primary reason for the system revision was due to pacemaker syndrome. The 2012 HRS/ACC Expert consensus statement on pacemaker device and mode selection defines pacemaker syndrome as the occurrence of overt symptoms, such as fatigue, chest discomfort, dyspnea, cough, confusion, presyncope, or syncope due to adverse hemodynamics that result from loss of AV synchrony and occurrence of ventriculoatrial conduction or atrial contraction against closed AV valves in patients with an implanted pacemaker.[5] If the primary reason for the system modification is pacemaker syndrome then collect the subject's blood pressure and 12-lead ECG prior to the system modification procedure.

Where possible complete an initial and final (if applicable) device interrogation and save on a USB drive or diskette. Device interrogation data (.pdd file) should be sent to Medtronic using a secure, electronic transfer.

If a new Micra AV device is implanted during the system modification, repeat the implant visit procedures as described in section 8.7 and complete a new implant e-CRF. However, the follow-up schedule for the subject will remain unchanged, with day 0 being the day of the initial implant.

Following a system modification where the Micra AV is no longer active the subject may be exited following the resolution of any system or procedure related AEs.

8.12. Medication Compliance

This section is not applicable.

8.13. Assessment of Efficacy

The study's primary and secondary objectives (see sections 4.1.1 and 4.1.2) will be the primary means by which the efficacy of the Micra AV system are evaluated.

8.14. Assessment of Safety

[redacted] Additionally, any device deficiencies and any unsuccessful Micra AV implants that occur during the study will be collected and summarized.

8.15. Recording Data

Subject data and product accountability data will be collected on the e-CRFs and will be reported to Medtronic via the RDC System, Oracle Clinical.

Non-CRF data including device interrogation data, 12 lead ECG, and X-ray images will be saved on supported media and will be delivered to Medtronic electronically via a secure web-based application, e.g. Medtronic Box.

Data saved on the Holter monitor SD card(s) will be delivered to Medtronic either electronically via a secure web-based application, e.g. Medtronic BOX.

Echo data will be saved on supported media and will be delivered to the Echo Core Lab either electronically via a secure web-based application, e.g. Medtronic BOX, or via mail. The Echo Core Lab will also enter data onto e-CRFs within the Oracle Clinical database.

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents may include but are not limited to, subject medical records, electronic device data, subject activity logs, study-guided worksheets, quality of life questionnaires, and subject symptom checklists. For the purposes of the AccelAV study, study-guided worksheets may be created and used to aid in compliance of protocol related data collection and to document real-time source data, e.g. blood pressure measurements, subject symptom checklists, and quality of life questionnaires. These will be signed and dated by personnel who record data on the study-guided worksheets. If someone other than the site team member records data on the worksheet, a site team member will review, sign, and date worksheets upon completion. The data will be transferred and reported onto the e-CRFs in a secure, password-protected database, and shall be derived from source documents and be consistent with these source documents, and any discrepancies between the two shall be explained in writing.

8.16. Deviation Handling

A study 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 safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject inability or illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report 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.

All study deviations must be reported on the e-CRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. Multiple deviations of the same type at the same visit may be reported on one e-CRF.

In the event the deviation involves a failure to obtain a subject's 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 Ethics Board as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with Ethics Board policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation.

Reporting of deviations must comply with Ethic Board policies, local laws, and/or regulatory agency requirements. Refer to Investigator Reports (Table 9), for geography-specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

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 result in initiation of 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.

Examples of study deviations include but are not limited to:

- Failure to obtain proper patient informed consent
- Failure to collect required study data (e.g. required echocardiogram)
- Inclusion/exclusion criteria not met
- Missing required device interrogation files
- Missing Holter data
- Missed visit

8.17. Subject Withdrawal or Discontinuation

A subject can withdraw from the study at any time. If a subject is withdrawn from the clinical study, the reason for withdrawal will be recorded in the e-CRF and in the subject's hospital record. In addition,

centers should follow their procedures for subject withdrawals or discontinuations as set forth by their Ethics Board. It is recommended that that subjects be followed until all Micra AV or study procedure related adverse events are resolved.

Subjects that exit the study prior to completing the study procedures will not be replaced since a sample size of up to 175 enrolled subjects accounts for the possibility that not all subjects may contribute usable Holter data as the target sample size requires approximately 150 usable Holter datasets.

Possible reasons for premature withdrawal from the study are:

- Subject chooses to withdraw (e.g. consent withdrawal)
- Subject did not meet inclusion/exclusion criteria after consent, but prior to Micra AV implant
- Subject lost to follow-up (not expected to occur due to the short study duration for individual subjects)
- Investigator withdrew subject from the study for technical reasons (e.g. Holter telemetry)
- Investigator withdrew subject from the study for medical reasons (e.g. inability to complete resting period and/or Holter recording)
- Unsuccessful Micra AV implant attempt. An unsuccessful implant attempt is defined as an implant attempt where an operating Micra AV device does not remain in the right ventricle following groin access site closure. If the Micra AV implant is unsuccessful, the subject should be exited from the study: 1) following the resolution of any collectable adverse events or 2) if the collectable adverse event is not resolved and no further Micra AV implant attempts are planned. An unsuccessful implant is not an adverse event, however, any adverse events occurring during an unsuccessful implant should be reported.
- System modification where a Micra AV device is no longer active following the system modification procedure.
- The sponsor decides the study will be closed or a particular center will be closed.

In the case that the subject is determined to be lost to follow-up at least two attempts to contact the subject are required. The method of attempt (e.g. one letter and one phone record or two letters) should be documented in the subject's medical record.

9. Risks and Benefits

9.1. 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.

All devices used in the AccelAV study with exception of the ER220 Holter Monitor, will be commercially released and used in accordance with their approved labeling. The safety and clinical performance of the algorithm used in the Micra AV system has been demonstrated through previous clinical studies. The potential risks and side effects associated with the Micra AV Transcatheter Pacing System can be found in the Instructions For Use (IFU) labeling (Appendices F) and the foreseeable adverse event list (Appendices E) consistent with market-released Micra Transcatheter pacing system. Subjects who are pregnant may be at increased risk (e.g., radiation exposure, and other unforeseen risk to the fetus), and are excluded from participation in the study. If a subject becomes pregnant during the study, she must notify the physician immediately. The subject will remain in the study, but the investigator will avoid any procedures that may be determined harmful. The risks must be continuously monitored, assessed and documented by the investigator.

The telemetry uplink mode during the Holter monitoring portion required by the study protocol is expected to reduce Micra AV battery longevity by a maximum of 2.7%, meaning approximately 3 to 6 months, depending upon the amount of pacing. The telemetry uplink time is a programmable parameter, which allows the user to choose the allotted telemetry uplink time required per the Accel AV protocol. Telemetry uplink will shut off automatically after the programmed time to reduce further battery drain of the device. This information will be disclosed in the patient informed consent.

There is potential risk of a skin and/or allergic reaction to adhesive when applying the ER220 Holter monitor per instructions for use, or when removing adhesive tape. To minimize this risk, information will be disclosed in the patient informed consent, and study sites will be trained by Medtronic on applying the ER220 Holter monitor per instructions for use. Participating sites will be provided standard electrode patches used within its labeling that have been provided by a Medtronic approved supplier for Holter monitor application.

