Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	**M**icra **A**tr**i**al T**R**acking Using A **V**entricular Acc**EL**erometer 2 Abbreviated Name: MARVEL 2 study
Clinical Investigation Plan Identifier	MARVEL 2 study
Study Product Name	MARVEL 2 Research System
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Local Sponsor	**Southeast Asia** Sheikh Abdul-Aziz, Principal Clinical Research Specialist Medtronic Malaysia Sdn Bhd B-23-1, Level 23 The Ascent, Paradigm No 1 Jalan SS7/26A Kelana Jaya 47301 Petaling Jaya, Selangor Malaysia Phone: +603-7883-8000
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Document Version	Version 2.0
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Lead Principal Investigator(s)	**United States:** [redacted] **Europe:** [redacted]

Confidentiality Statement

1 Investigator Statement

Study product Name	MARVEL 2 Research System
Sponsor	Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 Phone: +1-800-328-2518
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Manufacturer	Medtronic, Inc. 710 Medtronic Parkway Minneapolis, MN U.S.A. 55432 Phone: +1-800-328-2518
Clinical Investigation Plan Identifier	MARVEL 2 clinical study
Version Number/Date	Version 2.0/ 01NOV2018

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with Declaration of Helsinki, Clinical Investigation Plan, Good Clinical Practice and to the national and local laws, regulations, standards, and requirements. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

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

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

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5 Glossary

Term	*Definition*
A3	Accelerometer signal associated with passive ventricular filling (associated with E-wave on echo)
A4	Accelerometer signal associated with active ventricular filling (associated with A-wave on echo)
AE	Adverse Event
AF	Atrial fibrillation
ADE	Adverse Device Effect
AV	Atrioventricular
CEC	Clinical Event Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DMC	Data Monitoring Committee
EC	Ethics Committee
e-CRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMEA	Europe, Middle East, Africa
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

Term	*Definition*
GCP	Good Clinical Practice
IC	Informed Consent
ICF	Informed Consent Form
IRB	Institutional Review Board
ISF	Investigator Site File
LVOT	Left Ventricular Outflow Tract
MSM	Medtronic Secure Messaging
OIT	Oversensing Induced Tachyarrhythmias
RDC	Remote Data Capture
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAV	Sensing AV Delay
SDN	Medtronic Software Distribution Network
TPS	Transcatheter Pacing System
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
USB	Universal Serial Bus
VDD DL	Pacing acronym/Down Load
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

Term	Definition
	synchronized to atrial sensing. The behavior is similar to VVI pacing behavior. The ventricle is paced asynchronously to the atrium up to the programmed maximum tracking rate.
VTI	Velocity Time Integral
VVI pacing mode	Sensing and pacing occur only in the ventricle.
VVIR pacing mode	Rate adaptive VVI pacing

6 Synopsis

Title	MARVEL 2 Clinical Investigation Plan
Clinical Study Type	Pivotal
Product Name	MARVEL 2 Research System
Sponsor	Medtronic, Inc.
Local Sponsor	**United States** Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 Phone: +1-800-328-2518 **Europe Middle East, Africa (EMEA)** Medtronic, Bakken Research Center B.V. Endepolsdomein 5, 6229 GW Maastricht The Netherlands Phone: +31-433-566-566 **Southeast Asia** Medtronic Malaysia Sdn Bhd B-23-1, Level 23 The Ascent, Paradigm No 1 Jalan SS7/26A Kelana Jaya 47301 Petaling Jaya, Selangor Malaysia Phone: +603-7883-8000 **Hong Kong**

<table>
<tr><td></td><td>Medtronic Hong Kong Medical Ltd.
1104-11, 11/F, Tower 1, The Gateway,
Harbour City, Kowloon,
Hong Kong SAR, China
Phone +852-2919-1300</td></tr>
<tr><td>Indication under investigation</td><td>The investigational MARVEL 2 software is a new pacing mode algorithm that is downloaded (injected) into the market released Micra™ Model MC1VR01 transcatheter pacing system (TPS) to provide atrial synchronous ventricular pacing in patients with AV block. The Micra™ TPS will be used outside the approved intended use due to the investigational component of the download under study. Micra™ TPS is indicated for use in patients who have experienced one or more of the following conditions:
Symptomatic paroxysmal or permanent high-grade AV block in the presence of AF
Symptomatic paroxysmal or permanent high-grade AV block in the absence of AF, as an alternative to dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy
Symptomatic bradycardia tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy.</td></tr>
<tr><td>Investigation Purpose</td><td>The purpose of the Micra Atrial TRacking Using A Ventricular AccELerometer 2 (MARVEL 2) study is to demonstrate safe and effective operation of an accelerometer based atrial sensing algorithm providing AV synchronous pacing in patients with normal sinus node function and AV block. The MARVEL 2 clinical study will be used as pivotal evidence to support market approval of the Micra AV device for expanding the use of transcatheter pacing systems into patients with normal sinus node function and AV node block where an atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy.</td></tr>
<tr><td>Product Status</td><td>
<table>
<tr><th colspan="3">MARVEL 2 System Components</th></tr>
<tr><th>Model Number</th><th>Component (Manufacturer)</th><th>Investigational or Commercially Available</th></tr>
<tr><td>MC1VR01</td><td>Micra ™TPS Implantable Device (Medtronic)</td><td>Commercially available in applicable geographies*</td></tr>
</table>
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	<table><tr><td>SW022</td><td>Micra™ Application Software (Medtronic)</td><td>Commercially available in applicable geographies</td></tr><tr><td>MRVL2</td><td>MARVEL 2 Software Rev.1.0 (Medtronic)</td><td>Investigational</td></tr><tr><td>9986</td><td>2090 Programmer Baseline Operating System Software (Medtronic)</td><td>Commercially available in applicable geographies</td></tr><tr><td>2090</td><td>Medtronic Carelink Programmer (Medtronic)</td><td>Commercially available in applicable geographies</td></tr><tr><td rowspan="2">Model ER220 Extended Range Holter Monitor**</td><td>ERX10 Extended Range Tel-B Antenna (Medtronic)</td><td>Investigational</td></tr><tr><td>DR220 Holter (NorthEast Monitoring, Inc)</td><td>Commercially available in applicable geographies</td></tr></table> *The Micra™ Model MC1VR01 device will be considered investigational the moment the MARVEL 2 software is downloaded and will no longer be investigational when the MARVEL 2 software is removed. Commercially available devices listed in the table above will be used inside the approved indications, except the Micra device. **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.
Primary Objective(s)	**Primary Efficacy Objective** Demonstrate the superiority of the MARVEL 2 features to provide atrioventricular synchronous pacing relative to Micra VVI pacing in subjects with normal sinus node function and persistent 3rd degree AV node block at rest. **Primary Safety Objective** Demonstrate that the MARVEL 2 features provide pacing as intended.
Secondary Objective(s)	**Secondary Objective** Demonstrate an increase in stroke volume, as measured by left ventricular outflow tract velocity time integral, with the MARVEL 2 features compared to VVI pacing in subjects with normal sinus node function and persistent 3rd degree AV node block. [redacted]

	
Study Design	The MARVEL 2 study is an acute, prospective, global, multi-center, software-download clinical study. The study is planned to be conducted in US, Europe, and Asia. The study is expected to be conducted at approximately 15-20 centers in up to 100 subjects to obtain at least 70 usable Holter datasets to meet the objectives of the study. The expected total study duration (from first subject enrollment to the exit of the last subject) is approximately 6-months; this represents the time necessary to enroll the target sample size of at least 70 subjects with usable Holter datasets. Software will be downloaded into patients implanted with a Micra device to allow the new algorithm performance to be measured in patients where a Micra device has already been chosen as most appropriate for the patient. Most enrolled subjects will complete the study procedures during a single study visit. However, subjects enrolling in the study at the time of their Micra implant (anticipated to be approximately 10 subjects) will have the investigational algorithm downloaded following Micra implant, prior to hospital discharge, and approximately 1-month post-implant. This subset of subjects with *de novo* Micra implants will allow the MARVEL 2 features to be tested at multiple points in the device life cycle. Since the download algorithm running in a Micra device significantly increases current drain, a 2-4 hour acute study is used to limit the reduction in device longevity.
Sample Size	A sample size of at least 70 subjects with usable Holter datasets following MARVEL 2 software download is required to test the study's primary objectives. This includes at least 35 subjects with a predominant heart rhythm of normal sinus node function and persistent 3rd degree AV block to provide at least 90% power to test the study's primary efficacy objective. Since all subjects may not have usable Holter data, up to 100 subjects may be enrolled to achieve the goal of 70 usable Holter datasets. Enrollment may end once the target number of usable Holter datasets has been obtained.

	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 20.
Enrollment Strategy	The intent is to ensure subjects enrolled early in the study contribute to the primary efficacy and secondary objectives, specifically subjects with normal sinus node function and persistent 3rd degree AV node block. Once at least 35 of these subjects have been enrolled, other subjects with a history of AV block may be enrolled to demonstrate the safety and utility of the MARVEL 2 algorithm in patients with other forms of AV block. These include subjects who may have predominantly intact AV conduction or AV block with sinus node dysfunction, and/or atrial arrhythmias. More than 35 subjects meeting the criteria for the primary efficacy objective may be enrolled. It is preferable to enroll subjects with *de novo* Micra implants early in the study since they will have a 1-month follow-up. The enrollment strategy and current target patient population available for enrollment to address the primary efficacy and secondary study objectives will be communicated to the study centers.
Inclusion/Exclusion Criteria	Inclusion Criteria • Subject has been implanted with a Micra TPS (Model MC1VR01) with remaining device longevity of 6 years or more or is expected to be implanted with a Micra TPS. • 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 function and persistent 3rd degree AV block and subjects with other forms of AV block. Exclusion Criteria • Subject is 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 is pregnant (if required by local law, women of child-bearing potential must undergo a pregnancy test within seven days prior to MARVEL 2 study procedures). • Subject meets any exclusion criteria required by local law (age or other).
Study Procedures and Assessments	After consent, enrollment, baseline data collection, and initial Micra™ TPS device interrogation, the investigational MARVEL 2 software will be downloaded into an implanted Micra device and a customized Holter monitor will be placed on the subject. The Holter will record surface ECG, EGM, accelerometer signals, and device and MARVEL 2 algorithm markers. The subject will sit or lie while an automatic setup is performed to determine the optimal accelerometer vector and sensing parameters. Following the automatic setup, the MARVEL 2 features will be evaluated at rest. Subsequently, the subject will perform a series of posture maneuvers and exercises. Subjects will have an echocardiogram performed while the MARVEL 2 features are programmed to adaptive mode (VDD pacing) and programmed to monitor mode (VVI pacing). After all study procedures have been completed, the MARVEL 2 software will be removed, a final Micra TPS device interrogation performed, the Micra TPS device will be programmed to its intended permanent device settings, and the subject will be exited. The in-office testing is expected to last 2-4 hours. It is expected that approximately 10 subjects with *de novo* Micra implants (i.e. those enrolling at the time of their Micra implant) may enroll in the MARVEL 2 study. Studying subjects with *de novo* implants ensures some accelerometer signals will be collected during/immediately after the implant procedure. In addition, studying these subjects prior to hospital discharge and at 1-month provides information on the evolution of the accelerometer signal and AV synchrony.
Safety Assessments	All adverse events (AEs) that occur from the time of enrollment through study exit will be collected and reported to Medtronic during the study. Additionally, any device deficiencies related to the Micra device or MARVEL 2 software will be collected. All Holter recordings will be evaluated for the presence of pauses exceeding two cardiac cycles and oversensing induced tachyarrhythmias (OIT) exceeding 100 bpm.
Statistics	A sample size of at least 70 subjects with usable Holter datasets following MARVEL 2 software download is required. This includes at least 35 subjects with a predominant heart rhythm of normal sinus node