The study requires the additional radiation associated with two chest X-rays of the Micra AV implant location. The amount used in a chest X-ray is small and considered low risk. The amount of radiation exposure for a chest X-ray is approximately 0.02% of the maximum lifetime diagnostic radiation exposure recommended by the American College of Radiology. In addition, subjects will undergo an echocardiogram examination with an echocardiography machine available on site at the hospital or clinic. The echocardiogram procedure poses negligible or no risk to the subjects and will be disclosed in the patient informed consent.

Lastly, during the study, risks will be continuously monitored, assessed and documented by the study investigators.

9.2. Potential Benefits

The potential benefits of having the Micra AV Transcatheter Pacing System is to provide VDD pacing in subjects who have adequate sinus rates and who may benefit from maintenance of AV synchrony. The

decision to implant the Micra AV should consider the benefits of leadless pacing versus the subject's need for continuous AV synchrony. In addition, subjects enrolled in the study may have additional contact with their physicians or other medical care staff beyond their normal standard of care visits, which may provide benefit from a patient care perspective.

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

Participation in the AccelAV study may offer no benefit to the subject.

9.3. Risk-Benefit Rationale

The potential risks associated with the commercially available Micra AV Transcatheter Pacing System were identified and have been successfully mitigated. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the Clinical Investigation Plan. In addition, investigators will be actively involved in the implantation and follow-up of the subjects. Risks will be minimized by careful assessment of each subject prior to, during, and after implant. Medtronic has further minimized the possibility of risks by product testing applicable to all commercially available devices prior to their use in this clinical study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling. Lastly, a summary of the risk-benefit analysis for the Micra AV Transcatheter Pacing System is documented in the Micra AV Risk Management Report (D00054473, or current approved version).

After implantation, subjects in this clinical study will be followed at regular intervals to monitor the condition of the implanted system. At each study-required follow-up, in all subjects, the investigator must interrogate the Micra AV device to verify appropriate device function and to assess any adverse events. Taking the risk mitigation and risk minimization into account, the potential benefits outweigh the potential risks for patients participating in this study.

10. Adverse Events and Device Deficiencies

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. The study is conducted in accordance with these procedures and regulations.

Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information.

10.1. Adverse Events

All Micra AV system or procedure related adverse events (AEs) and all cardiovascular related AEs regardless of their severity that occur from the time of enrollment (i.e., the time the informed consent is signed) through study exit will be collected and reported to Medtronic. Additionally, all deaths will be reported on an AE e-CRF with a fatal outcome. Reporting of these events to Medtronic will occur on an AE e-CRF, including date of AE onset, AE term, AE description, AE treatment and actions taken, AE outcome and resolution, and assessment of both the seriousness of the AE and the relatedness to the procedure and system components. Each AE must be recorded on a separate AE e-CRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

10.2. Device Deficiencies

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic. Note that DDs that result in an Adverse Device Effect (ADE) to the subject should be captured as an AE only. Device Deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting. For DDs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information.

10.3. Event Updates and Resolution

For any changes in status of a previously reported AE (e.g. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE form. All efforts should be made to continue following the subject until all unresolved system related adverse events, as classified by the investigator, are resolved.

10.4. Definitions/Classifications

For the purposes of the clinical report, Medtronic will classify each adverse event according to ISO 14155:2011 definitions. The study will follow the definitions, however is not claiming full compliance to ISO 14155:2011.

Where the definition indicates “device”, it refers to any device used in the study. This may be the device under investigation, or any market released component of the system.

Table 4: Adverse Event and Device Deficiency Definitions

General	
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, 3.2)
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 an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Device Deficiency (DD)	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, 3.15)
Relatedness	
Cardiovascular Related	An adverse event relating to the heart and the blood vessels or the circulation. (e.g., atrial fibrillation, myocardial infarction, stroke, peripheral vascular disease, heart failure).
Pacemaker Syndrome Related	The 2012 HRS/ACC Expert consensus statement on pacemaker device and mode selection defines pacemaker syndrome as the occurrence of overt symptoms, such as fatigue, chest discomfort, dyspnea, cough, confusion, presyncope, or syncope due to adverse hemodynamics that result from loss of AV synchrony and occurrence of ventriculoatrial

	conduction or atrial contraction against closed AV valves in patients with an implanted pacemaker.[5]
Procedure Related	An adverse event related to the Micra AV implantation or modification, or to the AccelAV study procedures. Micra Procedure related: an adverse event that occurs that is directly related to the implantation or modification of the Micra system AccelAV Procedure related: an adverse event that is related to the protocol required procedures
System Related	An adverse event that results from the presence or performance of any component of the system. Micra AV Device Related: An adverse event that results from the presence or performance (intended or otherwise) of the 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 presence or performance (intended or otherwise) of the Micra AV software. Programmer Related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer. Holter Related: An adverse event that results from the presence or performance (intended or otherwise) of the Holter.
Not Related	Relationship to the device or procedures can be excluded when: ▪ The event is not a known side effect of the product category the device belongs to or of similar devices and procedures. ▪ The event has no temporal relationship with the use of the device or the procedures. ▪ The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible. ▪ The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure) do not impact the serious event. ▪ The event involves a body-site or an organ not expected to be affected by the device or procedure. ▪ The serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors). ▪ The event does not depend on a false result given by the

	device used for diagnosis (when applicable). ▪ Harms to the subject are not clearly due to use error. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The event is associated with the device or study procedures beyond reasonable doubt when:

	▪ The event is a known side effect of the product category the device belongs to or of similar devices and procedures. ▪ The event has a temporal relationship with device use/application or procedures. ▪ The event involves a body-site or organ that the device or procedures are applied to or the device or procedures have an effect on. ▪ The serious event follows a known response pattern to the medical device (if the response pattern is previously known). ▪ The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) impact on the serious event (when clinically feasible). ▪ Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out. ▪ Harm to the subject is due to error in use. ▪ The event depends on a false result given by the device used for diagnosis (when applicable). ▪ In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Seriousness	
Serious Adverse Event (SAE)	<u>Adverse event that did one of the following:</u> 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 1: 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, 3.37)
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, 3.36)
Complication	An adverse event that includes the following is considered a complication: a) Results in death, b) Involves any termination of significant device function, or c) Requires an invasive intervention NOTE: Only system or procedure related AEs will be classified as complications or observations
Major Complication	A complication that results in any of the following: 1) Death 2) Permanent loss of device function due to mechanical or electrical dysfunction of the device (i.e., pacing function disabled, leaving device abandoned electrically) 3) Hospitalization 4) Prolonged hospitalization 5) System revision (explant, reposition, replacement) NOTE: Only system or procedure related AEs will be classified as complications or observations.
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). NOTE: Only system or procedure related AEs will be classified as complications or observations.
Observation	An adverse event that is not a complication. NOTE: Only system or procedure related AEs will be classified as complications or observations
Timing	

Pre-Implant AE	An adverse event that occurs after the consent form has been signed but before the skin incision during implant
During Implant AE	An adverse event that occurs during implant, after skin incision and prior to completion of skin closure
Post-Implant AE	An adverse event that occurs after the completion of skin closure for the implant
Other	
Unavoidable AE	An adverse event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration. Unavoidable AEs are not considered reportable unless the AE worsens or is present outside the stated timeframe.

Description	Timeframe (hours) from the Surgical Procedure
Anesthesia related nausea / vomiting	24
Low-grade fever (<100°F or <37.8°C)	48
Pain at the access site	72
Mild to moderate bruising / ecchymosis	168
Sleep problems (insomnia)	72
Back pain related to lying on table	72

10.5. Reporting of Adverse Events

All reported AEs and DDs will be reviewed by a Medtronic representative. Adverse events will be classified according to the definitions provided. Upon receipt of an AE or DD at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the investigator. Medtronic will use the Medical Dictionary for Regulatory Activities (MedDRA), to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs that could have led to a SADE will be completed according to local regulatory requirements. Refer to Table 6 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the Ethics Board responsible for oversight of the study.

Appendix E contains the Foreseeable Adverse Event List (FAL), which is a list of adverse events related to the Micra system that have been observed in previous studies and may be experienced by subjects.

For emergency contact regarding a SAE and/or SADE, contact a Medtronic study representative immediately (refer to the study contact list provided in the site's study documents binder, Investigator Site File or refer to the Sponsor Contact Information section provided in the CIP).

Adverse Events will be classified according to the standard definitions as outlined below in Table 5 .

Table 5: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Micra Implantable Device and Transfemoral Catheter Delivery System, Micra Software, Programmer and Programmer Software, ER220 Holter, Accel AV study procedures, Micra implant or modification procedure
	Sponsor	Micra Implantable Device and Transfemoral Catheter Delivery System, Micra Software, Programmer and Programmer Software, ER220 Holter, Accel AV study procedures, Micra implant or modification procedure
Seriousness	Investigator	SAE, Device Deficiency with SADE potential
	Sponsor	SAE, Complication/Observation (including major complication), Device Deficiency with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by investigator

10.6. Adverse Events and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs 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 site's Ethics Board. If an Adverse event is related to a market-released device used during the study, post market surveillance is also applicable, and the investigator is responsible for immediate reporting of the product complaint via the regulatory channels for market-released products. Adverse events and Device Deficiencies reporting requirements are outlined below in Table 6.

Table 6: Reporting Requirements

Adverse Device Effects (ADEs) and Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	**All geographies:** Report to the sponsor, without unjustified delay, all serious adverse events.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to Regulatory authorities per local reporting requirement.
All Device Deficiencies with SADE potential or without	
Investigator submit to:	
Medtronic	**All other geographies:** Submit or report as required per local reporting requirements.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to Regulatory authorities per local reporting requirement.

10.7. Subject Death

All subject deaths must be reported by the investigator to Medtronic on an Adverse Event form (AE with a fatal outcome) as soon as possible after the investigator first learns of the death. In case of death, there should be one AE with a fatal outcome.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable. If any system component is returned to Medtronic, return product reporting systems may be used to gather additional information about the returned device or component.

A copy of the death certificate, if available and allowed by national and local law, should be sent to the Medtronic clinical study team. 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 clinical study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic clinical study team, if available and allowed by national and local law. When the death occurs at a remote site, it is the investigational 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 and Save-to-Media (if available)

- Device disposition information
- Death summary/hospital records (if available and allowed by national and local law)
- Autopsy report (if available and allowed by national and local law)
- Death certificate (if available and allowed by national and local law)

11. Data Review Committees

11.1. CRO/Core Labs

This information in Table 7 may be subject to change during the clinical study. Periodic updates to study contact information will be sent to sites as needed.

Table 7: CRO and Core Laboratory Information

Contact Information	Role
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 United States Direct Phone: (201) 801-0233 Direct Fax: (201) 801-0243	Development of the study database, review of electronic case report forms, and management of discrepancies
Echocardiography Core Laboratory TBD (Information will be provided under separate cover)	Review and analysis of study echocardiograms

11.2. Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will conduct a medical review of AEs for subjects participating in the study.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating investigators for the study, including a CEC chairperson. At a minimum, the CEC will adjudicate all Micra AV system or procedure-related AEs, and all AEs with a fatal outcome (deaths). Medtronic personnel may facilitate and participate in a CEC meeting but will be non-voting members.

For AEs 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. For adverse events, classification includes Micra AV procedure and system relatedness, pacemaker syndrome relatedness (only for AEs resulting in a Micra AV system revision) and the additional adjudication of a cardiac death classification will be provided for all reported

deaths. Source documents to support adjudication will be requested for all AEs with an outcome of 'fatal' and may be requested for other events of interest on an as needed basis.

If the CEC disagrees with the investigator's classification of the event, the study site will be notified. If the investigator agrees with the CEC's adjudication, the case report form documenting the AE will be updated accordingly. CEC classifications will be used for analysis.

11.3. Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) is not needed for this study. This decision was made based on the following criteria:

1. Limited duration of subject participation in study
2. Short overall study duration (approximately 15 months)
3. Little safety risk to subjects participating in study

11.4. Steering Committee

A Steering Committee will serve to oversee and guide the conduct of the study as well as develop publications and presentations. The Steering Committee is independent from Medtronic. The Steering Committee will also serve as a publication committee and will be primarily responsible for the creation, review, and submission of publications and presentations related to the study. A publication plan will be developed in conjunction with the Sponsor prior to the start of the trial. This publication plan may need to be adjusted, as appropriate, based on the progress of the study.

12. Statistical Design and Methods

12.1. General Considerations

Medtronic employees or their designated representatives will perform all statistical analyses.

A Statistical Analysis Plan (SAP) will be created prior to analysis of the primary objective. The SAP will elaborate on the statistical methods described below and include a comprehensive description of the pre-specified statistical methods to be included in study report(s). Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP will be described in the SAP and in the clinical study report.

Note that the goal of the AccelAV study is to estimate the rate of AV synchrony in the real-world population rather than test a specific hypothesis with specific type I error control.

12.1.1. Standard Baseline Variables

Standard baseline and relevant medical history will be collected on the e-CRFs for all enrolled subjects. Baseline variables to be summarized include, but are not limited to: age, sex, physical exam findings, pacing indication, arrhythmia history, medical and surgical history, and cardiovascular medications. Baseline variables will be summarized for all enrolled subjects, all subjects with a successful Micra AV implant, and all subjects contributing to the primary objective (i.e., those subjects with a predominant rhythm of 3rd degree AV block and normal sinus node function during the 1-month visit).

For continuous variables, mean, standard deviation, median, and range will be reported. For categorical variables, frequency and percentage will be reported.

12.2. Usable Holters

A Holter dataset (i.e., device data and surface ECG recordings telemetered to the Holter memory) will be considered usable if there is readable telemetry signal as determined by the presence of visible device marker channel. Additionally, to be included in the analysis of the primary efficacy objective [redacted], visible P-waves must be present on the surface ECG recordings.

12.3. Classification of Predominant Heart Rhythm During Echo

Atrial and ventricular heart rates, along with the PR interval will be used to determine each subject's predominant heart rhythm at the time of the echo. Specifically, both the sinus function and AV block status will be assessed. The AV conduction status will be categorized as 3rd degree AV block, intact AV conduction, or other (e.g. 1st or 2nd degree AV block). The sinus node function will be categorized as normal sinus node function, sinus node dysfunction (sinus bradycardia, sinus tachycardia, or other) or atrial arrhythmia.

12.4. Classification of Predominant Heart Rhythm During Holter Monitoring

Holter data from the VDI data collection period and resting period will be used to determine each subject's predominant heart rhythm. Specifically, both the sinus function and AV block status will be assessed. The AV conduction status will be categorized as persistent 3rd degree AV block, intact AV conduction, or other (e.g. 1st or 2nd degree AV block). The sinus node function will be categorized as normal sinus node function, sinus node dysfunction (sinus bradycardia, sinus tachycardia, or other) or atrial arrhythmia.