	function and persistent 3rd degree AV block to provide at least 90% power to test the study's primary objectives at an overall alpha level of 0.05. Up to 100 subjects may be enrolled to collect at least 70 usable Holter datasets). However, enrollment may end once the target number of usable Holter datasets has been obtained. A single analysis to support pre-market approval will occur once all enrolled subjects have had the opportunity to complete the MARVEL 2 study procedures and the Holter recordings have been processed. For the study to be considered a success, the null hypothesis for both the primary efficacy and primary safety objective must be rejected. For the primary efficacy objective, the primary efficacy endpoint will be considered met if the percentage of AV synchronous beats during rest exceeds 70%. McNemar's test will be used to test the null hypothesis since each subject will be tested when the MARVEL 2 features are programmed to adaptive mode (VDD pacing) and monitor mode (VVI pacing). For the primary safety objective, a subject will meet the primary safety endpoint if they are free from pauses exceeding two cardiac cycles and free from oversensing induced tachycardia exceeding 100 bpm for more than 3 minutes during the entire Holter monitoring period while the MARVEL 2 features are enabled.

7 Introduction

7.1 Background

The Micra™ TPS 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 ™ TPS 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] Currently, Micra is approved for use in the all geographies where the MARVEL 2 study will be conducted, specifically: US, Europe, and Asia. Micra also provides rate response via a 3-axis intracardiac accelerometer.[4] However, the majority of patients requiring pacing are not recommended for VVI pacing. Other pacing modalities including VDD or DDD are recommended for patients with atrioventricular (AV) block and normal sinus node function where there is a need to preserve atrioventricular synchrony.[5] Thus, the majority of patients with AV block cannot currently benefit from current intracardiac pacemakers.

The MASS/MASS2 studies collected the intracardiac accelerometer signal from 39 subjects with an implanted Micra device 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's intracardiac accelerometer to mechanically detect atrial contraction. 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 ($p<0.001$).[6] 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 collect and compare the accelerometer signals and AV synchrony at two time-points. The mean time between visits was 7.1±0.6 months. MARVEL-Evolve 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 rate. The performance of the enhanced algorithm is the focus of the MARVEL 2 study. The MARVEL 2 clinical study will be used as pivotal evidence to support market approval of the Micra AV device for expanding the use of transcatheter pacing systems into patients with AV block and normal sinus node function.

7.2 Purpose

The purpose of the **M**icra **A**trial T**R**acking Using A **V**entricular Acc**EL**erometer 2 (MARVEL 2) study is to demonstrate safe and effective operation of the MARVEL 2 features for providing AV synchronous pacing in patients with normal sinus node function and AV block.

8 Objectives and Endpoints

8.1 Objectives

8.1.1 Primary Objective(s)

8.1.1.1 Primary Efficacy Objective

Demonstrate the superiority of the MARVEL 2 features to provide atrioventricular synchronous pacing relative to Micra VVI pacing in subjects with normal sinus node function and persistent 3rd degree AV block at rest.

8.1.1.2 Primary Safety Objective

Demonstrate that the MARVEL 2 features provide pacing as intended.

8.1.2 Secondary Objective

Demonstrate an increase in stroke volume, as measured by left ventricular outflow tract velocity time integral, with the MARVEL 2 features compared to VVI pacing in subjects with normal sinus node function and persistent 3rd degree AV block.

8.2 Endpoints

8.2.1 Primary Endpoint(s)

8.2.1.1 Primary Efficacy Endpoint

A subject will meet the primary endpoint if a paced or sensed ventricular beat is within 300 ms following an ECG confirmed P-wave for at least 70% of the ECG confirmed P-waves. The primary endpoint will be evaluated during the MARVEL 2 setup phase (VDI pacing which is effectively VVI pacing) and during the 20-minute resting period in which the MARVEL 2 features are enabled.

Rationale for Endpoint

Rationale for 300 ms Synchronous Beat Definition

A paced or sensed R-wave within 300 ms of following an ECG confirmed P-wave that occurs during normal sinus function indicates a level of atrioventricular synchrony that is clinically acceptable. Specifically, currently available dual chamber Medtronic pacing systems utilize the Search AV+® algorithm that allows for maximum nominal AV intervals to be lengthened to 290 ms (for intrinsic sensed events) and 320 ms (for paced events) to limit unnecessary ventricular pacing. This feature has been shown to minimize ventricular pacing and reduce atrial fibrillation in patients with sinus node disease.[7] Therefore, a pace or detection of a sensed R-wave following within 300 ms of an ECG confirmed P-wave would indicate an acceptable level of atrioventricular synchrony.

Additionally, only P-waves identified on surface ECG that occur during normal sinus node function will be considered for the endpoint. Therefore, P-waves occurring during atrial arrhythmias are not included in the endpoint definition. This criterion was selected so that atrial beats that should not or could not be tracked by the algorithm with a paced or sensed ventricular beat are not included in the endpoint determination. Note that the 300 ms P-V interval required to consider a beat synchronous is identical to what was used for the MARVEL study.

Rationale for 70% AV Synchrony Requirement

There is no recognized consensus on a clinically relevant level of atrioventricular synchrony for subjects with AV block and without AF who require pacing. Importantly, the largest randomized trial (UKPACE) comparing VVI and DDD pacing in patients with normal sinus function and AV block did not identify a difference in pacing modes with respect major clinical outcomes including all-cause mortality, atrial fibrillation, or heart failure.[8] However, as observed in the MARVEL study, increasing the level of synchrony in this population can increase cardiac stroke volume.[6]

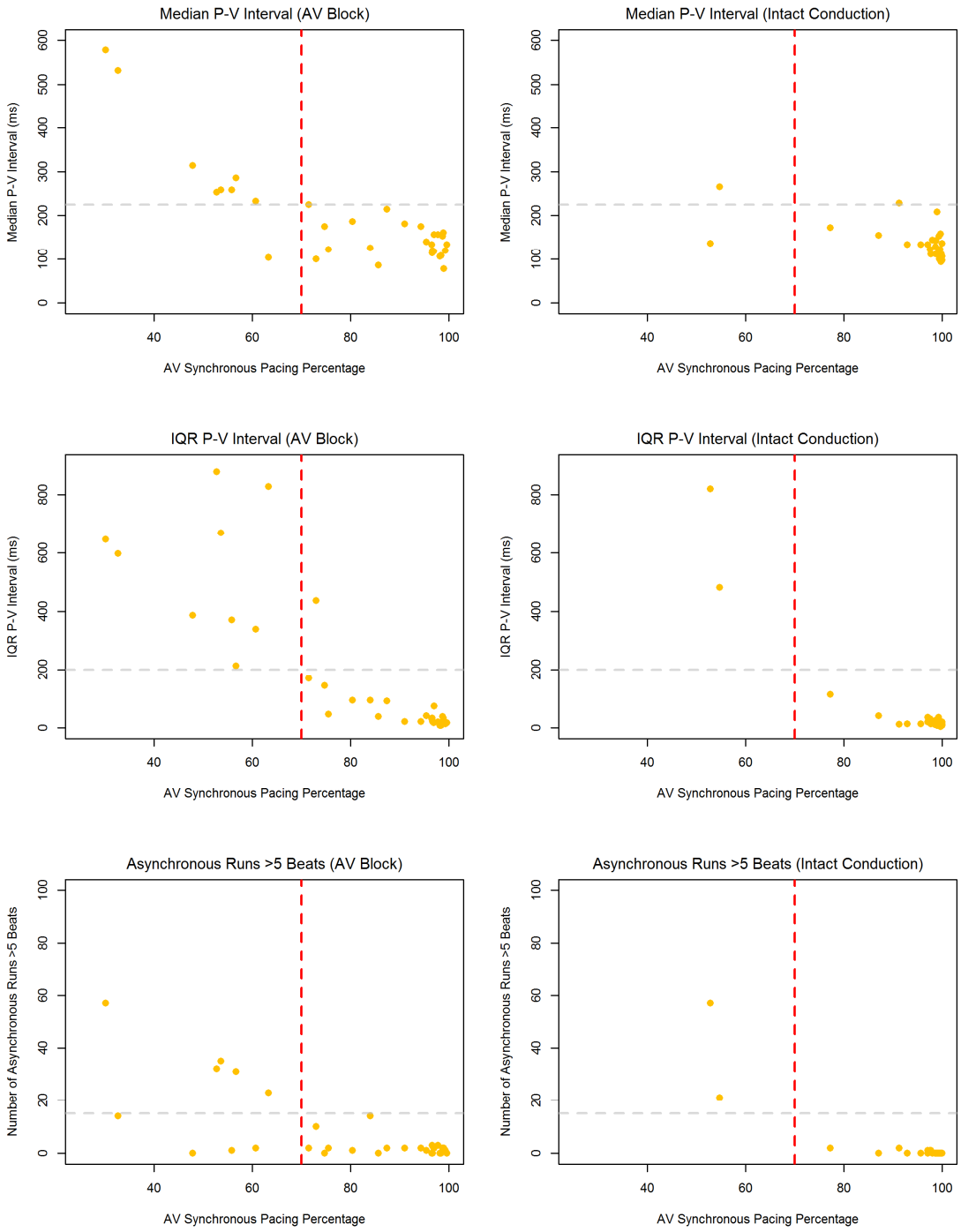
Pacing modalities designed to improve AV synchrony percentage must generally minimize the P-V interval to less than 300 ms, minimize the variation in the P-V intervals to levels observed during intrinsic AV conduction, and minimize the number of consecutive dyssynchronous beats when AV synchrony is lost.