A subject's 1-month and 3-month visit Holter will be assessed individually for predominant rhythm classification. Thus, a subject may have different predominant rhythms at each study visit (e.g., 3rd

degree persistent AV block with normal sinus node function at the 1-month visit, but intact AV conduction at the 3-month visit).

12.5. Primary Objective

Characterize AV synchrony during rest at 1-month post-implant in subjects with persistent 3rd degree AVB with normal sinus node function.

12.5.1. Endpoint Definition

For each ECG confirmed P-wave that occurs during the 20-minute resting period at the 1-month visit, the endpoint will be considered met if a ventricular beat (ventricular pace or sensed event) is within 300 ms following an ECG confirmed P-wave.

12.5.2. Performance Requirement

There is no pre-specified performance requirement for this study.

12.5.3. Analysis Methods

At the 1-month study visit, a Holter monitor will be placed on the subject. Each subject's Holter monitor will record surface ECG and Micra AV markers. Specifically, the Holter will record whether the Micra AV senses an atrial contraction (A4 signal representing active ventricular filling detected by the accelerometer), delivers a pacing spike, or inhibits a pacing spike based on a sensed intrinsic R-wave. Similar to the MARVEL and MARVEL 2 studies, Holter files will be processed and reviewed by Medtronic personnel experienced in the review of Holter recordings using Holter and MATLAB utilities. A human overread will also be used to truth each P-wave. Device markers will not be used by the MATLAB scripts or human overread to identify P-waves. Finally, a MATLAB script will collate the identified P-waves, times corresponding to distinct study procedures, and Micra AV markers in a .csv format file. This .csv file will indicate the time after each P-wave a ventricular pace or intrinsic sensed R-wave occurred. Comparison of this P-R interval to 300 ms will determine whether a beat was synchronous.

A logistic regression model using generalized estimating equations, to account for the fact that the Micra AV's performance may be correlated within a study subject, will be used to construct a single estimate of the rate of AV synchrony and its 95% two-sided confidence interval across all subjects. Specifically, the model outcome will be each successful/unsuccessful synchronous beat during the approximately 20 minutes resting period at the 1-month visit and the model will contain an intercept term and consider observations repeated across subjects with an exchangeable working correlation structure.

Additionally, point estimates for the percentage of synchronous beats at the 1-month visit will also be calculated for each individual subject by dividing the number of synchronous beats by the total number of evaluable cardiac cycles.

12.5.4. Sample Size

The MARVEL 2 study reported an average AV synchrony rate during rest of 89.2% (95% CI: 84.8% - 92.5%) with a median of 94.3% across the 40 subjects with a predominant heart rhythm of 3rd degree AV block and normal sinus node function and P-waves visible on their Holter ECG channel. The remaining subjects included 17 subjects with intact AV conduction, and 7 subjects with other predominant rhythms. Based on the distribution of predominant rhythms in the MARVEL 2 study together with the enrollment strategy described in section 7.5 it is expected that approximately half of the subjects with usable Holters will have a predominant rhythm of 3rd degree AV block and normal sinus node function at their 1-month visit.

A simulation based on resampling with replacement from the MARVEL 2 subjects suggests that a sample size of 75 subjects with Holter recordings and with a predominant rhythm of 3rd degree persistent AV block and normal sinus node function at the 1-month visit will enable the percentage of AV synchrony to be measured with a precision (distance from point estimate to lower 2-sided 95% confidence interval) of <3.5% with 89.7% probability. Since it is expected that approximately half of the subjects with usable Holter data at the 1-month visit will have a predominant rhythm of persistent 3rd degree AV block and normal sinus node function, approximately 150 subjects with usable Holter files will be required to evaluate the primary objective. To account for the possibility of unusable Holters, unsuccessful Micra AV implant attempts, and study attrition, approximately 175 subjects may be enrolled.

Since the number of subjects that will have a predominant rhythm of 3rd degree AV block at the 1-month visit is somewhat unknown, Table 8 displays the relationship between the number of subjects that will contribute to the primary efficacy analysis and the distance between the point estimate and lower 95% confidence interval for sample sizes ranging from 40 to 90 subjects.

Table 8: Relationship Between Sample Size and Confidence Interval Width

n[1]	Median Point Estimate (%)[2]	Median Lower 95% CI	Median Distance from Point Estimate to Lower CI	Probability Distance <3.5%
40	88.76%	84.83%	4.1%	37.7%
50	88.73%	85.19%	3.5%	45.2%
60	88.79%	85.58%	3.2%	63.0%
70	88.82%	85.90%	2.9%	81.9%
75	88.76%	85.87%	2.9%	89.7%
80	88.73%	85.96%	2.8%	92.9%
90	88.76%	86.13%	2.6%	98.6%

[1]n is the number of subjects with usable Holter files with a predominant rhythm of persistent 3rd AV block and normal sinus node function at the 1-month visit.
[2]Based on 1000 bootstrap samples from 40 subjects in the MARVEL 2 study with a predominant rhythm of persistent 3rd AV block and normal sinus node function during Holter monitoring.
Program Name: V:\AccelAV\Sample_Size

12.5.5. Determination of Subjects and Data for Analysis

All enrolled subjects with usable Holter data, a predominant rhythm of persistent 3rd degree AV block and normal sinus node function at the 1-month visit, and at least 500 evaluable beats during resting period at the 1-month visit will be included. Specifically, data from the approximately 20 minute resting period at the 1-month visit will be included in the analysis of the primary objective.

12.5.6. Missing Data

Given the relatively short duration of the study, missing data is not expected to be a serious issue. However, missing data may occur if the Holter telemetry signal is lost or the Holter data file is otherwise corrupted (i.e., Holter file is not considered usable).

Since telemetry dropout may influence the number of evaluable beats, the total number of heart beats and total number of evaluable beats will be summarized.

If any subjects do not have usable Holter data during the study, the reason the Holter data was not usable will be discussed.

Additionally, a sensitivity analysis will be performed to assess the sensitivity of the observed AV synchrony percentage estimate with respect to the missing data. The analysis will consist of including in the statistical model all subjects that had some usable Holter data during the 20-minutes resting period

at the 1-month visit regardless of the number of evaluable beats. Other stochastic based methods to investigate the sensitivity of the results to the number of unevaluable beats due to telemetry lost may be utilized if necessary.

12.5.7. Other Planned Analyses

As described in section 12.3 subjects may have different predominant heart rhythms at their 1-month and 3-month visits. For example, a subject may have intact AV conduction at their 1-month visit but have persistent 3rd degree AV block and normal sinus node function at their 3-month visit. Thus, an estimate of percent AV synchrony will also be computed using the methods described in section 12.5.3 using each subject's 3-month visit Holter recording where they have at least 500 evaluable beats and have a predominant rhythm of persistent 3rd degree AV block and normal sinus node function.

The AV synchrony percentage will also be computed using the methods described in section 12.5.3 for subjects not included in the primary objective analysis cohort including those subjects with intact AV conduction and other predominant rhythms.

12.6. Secondary Objective #1

Characterize the stability of AV synchrony during rest between 1-month and 3-months post implant in subjects with persistent 3rd degree AVB and normal sinus node function.

12.6.1. Endpoint Definition

The endpoint for secondary objective #1 will be the same as for the primary objective (see section 12.5.1) with the exception that ECG confirmed P-waves that occur during the 20-minute resting period at both the 1-month and 3-month visits will be included in the analysis.

12.6.2. Performance Requirement

There is no pre-specified performance requirement for this study.

12.6.3. Analysis Methods

A Holter monitor will be placed on each subject at the 1-month and 3-month visits. Each Holter file will be processed as described in section 12.5.3 and the AV synchrony during the 20-minutes resting periods at the 1-month and 3-months visits will be compared using a generalized linear model incorporating generalized estimating equations. The response for this model on an individual heart beat basis will be AV synchrony endpoint met as defined in section 12.5.1 (i.e., 1= yes, 0=no). The model will also incorporate an intercept term and indicator for visit (1-month or 3-month visits) and utilize an exchangeable working correlation structure to account for the fact that the atrioventricular synchrony

may be correlated within subject. The difference in the least squared means between visits on the linear scale (i.e., when utilizing the identity link function with the binomial distribution) and its related 95% confidence interval will be used to assess the stability of the AV synchronous pacing rate between study visits.

12.6.4. Determination of Subjects and Data for Analysis

All subjects with persistent 3rd degree AVB and normal sinus node function and at least 500 evaluable beats during the approximately 20 minute period where the subject is resting quietly at both the 1-month and 3-month visits will be included in the analysis of this objective.

12.6.5. Missing Data

Similar to the primary objective, beats with no ventricular sense or pace markers and indication of telemetry dropout in the first 300 ms following a P-wave will be excluded (i.e., they are not evaluable beats). The total number of heart beats and total number of evaluable beats will be summarized for each subject and visit combination.

Additionally, a sensitivity analysis will be performed to assess the sensitivity of the estimated difference in AV synchrony percentage with respect to the missing data. Specifically, the analysis will include in the statistical model all subjects with persistent 3rd degree AV block and normal sinus node function and at least one evaluable cardiac cycle at the 1-month and 3-month visits respectively.

12.7. Secondary Objective #2

Characterize the percentage of ambulatory AV synchrony at 1-month in subjects with persistent 3rd degree AVB and normal sinus node function.

12.7.1. Endpoint Definition

The endpoint for secondary objective #2 will be the same as for the primary objective (see section 12.5.1) with the exception that ECG confirmed P-waves that occur during the ambulatory period during the 1-month Holter recording will be used in the analysis.

12.7.2. Performance Requirement

There is no pre-specified performance requirement for this objective.

12.7.3. Analysis Methods

At the 1-month visit, a Holter monitor will be placed on the subject and following the in-clinic study procedures the subject will wear the Holter monitor for approximately 24 hours as they go about their

activities of daily living. The Holter files will be processed as described in section 12.5.3 and a logistic regression model using generalized estimating equations will be used to construct a single estimate and 95% confidence interval for algorithm performance across all subjects using the methods described in section 12.5.3. For analysis purposes, the ambulatory period will be defined as starting at the end of the 20-minute resting period.

12.7.4. Determination of Subjects/Data for Analysis

All subjects with a predominant rhythm of persistent 3rd degree AVB and normal sinus node function and at least 500 usable beats during the ambulatory Holter monitoring period will be included in the analysis of this objective.

12.7.5. Missing Data

Similar to the primary objective, beats with no ventricular sense or pace markers and indication of telemetry dropout in the first 300 ms following a P-wave will be discarded (i.e., they are not evaluable beats). The total number of heart beats and total number of evaluable beats will be summarized for each subject.

Additionally, a sensitivity analysis will be performed to assess the sensitivity of the AV synchrony percentage estimate with respect to the missing data. Specifically, the analysis will include in the statistical model all subjects with persistent 3rd degree AV block and normal sinus node function and at least one evaluable cardiac cycle during the ambulatory period at the 1-month will be included.

12.7.6. Other Planned Analyses

The AV synchrony percentage will also be computed during the 1-month ambulatory period for subjects with predominant rhythms other than persistent 3rd degree AV block and normal sinus node function including those with intact AV conduction and other predominant rhythms.

12.8. Secondary Objective #3

Characterize the change in stroke volume, as measured by left ventricular outflow tract velocity time integral, during Micra AV mediated VDD pacing and VVI pacing in subjects with persistent 3rd degree AVB and normal sinus node function.

12.8.1. Endpoint Definition

The endpoint is LVOT VTI as obtained from echocardiogram and measured by the Echo Core Lab while the Micra AV is programmed to VDD and VVI pacing.

12.8.2. Performance Requirement

There is no pre-specified performance requirement for this objective.

12.8.3. Analysis Methods

Echocardiograms will be collected for each subject during VDD pacing and during VVI pacing within 48 hours of the Micra AV implant. To ensure that the Echo Core Lab is blinded to subject and programmed pacing mode, randomly generated numbers will be used to label the echo recording. Specifically, a random 5-digit number ("echo id") will be assigned to label the echo recording and link the Echo Core Lab results to an individual study subject and pacing mode. Additionally, study sites will be randomized to perform the echo while the Micra AV system is programmed to VDD pacing first followed by VVI pacing or to VVI pacing first followed by VDD pacing. This strategy will blind the Echo Core Lab personnel to study site, subject, and pacing mode and allow the "echo id" to link to the appropriate center, subject, and pacing mode.

Since subject is the experimental unit, the difference in LVOT VTI during the VDD and VVI pacing will be computed within each subject and a 95% confidence interval for the mean difference will be constructed based on the t-distribution.

12.8.4. Determination of Subjects/Data for Analysis

All subjects with persistent 3rd degree AV block and normal sinus node function at the time of their echocardiogram with paired LVOT VTI measurements during VDD and VVI pacing will be included in the analysis.

12.8.5. Missing Data

Since the echocardiogram is expected to be performed prior within 48 hours of the Micra AV implant, missing data is not expected to be a serious issue. However, missing data may arise if a subject does not perform the echocardiogram or the echocardiogram is uninterpretable by the Echo Core Lab. Note that both reasons for missing data may plausibly be considered independent to change in LVOT VTI.

12.8.6. Other Planned Analyses

Point estimates for the mean difference in LVOT VTI between VDD and VVI pacing and its corresponding 95% confidence interval will also be constructed for subjects not included in the analysis cohort for this objective including those with intact AV conduction or with other predominant rhythms.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13. Ethics

13.1. Statement(s) of Compliance

The study will be conducted according to the Declaration of Helsinki, Clinical Investigation Plan, Good Clinical Practice (GCP) and in accordance to the national and local laws, regulations, standards, and requirements of the countries/geographies in which the study is conducted. The principles of the Declaration of Helsinki have been implemented through the patient informed consent (IC) process, Ethics Board/IRB/MEC approval, study training, clinical trial registration, risk-benefit assessment and publication policy.

The clinical investigation shall not begin until all required approvals and documents from the Ethics Board and regulatory authorities, if needed, have been received. Any additional requirements imposed by the Ethics Board or regulatory authority shall be followed, if appropriate.

This study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent Ethics Board/IRB/MEC before initiating a study, continuing review of an ongoing study by an Ethics Boards and obtaining and documenting the freely given informed consent of a subject before initiating the study.

All devices used in the AccelAV study, with exception of the ER220 Holter Monitor, will be commercially released and used within scope of approved labeling, indications, and patient population. The ER220 Holter is an investigational device but will be used as a noninvasive diagnostic/data collection only and introduces no increased risks to subjects as compared to standard of care. The study is considered exempt per 21 CFR 812.2(c)(3):

812.2(c)(3) Noninvasive diagnostic device	(3) A diagnostic device, if the sponsor complies with applicable requirements in Sec. 809.109(c) and if the testing: (i) Is noninvasive,

	(ii) Does not require an invasive sampling procedure that presents significant risk (iii) Does not by design or intention introduce energy into a subject, and (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure

In addition, the study does not meet the FDA definition of a significant risk device as defined by 21 CFR 812.3 (m). This study is not designed to determine safety and effectiveness and does not introduce new or increased risks to study subjects. For further information of study risks, please go to section 9.1.