Figure 1 displays the relationship between AV synchrony percentage and several measures of AV synchrony observed during the 30-minute resting period during the MARVEL study. Specifically, the

rows of Figure 1 display the relationship between AV synchrony percentage and median P-V interval (top row), interquartile range for the P-V interval (middle row), and the number of episodes of dyssynchrony exceeding 5 consecutive beats (bottom row). The columns of Figure 1 display the relationships for the 33 MARVEL subjects with a predominant rhythm of high-grade AV block (left column) and 31 MARVEL subjects with a predominant rhythm of intact AV conduction. The red dashed vertical line indicates 70% AV synchrony on each plot.

Careful examination of Figure 1 indicates that subjects with >70% AV synchrony had a median P-V interval of 225 ms or lower, and this was true for all subjects with >70% AV synchrony regardless of predominant rhythm. The middle row of Figure 1 shows that all the 9 subjects (100%) with high-grade AV Block and <70% AV synchrony had an interquartile range or their P-V intervals exceeding 200 ms while 22 or the 23 (96%) of the subjects with high-grade AV block and >70% AV synchrony had a P-V interval interquartile range less than 200 ms. Similarly, for the subjects with intrinsic AV conduction, the two subjects with <70% AV synchrony had P-V interval interquartile ranges exceeding 200 ms, while all 29 subjects with >70% synchrony had P-V interval interquartile ranges less than 200 ms. Finally, the bottom row of Figure 1 shows that none of the 23 subjects with high-grade AV block and none of the 29 subjects with intact AV conduction and >70% AV synchrony had more than 15 instances of more than 5 consecutive beats of dyssynchrony. This analysis further suggests that the requirement for at least 70% AV synchrony is appropriate.

Figure 1: Atrioventricular Pacing Percentage versus Components of AV Synchrony



SAS Program: V:\MARVEL\Reports\Final_Report\AdHocDataRequests\MARVEL2\summarizeAsynchronousBeats.sas
R Program: V:\MARVEL\Reports\Final_Report\AdHocDataRequests\MARVEL2\plotAsynchronyDistribution.R

8.2.1.2 Primary Safety Endpoint

A subject will meet the primary endpoint if they are free from the following MARVEL 2 software related events during the entire Holter monitoring period where the MARVEL 2 features are enabled:

1. Pauses lasting longer than two cardiac cycles (where cardiac cycle length is defined by the programmed lower rate interval), AND
2. Episodes of oversensing induced tachycardia exceeding 3-minutes, defined as oversensing accelerometer signal leading to a heart rate exceeding 100 BPM

Rationale for Endpoint

The primary safety endpoint will ensure that the pacing functionality of the MARVEL 2 features are safe (i.e. the MARVEL 2 algorithm does not interfere with the Micra device's ability to provide pacing support). Specifically, the primary safety endpoint will allow the MARVEL 2 study to demonstrate that the MARVEL 2 features 1) provide adequate rate support and 2) do not pace too fast due to oversensing.

8.2.2 Secondary Endpoint

The secondary endpoint is left ventricular outflow tract (LVOT) velocity time integral (VTI) as obtained from echocardiogram while the MARVEL 2 features are in adaptive mode (VDD pacing) and while the MARVEL 2 features are in monitor mode (VDI pacing which is effectively VVI pacing). This will be measured by the echo core laboratory.

Rationale for Endpoint

LVOT VTI is a measure of stroke volume and correlated with cardiac function. Traditional dual chamber pacemakers (with a lead in both the right atrium and right ventricle) have been shown to improve stroke volume compared to VVI pacing. Demonstrating a significant increase in LVOT VTI in the study will show that the MARVEL 2 features also improve stroke volume compared to VVI pacing.[9]

[redacted]

9 Study Design

The MARVEL 2 study is an acute, prospective, global, multi-center, software-download clinical study to evaluate the performance of the MARVEL 2 software, which includes a comprehensive set of the anticipated Micra AV features. The study is planned to be conducted in the US, Europe, and Asia. In the United States, the study is being conducted under an Investigational Device Exemption (IDE). Overall, the study is expected to be conducted at approximately 15-20 centers and will enroll up to 100 subjects to obtain at least 70 usable Holter datasets to meet the sample size required to test the primary objectives of the study. Holter datasets will be considered usable if there is readable telemetry signal as determined by Medtronic personnel experienced in the review of Holter recordings.

The expected total study duration (from first subject enrollment to the exit of the last subject) is approximately 6-months with the proposed start date of January 2019. This represents the time necessary to enroll the target sample size of at least 70 subjects. A download study into patients with an existing Micra device allows the new algorithm performance to be measured in patients where a Micra device has already been chosen as most appropriate for the patient. Most enrolled subjects will complete the study procedures at a single 2 to 4-hour study visit. However, a subset of subjects who enroll in the study at the time of their Micra implant (anticipated to be approximately 10 subjects) will have the investigational algorithm downloaded following Micra implant, one day post-implant, and at approximately 1-month post-implant. Studying these subjects with *de novo* Micra implants will allow the MARVEL 2 software features to be tested at multiple points in the device life cycle.

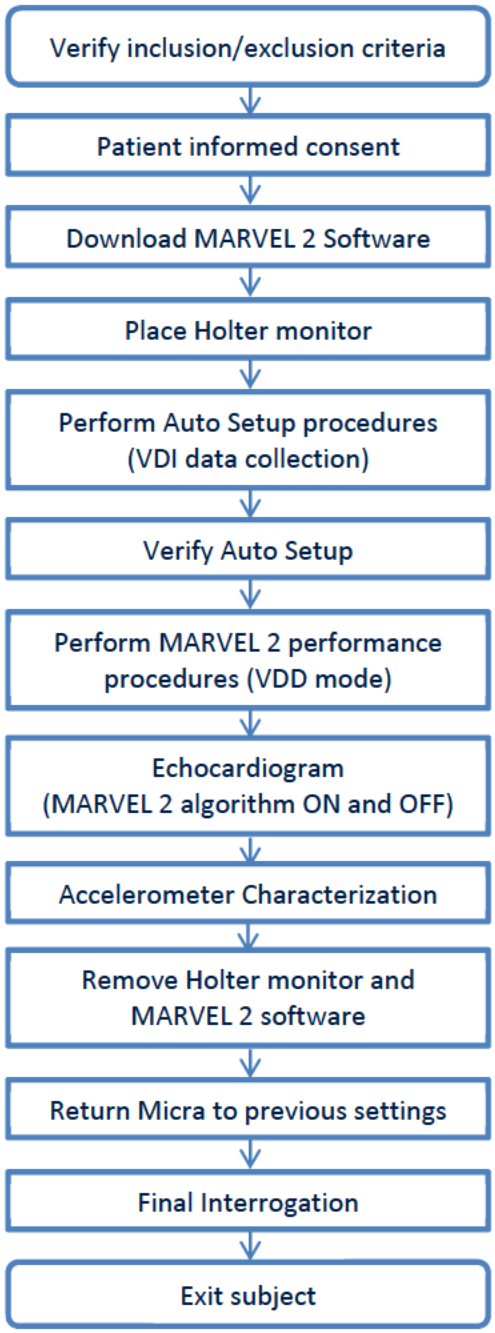
Additionally, study centers that participated in the MARVEL study may enroll up to three randomly selected subjects with normal sinus node function and persistent 3rd degree AV node block that participated in the MARVEL study. Allowing subjects enrolled in the MARVEL study to participate in the MARVEL 2 study will enable an assessment of AV synchrony at multiple points in time.

Because the download algorithm running in Micra device significantly increases current drain, a 2 to 4-hour acute study is used to limit the reduction in device longevity.

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 20.

Figure 2 displays the MARVEL 2 study flow for all study subjects.

Figure 2: MARVEL 2 Study Flow



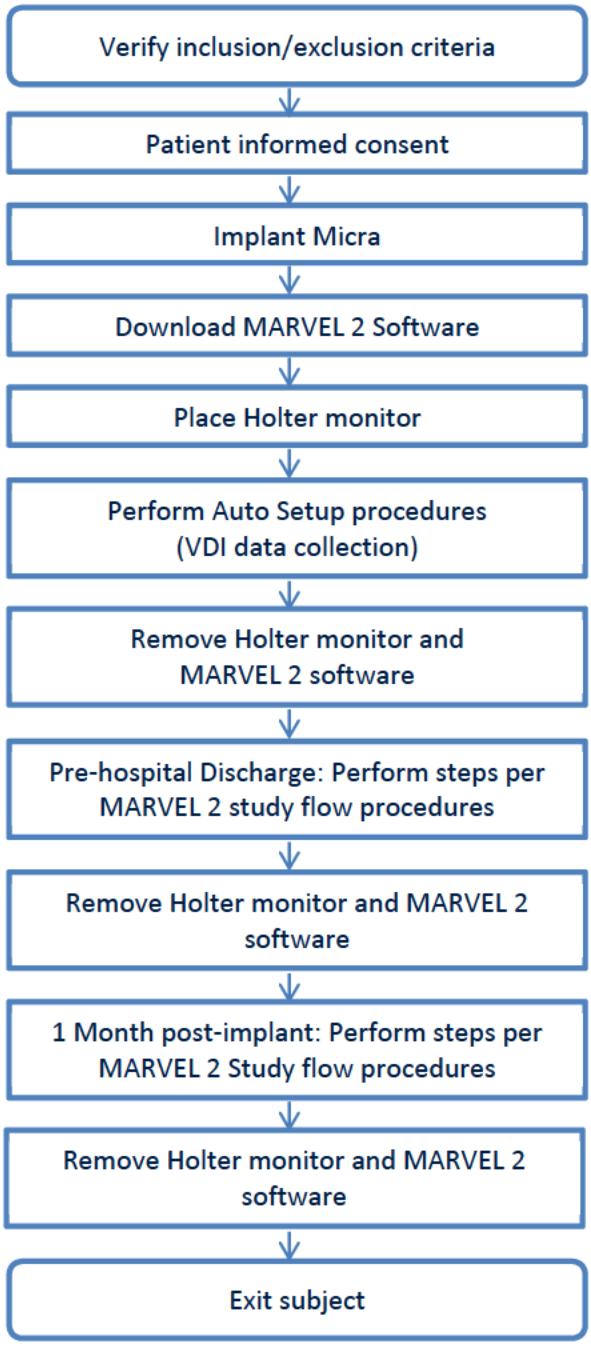
9.1.1 De Novo Subjects

De Novo subjects are those subjects that enroll in the MARVEL 2 study at the time of their Micra implant. Note that these will be subjects where the clinician and patient have determined that a Micra device is the most appropriate therapy for the patient's condition. It is expected that approximately 10 *de novo* subjects will enroll in the MARVEL 2 study. Studying these subjects with *de novo* Micra implants ensures some accelerometer signals are collected during or immediately after the implant procedure. In addition, studying these subjects prior to hospital discharge and at 1-month provides information on the evolution of the accelerometer signal and AV synchrony.

Specifically, following Micra implant and initial device interrogation, the investigational MARVEL 2 software will be downloaded into the Micra, and a custom Holter monitor will be placed on the subject. The Holter monitor will record surface ECG, EGM, accelerometer signals, and device and MARVEL 2 algorithm markers. The subject should be in a sitting or supine position while the automatic setup runs for approximately 20 minutes. Once completed, the MARVEL 2 software will be removed from the Micra, and the Holter monitor will be removed from the subject. Note that the MARVEL 2 software will be in monitor mode (VDI mode with no atrial tracking) on the day of the Micra implant. Prior to hospital discharge and at approximately 1-month post-implant *de novo* subjects will perform the MARVEL 2 study procedures as described in Figure 2 (however, the subject should not be exited after completing the study procedures at their pre-hospital discharge post-implant visit). Figure 3 describes the additional study procedures required for *de novo* subjects.

Thus, *de novo* subjects will be exposed to the investigational MARVEL 2 algorithm for a total of approximately 4.5 to 8 hours.

Figure 3: Additional Study Procedures for De Novo Subjects



9.1.2 Reenrollment of MARVEL Study Subjects

Study centers that participated in the previous MARVEL study may reenroll up to 3 subjects in MARVEL 2 who had normal sinus node function and persistent 3rd degree AV node block during the MARVEL study. Medtronic will provide these centers a list of subjects from the MARVEL study that are eligible for reenrollment in MARVEL 2. If 3 or fewer subjects are eligible for reenrollment the study center should approach *all* such subjects for participation in MARVEL 2. If more than 3 subjects are eligible for reenrollment in MARVEL 2, Medtronic will provide the center with the order in which eligible subjects should be approached for participation in MARVEL 2. In these cases, the ordered list will be a random permutation of all eligible subjects *without* regard to the MARVEL study results.

Attempts to re-enroll eligible MARVEL subjects will be documented on a site level e-CRF.

9.2 Duration

The expected total study duration (from first subject enrollment to the exit of the last subject) is approximately 6-months. For most subjects, the expected duration of study participation is less than 1 day as it is anticipated that the study procedures can be completed within 2 to 4 hours. *De novo* subjects will have the MARVEL 2 software downloaded on the day of implant, prior to hospital discharge, and at approximately 1-month post-implant as described above. Between visits, the MARVEL 2 software will be removed from the subject's Micra. Therefore, the maximum study duration for *de novo* subjects is approximately 1-month.

9.3 Rationale

The MARVEL study demonstrated improved atrioventricular synchronous pacing in humans using the intracardiac accelerometer in a Micra device to mechanically detect atrial contractions. However, 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 setup the accelerometer detection algorithm. To accomplish this, Medtronic enhanced the MARVEL detection 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 rate. The performance of these algorithm enhancements and the overall AV synchrony achieved by the enhanced algorithm will be the focus of the MARVEL 2 study. The MARVEL 2 clinical study will be used as pivotal evidence to support market approval of the Micra AV device and its features for expanding the use of transcatheter pacing systems into patients with AV block and normal sinus node function.

The MARVEL 2 features in their current downloadable implementation combined with the study's Holter telemetry requirements consumes energy at an unacceptable rate for long-term testing. Therefore, only an acute study is feasible.

9.4 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):

- Subjects will undergo screening to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment.
- All centers will use the same version of the clinical investigation plan and standardized case report forms.
- All investigational center personnel, echocardiogram core lab personnel, and Medtronic personnel will be trained using standardized training materials.
- An independent echocardiogram core lab will be blinded to the study center, subject, and the MARVEL 2 algorithm programmed mode (adaptive or monitor) when making echocardiographic measurements.
- A maximum of 20 subjects may enroll at any single study center.
- A statistical analysis plan will be developed prior to analyzing data. The plan will further document all pre-specified analyses and analysis methods.
- MARVEL 2 centers that participated in the MARVEL study may enroll up to 3 subjects that participated in MARVEL and had normal sinus node function and persistent 3rd degree AV node block. To minimize potential selection bias, centers that enrolled 3 or fewer eligible subjects should approach all such subjects for participation in MARVEL 2. For centers that had more than 3 such subjects, Medtronic will provide the center with the order in which eligible subjects should be approached for participation in MARVEL 2. In these cases, the ordered list will be a random permutation of all eligible subjects *without* regard to the MARVEL study results. This selection mechanism will ensure that participation in MARVEL 2 is independent from the original MARVEL study outcomes for eligible MARVEL subjects that may enroll in MARVEL 2.

10 Product Description

10.1 General

The MARVEL 2 Research System was developed to characterize the performance of the MARVEL 2 algorithm, which provides AV synchronous pacing via the implanted Micra™ TPS. Micra devices will be temporarily downloaded with software to expand their functionality to include an AV synchronous pacing mode. This downloaded algorithm will enable accelerometer-based detection of atrial activity, thus providing AV synchronous pacing in the ventricle. The MARVEL 2 Research System consists of a user interface for the Medtronic Carelink Programmer, software to be downloaded into the Micra™ TPS, and a custom Holter monitor. The ER220 Holter monitor will be used to record surface ECG, EGM, accelerometer signals, and device and MARVEL 2 algorithm markers. The components of the system are detailed below in Table 1.

Table 1: MARVEL 2 Research System

Model Number	Component (Manufacturer)	Investigational or Commercially available
MC1VR01	Micra™ TPS Implantable Device (Medtronic)	Commercially available in applicable geographies*
SW022	Micra™ Application Software (Medtronic)	Commercially available in applicable geographies
MRVL2	MARVEL 2 software Rev. 1.0 (Medtronic)	Investigational
9986	2090 Programmer Baseline Operating System Software (Medtronic)	Commercially available in applicable geographies
2090	Medtronic Carelink Programmer (Medtronic)	Commercially available in applicable geographies
Model ER220 Extended Range Holter Monitor**	ERX10 Extended Range Tel-B Antenna cable (Medtronic)	Investigational
	DR220 Holter (NorthEast Monitoring, Inc.)	Commercially available in applicable geographies

*The Micra device will be considered investigational the moment the MARVEL feature (MARVEL 2 software) is downloaded and will no longer be investigational when the MARVEL software (MARVEL 2 software) is removed. Commercially available devices listed in the table above will be used inside the approved indications, except the Micra device.

**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.

10.1.1 Micra Implantable Device

The Micra™ TPS (MC1VR01) is a commercially available miniaturized, single chamber pacemaker that provides bipolar sensing and pacing in the right ventricle. The device has an activity sensor that detects the subject's body and heart movement. The Micra device will be considered investigational the moment the MARVEL 2 software is downloaded and will no longer be investigational when the MARVEL 2 software is removed.

10.1.2 Medtronic Carelink Programmer (2090), 2090 Programmer Desktop Software, and Micra Software (SW022)

The Medtronic Carelink Programmer (2090) and Micra Software (SW022) are used to communicate with the Micra device. The use of a programmer head is required for communication between the Micra device and the Medtronic Carelink Programmer. In all geographies, Medtronic Carelink Programmers will be used in the MARVEL 2 clinical study and are commercially available.

The Model 9986, 2090 Programmer Desktop is the operating system software that resides on the Medtronic Carelink Programmer. This commercially available software enhances the display of the accelerometer waveform on the Medtronic Carelink Programmer.

The MARVEL 2 Medtronic Carelink Programmer software application will be installed onto the Medtronic Carelink Programmer. To use the investigational MARVEL 2 software with a Medtronic Carelink Programmer, the software must first be installed on the Medtronic Carelink Programmer via a Medtronic USB drive. After the investigational MARVEL 2 software application is downloaded into the Medtronic Carelink Programmer, the Medtronic Carelink Programmer will be labeled per local requirements to indicate that it contains investigational software. The installation only needs to be done once per programmer.

When the MARVEL 2 study is complete, the software application will be uninstalled from the Medtronic Carelink Programmers on which it was installed by referring to the instructions in the MARVEL 2 User Manual.

10.1.3 MARVEL 2 Software

The investigational MARVEL 2 software, created by Medtronic, will be downloaded into the Micra device using the Medtronic Carelink Programmer. The MARVEL 2 software detects atrial contraction from the accelerometer signal to provide AV synchronous pacing and enables telemetry transmission of accelerometer data from the Micra device to the Holter monitor.

Prior to downloading the MARVEL 2 software into the subject's Micra device, an access code is required to be entered on the Medtronic Carelink Programmer. This access code is unique for each Micra device serial number and will be provided by the Medtronic Study Team. This provides a level of security to ensure that the MARVEL 2 software is only downloaded into Micra devices of study subjects. An example of this interface is shown in Figure 4.

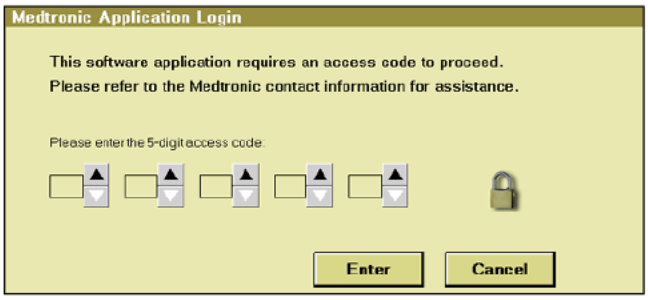


Figure 4: Medtronic Application Login

The MARVEL 2 software can be manually removed from the Micra device using the Medtronic Carelink Programmer. If the software is not manually removed, it automatically deactivates after 5 hours.

10.1.4 Extended Range Holter Monitor System

All subjects in this study will use a customized investigational Extended Range Holter Monitor System (ER220). This ER220 system uses a market-released Model DR220 Holter Monitor and an investigational accessory cable 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) (One 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 MARVEL 2 enrollment rates for participating sites, it is expected that approximately 2-5 sets per site need to be provided. The investigational site and sponsor will use Holter and software disposition logs to track these items.