Ultimately, all sites in all geographies will and comply with:

- Principles of Declaration of Helsinki
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- The Clinical Trial Agreement
- The procedures described within this CIP
- Local Ethics Board Requirements
- 809.10(c) Labeling

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to the following:

In the United States, the study is in compliance with 21 CFR Parts:

- 50: Protection of Human Subjects
- 56: Institutional Review Boards
- 809.10(c) Labeling
- 21 CFR Part 11: (Electronic Records, Electronic Signatures)
- 21 CFR Part 803: Medical Device Reporting

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act FDAAA and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where

required by local law. Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators
- An independent medical ethics committee or institutional review board

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above-mentioned groups prior to implementation of the revised CIP at the site.

14. Study Administration

14.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study per regulations. Trained Medtronic personnel may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Patient Informed Consent, and Clinical Trial Agreement. The consent form or other privacy language where required by law must be available for monitoring and auditing. The principal investigator should also be available during monitoring visits.

Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to Ethics Board approval and review of the study, maintenance of records and reports, and review of source documents including source data verification in accordance to the study-specific monitoring plan. Monitors review site regulatory and study compliance by identifying findings (non-compliances) 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 center.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, observations from previous monitoring

visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study center.

14.2. Data Management

The e-CRF data reported to Medtronic will be stored in a secure, password-protected database. Data will be reviewed using programmed and manual data checks. Data queries will be made available to centers for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

The investigator must ensure accuracy, completeness and timeliness of the data reported in the e-CRFs. Only authorized persons can complete and sign e-CRFs, as specified on the Delegated Tasks List included in the Investigator Site File.

The Device interrogation data, Holter data, X-ray, ECG, and Echo data delivered to Medtronic will be downloaded or saved to a secure network drive prior to being processed.

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 X-ray images.

The data reported on the e-CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

Device data from transmissions will be uploaded to secure servers. Save-to-disk data collected at clinic visits will be sent to Medtronic. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

14.3. Direct Access to Source Data/Documents

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

Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

The sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, Ethics Board review and regulatory inspection by providing direct access to source data/documents.
Study sites should inform Medtronic upon notification of an inspection by a regulatory body immediately. A list of acceptable source documents is described in data management, section 14.2.

14.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. A unique subject identification number (SID) will be assigned to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all subject related study documents to link them to the subject's medical records at the site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. In the US, "Protected Health Information" (PHI) will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the Informed Consent Form. This scenario will be covered in the Informed Consent Form. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g. digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

14.5. Liability

Warranty information is provided in the product packaging for the commercially released transcatheter pacing system and additional copies are available upon request.

14.6. Insurance (US)

Medtronic, plc maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical trial insurance statement or certificate will be provided to the Ethics Board.

14.7. Insurance (Hong Kong)

Medtronic Hong Kong Medical Ltd is a wholly owned subsidiary of Medtronic, which as the parent company of such entities 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. If required, a Clinical Trial insurance statement or certificate will be provided to the Ethics Committee.

14.8. CIP Amendments

Medtronic will submit any significant amendment to the CIP, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their Ethics Board, if applicable. Administrative amendments to the Clinical Investigation Plan will be submitted to the Institution Review/Ethics Board and appropriate regulatory authorities for notification, if applicable. Any revisions or amendments to the CIP or Informed Consent Form, along with a statement of justification for the changes, will be submitted to all affected governing Ethics Boards, according to applicable regulations. All amendments to the CIP shall be agreed upon between Medtronic and the principal investigator(s). Approval by Institution Review/Ethics Board (where applicable) must be obtained prior to implementing a CIP revision at the site.

In case the investigator will propose any appropriate modification(s) of the CIP, Medtronic will review this proposal and decide whether the modification(s) will be implemented.

14.9. Record Retention

All study-related documents must be retained for a period of at least 2 years after study closure (or longer if required by local law/regulation hospital administration requirements). Medtronic will inform the investigator/site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between Medtronic and the investigator. The investigator should take measures to prevent accidental or premature destruction of documents. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic will retain the study records according to Medtronic policy.

14.10. Investigator Records

The investigator is responsible for the preparation and retention of the records including, but not limited to, those cited below. All of the below records, with the exception of case report forms, should be kept in the ISF (i.e., the study binder provided to the investigator) or Subject Study Binder. E-CRFs must be maintained and signed electronically within the electronic data capture system during the study. The

following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date on which the investigation is terminated.

- Correspondence between the IRB/EC, sponsor, monitor, and/or the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated Informed Consent Form, in accordance with local requirements
  - Observations of adverse events/adverse device effects/device deficiencies
  - Medical history
  - Baseline, study procedure, and follow-up data (if applicable)
  - Documentation of the dates and rationale for any deviation from the protocol
- Electronically signed and dated e-CRFs and a blank set of CRFs where required by local law
- All approved versions of the CIP and ICF
- Fully executed Clinical Trial Agreement
- Ethics Committee approval documentation. Written information that the investigator or other study staff, when member of the Ethics Committee, did not participate in the approval process. Approval documentation must include the Ethics Board composition, where required per local law.
- List of investigational sites: This list is not yet final at the time of CIP development. The list will be provided under a separate cover and will be maintained by the sponsor.
- Subject Identification and enrollment log
- Device traceability logs and internal tracking of investigational product
- Current curriculum vitae (signed and dated) of principal investigators (US and Hong Kong)
- Documentation of delegated tasks
- Study training records for investigational site team
- Insurance certificates
- Final Study Report including the statistical analysis

14.11. 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 the clinical investigation plan. If any action is taken by an Institution Review/Ethics Board with respect to this clinical 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.

Safety data investigator reporting requirements are listed in Section 10.6 of the Adverse Event section. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 9: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Board approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing Ethics Board of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and Ethics Board	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	Ethics Board and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

14.12. Sponsor records

Medtronic shall maintain the following accurate, complete, and current records that includes, but is not limited to:

- Correspondence that pertains to the AccelAV Study
- Executed Clinical Trial Agreement
- Current curriculum vitae of investigators
- Device accountability logs and internal tracking of investigational products
- Electronically signed and dated e-CRFs
- All approved informed consent templates, and other information provided to the subjects and advertisements, including translations
- Copies of all Ethics Committee approval letters and relevant Ethics Committee correspondence

and Ethics Committee voting list/roster/letter of assurance

- Names and addresses of the institutions in which the AccelAV study will be conducted: This list is not yet final at the time of CIP development. The list will be provided under a separate cover and will be maintained by the sponsor
- Regulatory authority correspondence, notification and approval as required by national legislation
- Insurance certificates
- Names and contact addresses of monitors
- Monitoring reports (interim monitoring visit reports, follow-up letters and close-out visit reports)
- Statistical analyses and underlying supporting data
- Final report of the AccelAV study
- The approved Clinical Investigation Plan, and study related reports, and revisions
- Documentation of delegated tasks
- Site qualification reports and/or waivers
- Study training records for site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained

14.13. Sponsors reports

Medtronic shall prepare and submit the complete, accurate, clinical study reports to participating investigators and Institutional Review/Ethics Board. Additionally, upon request, Medtronic will provide accurate, complete, and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in the Adverse Event section.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study.