10.2 Dosage Form and Route of Administration

This section is not applicable.

10.3 Manufacturer

Each of the MARVEL 2 Research System components is manufactured by Medtronic except for the commercial DR220 Holter Monitor manufactured by NorthEast Monitoring Inc.

10.4 Packaging

The investigational MARVEL 2 software application uses a USB drive for installation onto the Medtronic Carelink Programmer. The USB drive will be labeled to indicate that it contains investigational software.

When the investigational MARVEL 2 software is installed on the Medtronic Carelink Programmer, the Medtronic Carelink Programmer will be labeled to indicate that it contains investigational software. The investigational Holter will be labeled according to the local regulatory requirements.

10.5 Intended Population

The target population will consist of subjects with normal sinus node function and AV block, aged ≥18 years, and implanted with a Micra™ TPS.

10.6 Equipment

The maintenance and calibration of the Medtronic Carelink Programmer used for this study will be conducted using the standard Medtronic processes and is not part of this clinical study. Sites are responsible for maintaining and calibrating e.g. echo machine and programmer equipment used during this study in accordance with established site practice or local regulation. Records should be kept and able to be provided upon request by the Sponsor or regulatory agency.

10.7 Product Use

Principles of operation of the Investigational MARVEL 2 software and investigational ER220 Holter monitors will be provided in the MARVEL 2 User Manual and ER220 Instruction Sheet, respectively.

10.8 Product Training Requirements

Training on the MARVEL 2 Research System is required prior to the clinical site's first study procedure.

10.9 Product Receipt and Tracking

The date when the site downloads the MARVEL 2 software into the Medtronic Carelink Programmer via the USB drive, will be recorded and maintained during the clinical investigation. Each Medtronic Carelink Programmer downloaded with the MARVEL 2 software application will be traced with the Medtronic Carelink Programmer serial number.

The date when the site receives the Holter monitors will be maintained during the clinical investigation. Each received Holter monitor will be traced with the Holter serial number.

10.10 Product Storage

Storage area of ER220 Holter monitors and USB drive should be locked and secure with access limited only to approved study trained personnel.

The MARVEL 2 software application will be installed onto Medtronic Carelink Programmers. This application is considered investigational and should not be used outside this study. The use of the MARVEL 2 software application is limited to MARVEL 2 study subjects by requiring an access code to be entered before the MARVEL 2 software can be downloaded into Micra devices. This access code is unique for each Micra device serial number and will be provided by the Medtronic Study Team. This provides a level of security so that the MARVEL 2 software is only downloaded into study subjects.

The Medtronic Carelink Programmer installed with the MARVEL 2 software application can be used for commercial use and there are no special storage requirements.

10.11 Product Return

ER220 Holter monitors and USB drive will be shipped back to Medtronic Operational Support at 8200 Coral Sea St. NE, RM S1221, Mounds View, MN 55112|U.S.A. at the end of the clinical study.

The investigational MARVEL 2 software application will be uninstalled from the Medtronic Carelink Programmers on which it was installed by referring to instructions in the MARVEL 2 User Manual.

10.12 Product Accountability

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 least: date of receipt, installation of the investigational components, serial number of the investigational components, location of the investigational components, date and reason for return, and uninstallation of the investigational components and software.

11 Selection of Subjects

11.1 Study Population

The target population will consist of patients ≥18 years in age, with documented history of AV block, and implanted with a Micra with remaining device longevity of 6 years or more or expected to be implanted with a Micra.

11.2 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 occur. 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.

11.3 Inclusion Criteria

- Subject has been implanted with a Micra TPS (Model MC1VR01) with remaining device longevity of 6 years or more or is expected to be implanted with a Micra TPS.
- 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 function and persistent 3rd degree AV block and subjects with other forms of AV block.

11.4 Exclusion Criteria

- Subject is 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 is pregnant (if required by local law, women of child-bearing potential must undergo a pregnancy test within seven days prior to MARVEL 2 study procedures).

- Subject meets any exclusion criteria required by local law (age or other).

11.5 Enrollment Strategy

The intent is to ensure subjects enrolled early in the study contribute to the primary efficacy and secondary objective, specifically subjects with normal sinus node function and persistent 3rd degree AV node block. Once at least 35 of these subjects have been enrolled, other subjects with a history of AV block may be enrolled to demonstrate the safety and utility of the MARVEL 2 algorithm in patients with other forms of AV block. These include subjects who may have predominantly intact AV conduction or AV block with sinus node dysfunction and/or atrial arrhythmias. More than 35 subjects meeting the criteria for the primary efficacy objective may be enrolled. It is preferable to enroll subjects with *de novo* Micra implants early in the study since they will have a 1-month follow-up.

The enrollment strategy and current target patient population available for enrollment to address the primary efficacy and secondary study objectives will be communicated to the study centers.

12 Study Preparation

12.1 Investigator/Investigation site selection

An investigator and investigation site may be included in this study if the investigator and investigation site comply with the following requirements:

- Investigator and investigation site is qualified by training, education, and relevant experience appropriate to the use of the product under investigation and associated procedures
- Investigator and investigation site expects to have adequate time and resources to conduct the study throughout the duration of the study
- Investigator and investigation site has access to an adequate number of eligible subjects
- Investigator and investigation site will comply with applicable Ethics Board and regulatory requirements
- Investigator is not debarred, disqualified, or working under sanctions in applicable regions
- Investigation site has an echo machine available to conduct the echo recording per protocol procedures

12.2 Site activation

Ethics Board approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the clinical study at an investigation site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. In addition, the approval letter needs to be accompanied by an Ethics Board roster or letter of compliance, to allow verification that the investigator, other investigation site personnel, and/or Medtronic personnel are not members of the Ethics Board. If they are members of the Ethics

Board, written documentation is required stating that he/she did not participate in the approval process. Investigators must inform Medtronic of any change in status of Ethics Board approval once the investigation site has started enrollment. If any action is taken by an Ethics Board with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

Before performing study related activities, all requirements shall be fulfilled, including, but not limited to the following:

- Ethics Board approval (and voting list, as required by local law) of the current version of the Clinical Investigation Plan (CIP) and Informed Consent Form (ICF).
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Current Curriculum Vitae (CV) (signed and dated as required by local law) of investigators and key members (as required by local law) of the investigation site team on file with the sponsor
- Documentation of delegated tasks
- Documentation of MARVEL 2 study training including required training of CIP, Informed consent, data collection tools and regulations

Additional requirements imposed by the Ethics Board and regulatory authority shall be followed, as appropriate.

Medtronic may distribute a pre-populated study-specific Investigator Site File (ISF) and will provide site with documentation of study center/investigator readiness. Evidence of investigator and investigation site readiness must be received prior to subject enrollment and must be filed in the ISF.

13 Study Procedures

13.1 Schedule of Events

A subject may be at the investigational site specifically for the MARVEL 2 study or for other reasons independent from the MARVEL 2 study, such as routine clinical care. Study procedures for subjects with existing Micra devices will be conducted in a one day in-office visit. Study procedures for *de novo* subjects with a new Micra implant will be conducted over a 1-month period to collect the study procedures at up to 3 points in time. Data collection specific for the MARVEL 2 study are summarized in Table 2.

Table 2: Summary of Study Procedures

MARVEL 2 Study Data Collection	Micra In-clinic Subject		Micra De Novo Subject			
	Baseline	MARVEL 2 Procedure	Baseline	Implant	Pre-Hospital Discharge MARVEL 2 Procedure	1 month-MARVEL 2 Procedure
Inclusion/exclusion assessment	X		X			
Patient informed consent	X		X			
Demographics and pacing indication	X		X			
Medical history	X		X		X	X
Micra Implant				X		
Cardiovascular medications	X		X		X	X
Physical Examination	X		X		X	X
12 Lead ECG	X		X		X	X
X-Ray image(s) of Micra implant location	X[1]		X[1]			
Initial device interrogation Save to media		X		X	X	X
Download MARVEL 2 software		X		X	X	X
Holter monitoring (Auto Set-up phase) VDI data collection Selects best vector combination Selects sensing parameters		X		X	X	X
Holter monitoring (In-clinic Evaluation phase) Perform quiet resting period Perform posture testing and hall walks Accelerometer Characterization		X			X	X
Echocardiogram		X			X	X
Remove MARVEL 2 software		X		X	X	X
Final device interrogation Save to media		X		X	X	X
Study exit		X				X
Adverse Events	If Occur					
Study Deviations						
Device Deficiencies						
System Modification						

[1]If available. If not available, no additional x-ray images will be collected.

13.2 Role of the Sponsor Representatives

Sponsor representatives may provide support as required for the study under supervision of the Principal Investigator, including:

- Study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities.
- Technical support in installing or uninstalling the MARVEL 2 software into or from the Medtronic Carelink Programmer via the USB drive.
- Technical support in downloading or removing the MARVEL 2 software into or from the implanted Micra device, under the supervision of a study investigator
- Technical support in the setup and operation of the MARVEL 2 algorithm, under the supervision of a study investigator

Sponsor representatives may conduct monitoring and auditing activities for this study.

No data entry shall be performed by Medtronic personnel or their representatives at sites.

13.3 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 study visit to confirm the subject meets the inclusion/exclusion criteria.

13.4 Prior and Concomitant Medications

There are no restrictions regarding prior or concomitant medications. All cardiovascular medications prescribed to the subject at the time of the study visit are to be documented on the case report forms (e-CRFs).

13.5 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 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. 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.

13.6 Randomization and Treatment Assignment

The MARVEL 2 study is not a randomized study. However, to blind the echocardiography (echo) core laboratory to study site, study subject and pacing mode, the following randomization procedures will be incorporated in the MARVEL 2 study. Specifically, a random 5-digit number will be assigned to label the echo recording medium and link the echo core lab results to an individual study subject. Additionally, study sites will be randomized to perform the echo while the MARVEL 2 algorithm is programmed to Adaptive mode first followed by Monitor Mode second or while the MARVEL 2 algorithm is programmed to Monitor mode first followed by Adaptive mode. This strategy will blind the echo core lab personnel to study site, subject, and pacing mode.

Additionally, as described in section 9.1.2 a randomly permuted list of MARVEL study subject IDs who are eligible for reenrollment in MARVEL 2 will be used to select the order in which MARVEL subjects should be approached for reenrollment in MARVEL 2 in centers that have more than 3 eligible subjects.

13.7 Study Procedure Visit

13.7.1 Study Procedure Visit

A patient is considered a subject enrolled in the study upon completion of the informed consent process. The date the subject signed the Informed Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, as required by law, must be documented in the subject's medical records.