14.14. Publication and Use of Information

Results may be submitted for publication. If results from the Accel AV study will be published, they will be handled according to Medtronic Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

14.14.1. Publication Committee

Medtronic may form an Accel AV Publication Committee from study investigators. Medtronic personnel may serve as members of the committee. 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 in Appendices H, 2) develop the final Publication Plan as outlined in Appendix H, 3) execute the Publication Plan, 4) oversee the publication of primary, secondary [redacted] 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 at a regular interval, as needed.

14.14.2. Management of Publications

A Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the Clinical Investigation Plan.

An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this clinical study, and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

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

14.14.3. 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
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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 Accel AV Clinical 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.

14.14.4. 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 Board and Competent Authorities of participating countries 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 after the study ends
- 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 centers study data accessible to the corresponding investigator after the completion of the study, if requested

14.15. Suspension or Early Termination

Medtronic or a Regulatory Authority may decide to suspend or prematurely terminate the clinical study (e.g., if information becomes available that the risk to study subject is higher than initially indicated). If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical

investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing Ethics Board, the study subjects, and the general practitioner.

Medtronic, Ethics Board or Regulatory Authority may decide to suspend or prematurely terminate an investigational site (e.g., in case of expiring approval of the reviewing Ethics Board, non-compliance to the Clinical Investigation Plan or lack of enrollment). If an investigational site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing Ethics Board, if required, the study subjects and general practitioner.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigational site and immediately inform the sponsor and Ethics Board, if applicable. Risks will be continuously monitored, assessed and documented by the investigators.

In case of early investigational site suspension or termination subjects will be followed-up as per standard of care.

14.15.1. Early Termination or Suspension

Early termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single center. 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 center.

Study 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 or suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Technical issues during the manufacturing process

Investigator/center termination or suspension

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

- Failure to obtain initial Ethics Board approval or annual renewal of the study

- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria)
- Lack of enrollment
- 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 queries and monitoring findings in a timely manner, etc.)
- Ethics Board suspension of the center
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

14.15.2. Procedures for Termination or Suspension

Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required
- In the case of study termination or suspension for reasons other than a temporary Ethics Committee approval lapse, the investigator will promptly inform the Ethics Committee along with the reason(s) for termination or suspension
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare.

Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the Ethics Committee and provide detailed explanation of termination/suspension
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

Ethics Board-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)
- The investigator will promptly inform the subjects and the personal physician of the subjects, with the rationale for the study termination or suspension

14.15.3. Planned Study Closure

Study closure is a process initiated by distribution of a 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 Clinical Investigation Plan 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 Ethics Board oversight is required until the overall study closure process is complete. Upon study closure, subjects should be managed and followed per physician discretion.

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16. Appendices

APPENDIX A: DATA COLLECTION ELEMENTS (ELECTRONIC CASE REPORT FORMS)

Electronic Case Report Forms for the AccelAV clinical study will be provided under separate cover. Final e-CRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.

APPENDIX B: INFORMED CONSENT TEMPLATE(S)

Geography-specific Informed Consent templates will be provided under separate cover.

APPENDIX C: PARTICIPATING INVESTIGATORS AND INSTITUTIONS

At the time of AccelAV CIP Version 1.0 completion, site confirmation was not finalized. A complete list of participating investigators and institutions (including names, titles/professional positions, address(es), and telephone numbers) where study activities will be conducted will be distributed under a separate cover when available.

APPENDIX D: ETHICS COMMITTEE

At the time of AccelAV CIP Version 1.0 completion, site confirmation was not yet finalized. Therefore, a complete list of participating Ethics Committee and the Chairperson(s) will be distributed under separate cover when available upon request.

APPENDIX E: FORESEEABLE ADVERSE EVENT LIST

The information provided in this section pertains to foreseeable adverse events that may be observed in the AccelAV Study and may assist in identifying those events that are unexpected in nature. Potential risks and associated adverse events related to the patient's implanted Micra device are in alignment with the product labeling.

Potential risks associated with the AccelAV study as well as risk minimization are discussed within Section 9. Treatment required for AccelAV study related adverse events may include device reprogramming, medications, or other surgical and medical remedies. Evaluation of potentially anticipated events may involve data in this Clinical Investigation Plan as well as a thorough review of all available information (e.g. labeling, current event reporting, published data, etc.).

Potential adverse events related to the presence or performance of Micra AV include:

- Inadequate rate adaptive pacing during study participation
- Unintended loss of capture
- Loss of pacing
- Skin rash/irritation, or allergic reaction
- Reduced device longevity resulting in early replacement procedure could result in complications from replacement procedure
- Dizziness
- Palpitations
- Angina
- Swelling in Feet
- Pulsation in neck
- Fatigue
- Shortness of breath
- Difficulty sleeping
- Syncope
- Decreased heart rate
- Arrhythmia
- Asystole
- Syncope/fainting
- Death

Table 10 provides examples of adverse events associated with the presence or performance of the Micra Transcatheter Pacing System that reported in the Micra IDE Clinical Study.

Table 10: Summary of System Related AEs by Severity and MedDRA Term (Micra IDE Clinical Study)

Number of Events (Number, % Subjects) (Denominator = 726 Subjects with Implant Attempt)			
Adverse Event Keyterm	**Event**	**Serious Event**	**Complication**
Total Adverse Events	**65 (60, 8.3%)**	**38 (37, 5.1%)**	**32 (30, 4.1%)**
Cardiac arrhythmias	**17 (16, 2.2%)**	**7 (7, 1.0%)**	**6 (6, 0.8%)**
Atrioventricular block complete	8 (8, 1.1%)	5 (5, 0.7%)	5 (5, 0.7%)
Bundle branch block right	4 (4, 0.6%)	1 (1, 0.1%)	0 (0, 0.0%)
Sinus node dysfunction	1 (1, 0.1%)	0 (0, 0.0%)	0 (0, 0.0%)
Ventricular fibrillation	1 (1, 0.1%)	1 (1, 0.1%)	1 (1, 0.1%)
Ventricular tachycardia	3 (3, 0.4%)	0 (0, 0.0%)	0 (0, 0.0%)
Traumatic Cardiac Injury	**13 (13, 1.8%)**	**12 (12, 1.7%)**	**12 (12, 1.7%)**
Cardiac perforation	3 (3, 0.4%)	3 (3, 0.4%)	3 (3, 0.4%)
Pericardial effusion	10 (10, 1.4%)	9 (9, 1.2%)	9 (9, 1.2%)
Pacing Issues	**9 (9, 1.2%)**	**4 (4, 0.6%)**	**2 (2, 0.3%)**
Device dislocation	1 (1, 0.1%)	1 (1, 0.1%)	1 (1, 0.1%)
Device pacing issue	8 (8, 1.1%)	3 (3, 0.4%)	1 (1, 0.1%)
Other	**26 (25, 3.4%)**	**15 (15, 2.1%)**	**12 (12, 1.7%)**
Angina pectoris	3 (3, 0.4%)	0 (0, 0.0%)	0 (0, 0.0%)
Cardiac failure	7 (7, 1.0%)	7 (7, 1.0%)	6 (6, 0.8%)
Chest pain	1 (1, 0.1%)	0 (0, 0.0%)	0 (0, 0.0%)
Non-cardiac chest pain	5 (5, 0.7%)	1 (1, 0.1%)	1 (1, 0.1%)
Pacemaker syndrome	5 (5, 0.7%)	3 (3, 0.4%)	2 (2, 0.3%)
Pericarditis	2 (2, 0.3%)	1 (1, 0.1%)	1 (1, 0.1%)
Presyncope	2 (2, 0.3%)	2 (2, 0.3%)	1 (1, 0.1%)
Syncope	1 (1, 0.1%)	1 (1, 0.1%)	1 (1, 0.1%)

Table 11 provides a summary of procedure related adverse events by MedDRA keyterm that occurred during the Micra IDE clinical study.