Baseline and medical history information can be a standalone visit or can be performed on the same day as the study procedures (preferred) to minimize multiple visits. A MARVEL 2 study worksheet will be used to provide step by step instruction of the study procedure visit and to capture real-time source data that will be maintained by the site and transferred to the study procedure e-CRF.

Study procedures for subjects with existing Micra devices will be conducted in a one day in-office visit. Study procedures for *de novo* subjects with a new Micra implant will be conducted over a 1-month period to collect study data at up to 3 points in time. Data collection specific for the MARVEL 2 Clinical study are summarized in Table 2. The order of study procedure steps are not prescribed and may be performed in an order different than listed.

13.7.2 Eligibility Assessment

Each subject will be assessed to confirm they meet all inclusion criteria and none of the exclusion criteria. Subjects that do not meet the inclusion/exclusion criteria following informed consent, should exit the study prior to MARVEL 2 software download.

13.7.3 Demographics and Pacing Indication

The subjects' demographics and pacing indication will be obtained and recorded.

13.7.4 Medical History

The subjects' medical history will be obtained and recorded. For *de novo* subject medical history, in addition to collection of medical history at baseline, will also be collected at the pre-hospital discharge and 1-month study visits.

13.7.5 Cardiovascular Medications

The cardiovascular medications prescribed to the subjects will be recorded. For *de novo* subjects the cardiovascular medications will be recorded at implant and at the pre-hospital discharge and 1-month study visits.

13.7.6 Physical Exam

A basic physical exam will be performed, including height and weight (if not in the subject's medical chart) and blood pressure. For *de novo* subjects a physical exam should be performed at implant and at the pre-hospital discharge and 1-month study visits.

13.7.7 12-Lead Electrocardiogram

A 12-lead electrocardiogram from the subject will be recorded. The recording of this electrocardiogram should be within seven days prior to the study procedure visit. For *de novo* study subjects, an electrocardiogram should be recorded prior to the implant procedure, at pre-hospital discharge, and 1-month study visits.

13.7.8 X-Ray (if available)

X-ray images documenting the implant location of the Micra will be collected, if available. If not available, no new x-ray image will be requested.

13.7.9 Initial Device Interrogation

An interrogation of the Micra device will be performed to verify device longevity is at least 6 years 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 CRF.

13.7.10 Download the MARVEL 2 Software

Details of the procedure for downloading the MARVEL 2 software into the Micra device are documented in the MARVEL 2 User Manual.

Upon downloading the MARVEL 2 software into the Micra device, the Micra device becomes investigational as described in Table 1: MARVEL 2 Research System.

As outlined in the MARVEL 2 User Manual, when the MARVEL 2 software is turned to adaptive mode, the algorithm will acquire the Micra accelerometer signal and begin tracking the A4 signal (the

accelerometer signal corresponding to atrial contraction). Ventricular pacing will then be initiated by the device if an intrinsic R wave is not observed between A4 detection and the programmable A4-VP interval.

13.7.11 Holter Monitor / ECG Setup

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

In addition to the ECG cable for the Holter monitor, an ECG cable 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.

13.7.12 Auto-Setup Phase / Parameter Settings Evaluation

During the auto-setup phase, the subject should remain in a consistent supine or sitting position. Prior to initiation of the auto-setup, the pacing mode will be programmed to VDI mode with a lower rate of 50 bpm. The auto-setup feature will be initiated from the Medtronic Carelink Programmer. After approximately 20 minutes, the auto-setup feature will complete, and programming recommendations will be displayed. Data collected during the auto setup phase will contribute to the VVI phase of the for the primary efficacy objective evaluation as the device will be programmed to a non-atrial tracking mode (i.e. VDI which is effectively VVI pacing).

Following the auto setup phase, proper operation of the auto-setup recommended settings will be verified first in VDI pacing mode (non atrial tracking mode) and then in VDD pacing mode (atrial tracking mode).

13.7.13 Evaluation Phase / Resting Period

Data collected during the resting period will contribute to the primary efficacy objective. The duration of the resting period will be approximately 20 minutes. During the resting period, the subject should remain in a consistent supine or sitting position. The pacing mode will be set to VDD (atrial tracking mode).

13.7.14 Evaluation Phase / Posture and Activity

During the posture and activity evaluation the subject will perform the following maneuvers. The times for each maneuver will be recorded on the MARVEL 2 procedure worksheet:

- Have the subject lie on their back for approximately 2 minutes
- Have the subject lie on their right side for approximately 2 minutes
- Have the subject lie on their left side for approximately 2 minutes
- Have the subject sit for approximately 2 minutes
- Have the subject stand for approximately 2 minutes
- Have the subject walk at a normal (comfortable) pace for approximately 2 minutes
- Have the subject walk at a vigorous pace for approximately 2 minutes with the goal of having the subject achieve a maximum heart rate of at least 100 bpm

Subjects will be allowed to have recovery time after the walking maneuvers as needed.

13.7.15 Echocardiogram

An echocardiogram (echo) will be performed both when the MARVEL 2 algorithm is programmed to Monitor and Adaptive modes.

The echocardiogram should be performed in accordance with the study required echo protocol. The echo views and measurements that will be collected include, but are not limited to, apical 4-chamber, left atrial volume, LVOT VTI, Mitral VTI, Mitral flow including E and A wave measurements. The original 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. Additionally, study sites will be randomized to perform the echo while the MARVEL 2 algorithm is programmed to Adaptive mode first followed by Monitor Mode second or while the MARVEL 2 algorithm is programmed to Monitor mode first followed by Adaptive mode. Note that this strategy will blind the echo core lab personnel to study site, subject, and pacing mode. The MARVEL 2 study worksheets will indicate the MARVEL 2 programmed mode sequence in which the echo images should be acquired.

[redacted]

13.7.17 Remove the MARVEL 2 Software and Holter

Details of the procedure for removing the MARVEL 2 software from the Micra device is documented in the MARVEL 2 User Manual.

The ER220 Holter will be removed from the subject. The data recorded on the SD card from the Holter monitor should be sent to Medtronic for evaluation.

The Micra device is to be programmed to its intended permanent settings for VVI(R) mode for the subject.

13.7.18 Final Device Interrogation

Before performing a final device interrogation and exiting the subject, the Micra device should be verified that it has been reprogrammed to its intended permanent settings. An interrogation of the Micra device should be saved on a USB drive or on a diskette. Device interrogation data (.pdd file) should be sent to Medtronic using a secure, electronic transfer utility. Missed device interrogations are considered a protocol deviation and must be documented in the protocol deviation CRF.

13.7.19 Implant Assessment (*de novo* subjects only)

De novo subjects will be enrolled prior to their Micra implant. The *de novo* subjects will be studied at three time points. The first study of a *de novo* subject will be immediately following the implant of the subject's Micra device. A Holter monitor will be placed on the subject (see Section 3.7.7) and the MARVEL 2 software will be downloaded into the subject's Micra (see Section 3.7.6). The auto-setup evaluation will then be performed (see Section 3.7.8). Following the auto-setup evaluation, the MARVEL 2 software will be removed from the subject's Micra and the Holter will be removed from the subject (see Section 3.7.12). Note, at this time point, the MARVEL 2 algorithm will not be programmed to adaptive mode (i.e. there will be no atrial tracking). This assessment would ideally be performed in the implant procedure room but could be performed in a recovery room.

If a *de novo* subject has an unsuccessful Micra implant attempt where an operating Micra device does not remain in the right ventricle following groin access site closure, the subject should be exited from the study following the resolution of any adverse events. Note that an unsuccessful implant is not an adverse event. However, all adverse events that occur during an unsuccessful implant procedure should be reported.

13.7.20 Post-Implant Assessment (*de novo* subjects only)

The second time the *de novo* subjects are studied is prior to discharge for their Micra implant. At this time point, all MARVEL 2 in-clinic study procedures will be performed (Sections 13.7.4 through 13.7.18). Note, that the MARVEL 2 software will be removed from the subject's Micra at the end of these study procedures.

13.7.21 One-Month Post-Implant Visit (*de novo* subjects only)

The final time the *de novo* subjects are studied is approximately one month following their Micra implant. At this time point, all in-clinic MARVEL 2 study procedures will be performed (Sections 13.7.4 through 13.7.18). Note, that the MARVEL 2 software will be removed from the subject's Micra at the end of these study procedures and the subject will be exited from the study. The visit window for the 1 month follow-up visit is shown in Table 3.

Table 3: 1 Month Visit Window

1 Month Follow-Up Visit			
Follow Up	**Window Start**	**Target**	**Window End**
1 month	**21 days**	**28 days**	**42 days**

Note: day of implant is considered day zero.

13.7.22 System Modification (*de novo* subjects only)

A system modification will be reported in the event the Micra device requires an invasive modification or programmed off after the initial successful implant (e.g., explant, replacement, repositioning, programmed off). Details of the system modification should be reported on the system modification e-CRF.

The subject should be exited if the original Micra device is no longer active following the system modification procedure.

13.8 Treatment Compliance

Subject compliance to the Holter monitoring and echo examinations will be monitored by the Medtronic study team with a periodical review of received data.

13.9 Assessment of Efficacy

The primary efficacy objective (see section 8.1.1.1) will be the primary means by which the efficacy of the MARVEL 2 features as implemented in the MARVEL 2 software are evaluated.

13.10 Assessment of Safety

Safety of the MARVEL 2 features will be evaluated as part of the primary safety objective (see section 8.1.1.2). Additionally, any adverse events or device deficiencies that occur while subjects are enrolled will be collected and summarized.

13.11 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.

Device interrogation data will be saved on supported media and will be delivered to Medtronic electronically via a secure web-based application.

Data saved on the Holter monitor SD card will be delivered to Medtronic either electronically via a secure web-based application, MSM, or via mail service.

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 or via mail. The Echo Core Lab will also enter data onto e-CRFs within a separate Oracle Clinical database.

13.12 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 10 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

13.13 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 the regulations set forth by their Ethics Board. It is recommended that that subjects be followed until all MARVEL 2 software or study procedure related adverse events are resolved or unresolved with no further actions planned.

Subjects that exit the study prior to completing the study procedures will not be replaced since a sample size of up to 100 enrolled subjects accounts for the possibility that not all subjects may contribute usable Holter data as the target sample size requires approximately 70 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 MARVEL 2 software download
- 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. unsuccessful software download or Holter telemetry)
- Investigator withdrew subject from the study for medical reasons (e.g. inability to complete posture and exercise test)
- Unsuccessful Micra implant attempt (*de novo* subjects only). An unsuccessful implant attempt is defined as an implant attempt where an operating Micra device does not remain in the right ventricle following groin access site closure. Note that the subject should be exited from the study following the resolution of any adverse events or the adverse event is not resolved, but no further action is planned.
- System modification where original Micra 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 subjects are withdrawn due to problems related to the MARVEL 2 software safety or performance, the subject shall be asked to be followed by the physician for collecting safety data outside the clinical study.