Table 11: Summary of Procedure Related AEs by Severity and MedDRA Term (Micra IDE Clinical Study)

Number of Events (Number, % Subjects) (Denominator = 726 Subjects with Implant Attempt)			
Adverse Event Keyterm	**Event**	**Serious Event**	**Complication**
Total Adverse Events	**117 (100, 13.8%)**	**48 (44, 6.1%)**	**50 (45, 6.2%)**
Cardiac arrhythmias	**17 (16, 2.2%)**	**8 (8, 1.1%)**	**7 (7, 1.0%)**
Atrioventricular block complete	8 (8, 1.1%)	5 (5, 0.7%)	5 (5, 0.7%)
Bundle branch block right	4 (4, 0.6%)	1 (1, 0.1%)	0 (0, 0.0%)

Number of Events (Number, % Subjects) (Denominator = 726 Subjects with Implant Attempt)			
Adverse Event Keyterm	**Event**	**Serious Event**	**Complication**
Ventricular fibrillation	1 (1, 0.1%)	1 (1, 0.1%)	1 (1, 0.1%)
Ventricular tachycardia	4 (4, 0.6%)	1 (1, 0.1%)	1 (1, 0.1%)
Embolism and thrombosis	**5 (5, 0.7%)**	**3 (3, 0.4%)**	**3 (3, 0.4%)**
Deep vein thrombosis	4 (4, 0.6%)	2 (2, 0.3%)	2 (2, 0.3%)
Pulmonary embolism	1 (1, 0.1%)	1 (1, 0.1%)	1 (1, 0.1%)
Events at Groin Puncture Site	**51 (49, 6.7%)**	**11 (11, 1.5%)**	**11 (11, 1.5%)**
Arterial injury	5 (5, 0.7%)	0 (0, 0.0%)	1 (1, 0.1%)
Arteriovenous fistula	5 (5, 0.7%)	4 (4, 0.6%)	4 (4, 0.6%)
Impaired healing	1 (1, 0.1%)	0 (0, 0.0%)	0 (0, 0.0%)
Incision site complication	1 (1, 0.1%)	0 (0, 0.0%)	0 (0, 0.0%)
Incision site haematoma	8 (8, 1.1%)	0 (0, 0.0%)	1 (1, 0.1%)
Incision site haemorrhage	18 (17, 2.3%)	3 (3, 0.4%)	2 (2, 0.3%)
Incision site infection	2 (2, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Incision site pain	3 (3, 0.4%)	0 (0, 0.0%)	0 (0, 0.0%)
Incisional drainage	6 (6, 0.8%)	2 (2, 0.3%)	2 (2, 0.3%)
Vascular pseudoaneurysm	2 (2, 0.3%)	2 (2, 0.3%)	1 (1, 0.1%)
Traumatic Cardiac Injury	**13 (13, 1.8%)**	**12 (12, 1.7%)**	**12 (12, 1.7%)**
Cardiac perforation	3 (3, 0.4%)	3 (3, 0.4%)	3 (3, 0.4%)
Pericardial effusion	10 (10, 1.4%)	9 (9, 1.2%)	9 (9, 1.2%)
Pacing Issues	**2 (2, 0.3%)**	**2 (2, 0.3%)**	**2 (2, 0.3%)**
Device dislocation	1 (1, 0.1%)	1 (1, 0.1%)	1 (1, 0.1%)
Device pacing issue	1 (1, 0.1%)	1 (1, 0.1%)	1 (1, 0.1%)
Other	**29 (28, 3.9%)**	**12 (12, 1.7%)**	**15 (15, 2.1%)**
Acute myocardial infarction	1 (1, 0.1%)	1 (1, 0.1%)	1 (1, 0.1%)
Angina pectoris	3 (3, 0.4%)	0 (0, 0.0%)	0 (0, 0.0%)
Back pain	1 (1, 0.1%)	0 (0, 0.0%)	0 (0, 0.0%)
Chest pain	1 (1, 0.1%)	0 (0, 0.0%)	0 (0, 0.0%)
Dysuria	1 (1, 0.1%)	0 (0, 0.0%)	0 (0, 0.0%)
Hypotension	3 (3, 0.4%)	1 (1, 0.1%)	3 (3, 0.4%)
Medication error	2 (2, 0.3%)	1 (1, 0.1%)	2 (2, 0.3%)
Metabolic acidosis	1 (1, 0.1%)	1 (1, 0.1%)	1 (1, 0.1%)
Non-cardiac chest pain[1]	6 (6, 0.8%)	1 (1, 0.1%)	1 (1, 0.1%)
Osteoarthritis	1 (1, 0.1%)	0 (0, 0.0%)	1 (1, 0.1%)
Pericarditis	2 (2, 0.3%)	1 (1, 0.1%)	1 (1, 0.1%)
Presyncope	5 (5, 0.7%)	5 (5, 0.7%)	3 (3, 0.4%)
Syncope	1 (1, 0.1%)	1 (1, 0.1%)	1 (1, 0.1%)
Urinary retention	1 (1, 0.1%)	0 (0, 0.0%)	1 (1, 0.1%)

[1]One event of non-cardiac chest pain was considered to have an unknown relationship to the Micra procedure.

APPENDIX F: LABELING

Labeling and packaging for all products used in this study will follow the local regulatory requirements. Labeling for all system components market released at study start in the respective geographies can be found with each package insert and/or will be available on http://manuals.medtronic.com.

The Model ER220 Extended Range Holter Monitor is investigational in certain geographies and will be labelled according to local requirements with the statements “For Medtronic Clinical Use Only. Not intended for commercial distribution."

APPENDIX G: INVESTIGATOR STATEMENT

The investigator Statement will be provided under a separate cover.

APPENDIX H: PUBLICATION PLAN

The Publication Plan will be provided under a separate cover.

APPENDIX I: ACCELAV Study Reference Guide for Cardiac Echocardiogram Data Acquisition

The AccelAV Study Reference Guide for Cardiac Echo Data Acquisition will be provided under a separate cover.

17. Version History

Version	Summary of Changes	Author(s)/Title
1.0 06JAN2020	Not Applicable, New Document	Nicole Wood, Pr CRS Kurt Stromberg, Sr Pr Statistician Francesca Lemme, Sr Statistician Vincent Splett, Pr Scientist
2.0 24JAN2020	Changed Version number & date of CIP. Pg. 13, 2. Synopsis: removed ‘this study will be conducted upon market approval of the Micra AV™ Transcatheter Pacing System’ Pg. 87, Appendix E-Foreseeable Adverse Events: ‘changed AccelAV software to AccelAV study’. Revised ‘Potential adverse events related to participation in the AccelAV study include:’ to ‘Potential adverse events related to the presence or performance of the Micra AV would include:’ Removed bullet ‘discomfort during exercise manuvers’. Page 90: retitled Echo Acquistion Manual to AccelAV Study Reference Guide for Cardiac Echocardiogram Data Acquistion	Nicole Wood, Pr CRS Kurt Stromberg, Sr Pr Statistician Francesca Lemme, Sr Statistician Vincent Splett, Pr Scientist