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.

13.13.1 Subject Exit

A study exit e-CRF is required for all subjects enrolled in the MARVEL 2 study. Subjects with existing Micra devices will be studied in a one day in-office visit and then exited from the study. *De Novo* subjects with a new Micra device will be studied over a 1-month period at 3 points in time, and then exited from the study. Study exit will occur following the final Micra device interrogation and final removal of the MARVEL 2 software.

Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system-, and/or procedure procedure-related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care.

14 Risks and Benefits

14.1 Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the development and clinical study of a product. The formal Hazard/Risk analysis of MARVEL 2 was done for MARVEL 2 study in accordance with ISO 14971:2012 (Medical Device Risk Management) and will be used to ensure that the level of risk is acceptable and reduced as low as possible prior to starting the MARVEL 2 study.

The MARVEL 2 study will use the commercially available Micra™ TPS and the ER220 Holter monitor for study collection activities. For the investigational components being used (refer to: System Component Information), their design capability is assessed as part of the Hazard Analysis. Assessment for negative system interactions, as well as verification and validation activities also form part of the Risk Management process followed for the study. The MARVEL 2 risks are analyzed, evaluated, and controls are put in place to address all identified risks. In addition, subjects will undergo an echocardiogram examination with the echo machine available on site at the hospital/clinic. The echo procedure poses negligible/no risk to the subjects. Lastly, during the study, risks will be continuously monitored, assessed and documented by the study investigators.

The risks are reduced as much as possible, with residual risk being documented within the Risk Management Report (DSN030148, Version 2.0 or currently approved version) and disclosed in the Patient Informed Consent forms provided to subjects. A summary of the risk analysis and risk assessment will also be listed in the MARVEL 2 Investigator's Brochure.

A list of potential risks, mitigations and risk controls associated with MARVEL 2 is summarized in Table 4. The comprehensive Hazard Analysis Log is documented in conjunction with the MARVEL 2 Risk

Management Report (DSN030148, Version 2.0 or currently approved version) at Medtronic and available upon request.

Any potential risks associated with this study are further minimized by selecting qualified investigators, training study personnel on the Clinical Investigational Plan and MARVEL 2 User Manual.

Table 4. Potential Risks and Minimizations

POTENTIAL RISK	POTENTIAL PATIENT HARM	MINIMIZATION
Security Vulnerability of Device Inappropriate access to MARVEL 2 research system	No risk if patient is enrolled in the study. Potential impact to therapeutic functionality or device longevity if patients are not enrolled in the study. May result in loss of usable data for the study.	Access code and precautions are in place for appropriate activation, including verifying the correct device models and version of Software, per MARVEL 2 system requirements.
Device Longevity Reduced The MARVEL 2 functionality and telemetry uplink mode will cause a current drain on the Micra device. Missed low battery exclusion criteria may result in premature end of service of Micra device	Reduced device longevity resulting in early replacement procedure could result in complications from replacement procedure.	The study personnel and a Medtronic representative will be trained on the investigational MARVEL 2 research system and study protocol. Subject inclusion criteria states remaining device longevity of 6 years or more is required, to minimize the longevity impact to the patient. Measures have been implemented to prevent longevity impacts greater than 4 months by limiting the duration of MARVEL 2 and uplink of sensor data using telemetry to a maximum of 15 hours. 15 hours is the maximum allowed time that the MARVEL 2 software will run for any individual patient based on the de novo patients' protocol, who have the MARVEL 2 software installed three times and each time it runs for the maximum duration of 5 hours.

POTENTIAL RISK	POTENTIAL PATIENT HARM	MINIMIZATION
		The MARVEL 2 feature set has an internal timer that automatically deactivates the software 5 hours after download and the mode will be set to VVI, lower rate no lower than 60 bpm until subject returns to clinic The MARVEL 2 software download into the Micra Device will be prevented if the device is at pre-RRT (Recommended Replacement Time)
Device corruption with download and removal of MARVEL 2 Pacing mode reverts to Power on Reset (POR) settings during the study	Increased risk of symptoms such as: Dizziness, palpitations, fatigue, and shortness of breath, decreased heart rate, until optimal programming occurs	In the unlikely event a POR were to occur during MARVEL 2 download/removal, the feature is designed to deactivate itself and the clinician would be notified on interrogation of the device using the 2090 programmer that a power-on-reset (POR) occurred. The device parameters will be restored to the Reset values as outlined in the Micra MC1VR01 Manual Document Number: M948893A001 REV. E
Inappropriate device programming: MARVEL 2 parameters	Increase risk of symptoms such as: Dizziness, palpitations, fatigue, and shortness of breath, decreased heart rate, until optimal programming occurs	The study personnel and a Medtronic representative will be trained in the proper way to program the investigational MARVEL 2 research system and study protocol. In addition, the MARVEL 2 User Manual will provide the proper instructions. MARVEL 2 algorithms are designed to assist in device setup and algorithms that automatically adjust MARVEL2 parameters are included to assist in response to physiologic changes.
Inappropriate Device Programming: Original settings not restored	Increase risk of symptoms such as: Dizziness, palpitations, fatigue, and shortness of breath, decreased heart rate, until optimal programming occurs	Risks normally associated with device follow-ups will be minimized by selecting investigators that have demonstrated previous experience with the programming, interrogation, and monitoring of these devices. The MARVEL 2 User Manual will provide the proper instructions related to device operation

POTENTIAL RISK	POTENTIAL PATIENT HARM	MINIMIZATION
		following MARVEL 2 software removal/expiration.
Inappropriate pacing: Atrial rate tracked to a higher pacing rate The procedure allows steps to temporary set pacing rate to approximately 80 bpm (above the subject's intrinsic rhythm) to collect vector data during parameter settings evaluation	Increased risk of symptoms such as: Dizziness, palpitations, heart racing, fatigue, decreased heart rate, shortness of breath, and difficulty sleeping	Subjects are under the supervision of an experienced Clinician during the protocol steps The A4 tracking window will typically limit tracking to around 100 bpm. A second, higher A3 threshold is utilized to track above that rate. By using the device's blanking periods, the maximum tracking rate may be programmed to lower than 150 bpm in patients who may be more susceptible to high rate pacing. The algorithm incorporates a tracking-check feature to confirm appropriate tracking above a programmable parameter (off, 90, 100(nominal), 110 bpm). If appropriate tracking is not confirmed, the atrial tracking rate will be limited to less than programmed rate.
Micra device features disabled / modified in MARVEL 2 operation may cause inappropriate pacing: Ventricular Capture Management, Manual Ventricular Capture Management, Rate Response, MRI mode, Sensing assurance. Device Oversensing or Undersensing Unintended Loss of Capture Loss of pacing	Increased risk of symptoms such as: Dizziness, palpitations, heart racing, fatigue, decreased heart rate, shortness of breath, and difficulty sleeping If a loss of pacing capture in pacemaker dependent subjects occur, this could cause syncope, decreased heart rate, fainting, asystole, and death	Device interrogation prior to software download will be performed. The subject will be monitored in clinic during the study. Activity Mode-Switch will monitor the rate response signal and if the tracking is significantly lower than the activity sensor rate, the device will change to VVIR mode. Clinician will be given the discretion to discontinue MARVEL 2 if subject becomes symptomatic In the case of emergency MRI, MARVEL 2 software can be removed
Skin reaction to adhesive when applying ER220 Holter	Increased risk of skin rash/irritation, or allergic reaction	Study sites will be trained by Medtronic on applying the ER220 Holter per instructions for use, and will be provided

POTENTIAL RISK	POTENTIAL PATIENT HARM	MINIMIZATION
per instructions for use, or when removing adhesive tape		standard electrode patches used within its labeling that have been provided by a Medtronic approved supplier for Holter monitor application
Patient exposure to physical injury due to MARVEL 2 Echocardiogram, posture, and Hall walk Test may worsen subject's health conditions.	Increased risk of symptoms such as: Physical injury, dizziness, palpitations, heart racing, fatigue, and shortness of breath	Subjects will not be enrolled in the MARVEL 2 if unwilling or not able to perform study requirement per the Inclusion/Exclusion criteria. Subject is allowed to have recovery time during the hall walk testing as needed. Activity Mode-Switch will monitor the rate response signal and if the tracking is significantly lower than the activity sensor rate, the device will change to VVIR mode.
Improper MARVEL 2 software download and manual removal: Download and manual removal of the MARVEL 2 software from the Micra device, if done improperly may impact implanted device functionality.	Increased risk of symptoms such as: Dizziness, palpitations, fatigue, decreased heart rate, and shortness of breath, until optimal programming occurs	Access codes, software version, and software limitation requirements (no other software present in the device RAM) are in place for MARVEL 2 download Programmer user is informed of presence of MARVEL 2 investigational software on the Micra device on user interface If the download of MARVEL 2 does not execute correctly, this will be detected by the Micra device and the software will not be activated The MARVEL 2 can be manually removed from the Micra device. The MARVEL 2 software has an internal timer that automatically deactivates the software 5 hours after the download occurs

Additional information can be found in the Foreseeable Adverse Event List (FAL) in APPENDIX C. The comprehensive Hazard Analysis Log is documented in conjunction with the MARVEL 2 Risk Management Report (DSN030148, Version 2.0 or currently approved version). There may be other discomforts and risks related to the MARVEL 2 software and this study that are not foreseen at this time. Interactions with concomitant medical treatment are not expected.

14.2 Potential Benefits

The MARVEL 2 Study offers no benefit to study subjects. The information from this study may benefit other subjects who require AV synchronous pacing in the future.

Additionally, information collected from this study may assist in the design of new products or therapies and/or instructions for use.

14.3 Risk-Benefit Rationale

The data collection and procedural steps for MARVEL 2 are assessed to be complete and sound in investigating improvements to synchronous pacing using the sensors in the Micra pacemaker, with all risks identified having been reduced to as low as possible for subjects' and investigators' safety.

15 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.

15.1 Adverse Event and Device Deficiency Assessment

15.1.1 Adverse Events

All Adverse Events (AEs) regardless of their severity or relationship to the Micra implant procedure, MARVEL 2 features, or study procedures will be collected throughout a subject's participation, starting from the time the informed consent form is signed. Reporting of these events to Medtronic will occur on an AE Form, including event description, date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the 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. In addition, AEs impacting users or other persons, Non-subject Adverse Events, (reportable per ISO 14155) will be collected.

15.1.2 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.

15.1.3 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.

15.2 Definitions/Classifications

For the purposes of the clinical report, Medtronic will classify each adverse event according 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 5: 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	
Procedure Related	An adverse event related to the Micra implantation or modification, or to the MARVEL 2 study procedures. Micra Procedure related: an adverse event that occurs that is directly related to the implantation or modification of the Micra system Marvel 2 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 Device Related: An adverse event that results from the presence or performance (intended or otherwise) of the device. Marvel 2 Software Related: An adverse event that results from the presence or performance (intended or otherwise) of the Marvel 2 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 were 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)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. c) led to fetal distress, fetal death or a congenital abnormality or birth defect

	NOTE 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)
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011, 3.42)
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 Non-invasive (FDA, CFR 21; 812.3 (k)): when applied to a diagnostic device or procedure, means one that does not by design or intention: Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os 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

15.3 Reporting of Adverse Events

15.3.1 Adverse Events and Device Deficiency Classification

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 AEs 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 7 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 C: FORESEEABLE ADVERSE EVENT LIST contains the Foreseeable Adverse Event List (FAL), which is a list of adverse events related to the system that have been observed in previous studies and may be experienced by subjects. This list may help to assess if an AE is unanticipated in nature.

For emergency contact regarding a UADE, 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 6.

Table 6: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Micra Device, Micra Software, Marvel 2 Software, Programmer, Holter, Marvel 2 study procedures, Micra procedure
	Sponsor	Micra Device, Micra Software, Marvel 2 Software, Programmer, Holter, Marvel 2 study procedures, Micra procedure
Seriousness	Investigator	SAE
	Sponsor	SAE, UADE/USADE, Complication/Observation, 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

15.3.2 Adverse Events and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and device deficiencies 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 compliant via the regulator channels for market-released products.

Table 7: Reporting Requirements

Serious Adverse Events (SAEs) including Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	**Europe**: Immediately after the Investigator first learns of the event or of new information in relation with an already reported event. *(ISO 14155 and local law)* **All geographies:** Report to the sponsor, without unjustified delay, all serious adverse events. (ISO 14155:2011)
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.

Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Unanticipated Adverse Device Effects (UADEs), Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator submit to:	
Medtronic	**US:** Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1)) **Europe:** Immediately after the investigator learns of the event or of new information in relation to an already reported event. *(ISO 14155 and local law)* **All other geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement
Ethics Committee	**US:** Submit as soon as possible, but no later than within 10 working days after the Investigator first learns of the event. (21 CFR 812.150(a)(1)) **All geographies:** Submit to Ethics Board per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**US:** Notification as soon as possible to FDA, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1)) **All geographies:** Submit to regulatory authorities per local reporting requirement.
Ethics Committee	**All geographies:** Notification as soon as possible and not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))
Investigators	**All geographies:** Notification as soon as possible and not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))

Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	**Europe:** Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency. *(ISO 14155 and local law)* **All other geographies:** Submit or report as required per local reporting requirements.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
All other reportable Adverse Events and Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.

15.4 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, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic 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 state/local law. When the death occurs at a remote site, it is the investigation 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 state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

16 Data Review Committees

16.1 Clinical Event Committee (CEC)

A Clinical Event Committee (CEC) is not needed for this study. The decision was made based on the following criteria:

- Limited study participant duration (maximum of approximately 8.5 hours of exposure to the MARVEL 2 software)
- Limited safety risk to study participants
- Very few adverse events expected to be collected
- Primary study endpoints are based on objective, quantifiable, and easily measured criteria collected on Holter

16.2 Data Monitoring Committee (DMC)

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

- Study duration of approximately 6 months makes a DMC impractical
- Limited study participant duration (maximum of approximately 8.5 hours of exposure to the MARVEL 2 software).
- Limited safety risk to study participants

16.3 CRO/Core Labs

This information in Table 8 may be subject to change during the clinical study. Periodic updates to study contact information will be sent to sites as needed.

Table 8: CRO and Core Laboratory Information

Contact Information	Role
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 United States [redacted]	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 of study echocardiograms

17 Statistical Design and Methods

17.1 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.

17.1.1 Description of Baseline Variables

Standard baseline and relevant medical history will be collected on the e-CRFs for all enrolled subjects. Baseline variables to be summarized, for both all enrolled subjects and for subjects with usable Holter data, include, but are not limited to: Age, sex, race, time since Micra implant, physical exam findings, pacing indication, arrhythmia history, medical and surgical history, and cardiovascular medications.

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

17.2 Type I Error Control

Formal analysis of the study's primary, secondary, and ancillary objectives will occur once all enrolled subjects have had the opportunity to complete the study visit, all Holter files have been processed, and the study databases have been locked.

For the study to be considered a success, the null hypothesis for both the primary efficacy and safety objectives must be rejected. Additionally, to make a statistically valid claim of significance for the secondary objective, the null hypotheses for both primary objectives must be rejected and the null hypothesis for the secondary objective must be rejected. This testing strategy guarantees a study wide type I error rate of 0.05.

17.3 Usable Holter Datasets

A Holter dataset (i.e. device data telemetered to the Holter flash memory and surface ECG recordings) will be considered usable if there is readable telemetry signal as determined by Medtronic personnel experienced in the review of Holter recordings. Additionally, to be included in the analysis of the primary efficacy objective (and other ancillary objectives requiring Holter data), visible P-waves must be present on the surface ECG recordings.

17.4 Classification of Predominant Heart Rhythm During Holter Monitoring

Holter data from the approximately 20-minute auto-setup phase 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 AV block or intact AV conduction. The sinus node function will be categorized as normal sinus, sinus node dysfunction (sinus bradycardia, sinus tachycardia, other) or atrial arrhythmia. Note that subjects with a predominant rhythm of persistent 3rd degree AV block with normal sinus function will be included in the analysis of the primary efficacy objective.

17.5 Primary Efficacy Objective

Demonstrate the superiority of the MARVEL 2 features to provide atrioventricular synchronous pacing relative to Micra VVI pacing in subjects with normal sinus node function and persistent 3rd degree AV block.

17.5.1 Hypothesis

H_o: $\pi_{AV} = \pi_{VVI}$, vs

H_a: $\pi_{AV} \neq \pi_{VVI}$

where π_{AV} is the proportion of subjects meeting the primary efficacy endpoint during MARVEL 2 adaptive mode (VDD) pacing and π_{VVI} is the proportion of subjects meeting the primary efficacy endpoint in VVI mode.

17.5.2 Performance Requirement

The percentage of subjects meeting the primary endpoint in the MARVEL 2 adaptive pacing mode is significantly greater (at the 0.05 level) than the percentage of subjects meeting the endpoint in VVI pacing mode.

Meeting the performance requirement for the primary efficacy objective will demonstrate that the MARVEL 2 features provide high rates of atrioventricular synchronous pacing and greatly exceed rates observed with VVI pacing in the patient population expected to benefit the most from atrioventricular synchronous pacing.

17.5.3 Sample Size

A sample size of at least 35 subjects with normal sinus node function and persistent 3rd degree AV block and a sufficient number of evaluable cardiac cycles during the vector setup and 20-minute resting period will provide greater than 90% power to reject the null hypothesis based on the following assumptions:

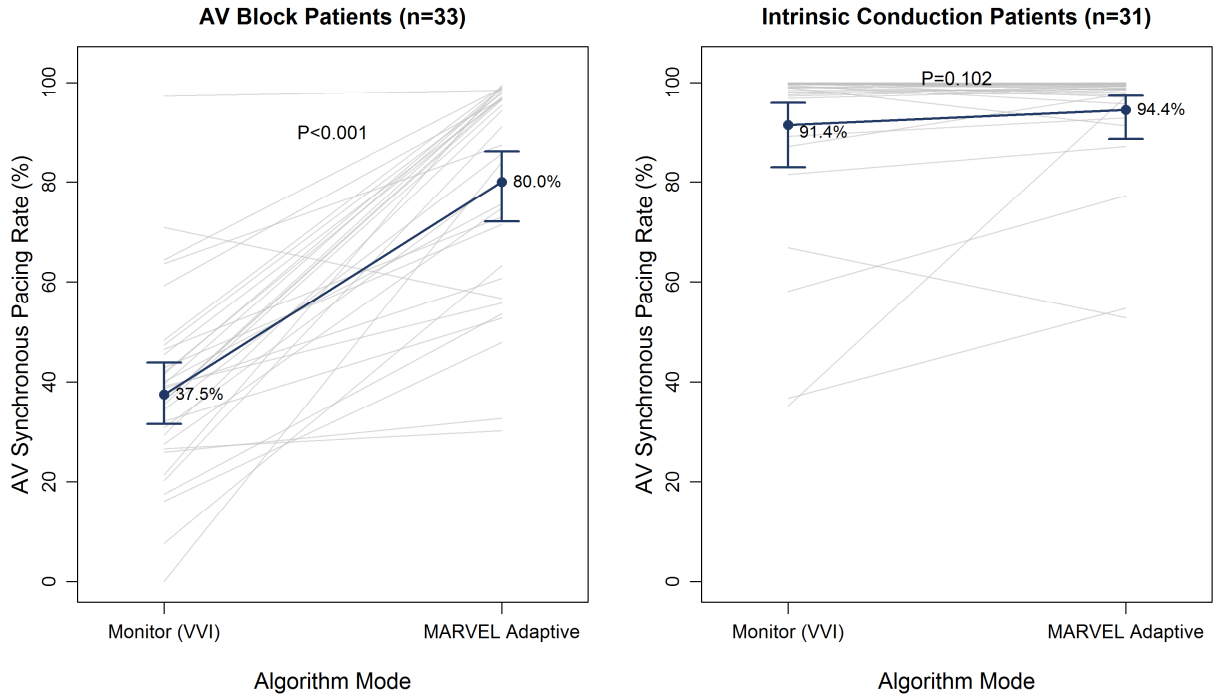
1. Two-sided type I error rate = 0.05
2. Single analysis after all enrolled subjects have had an opportunity to complete the MARVEL 2 study procedures and have had their Holter data evaluated
3. Each subject will have at least 500 evaluable beats* during the auto-setup phase (VVI pacing) period and during VDD pacing during the 20-minute resting period
4. The proportion of subjects meeting the primary efficacy endpoint in one pacing mode, but not the other (i.e. proportion of discordant pairs) will exceed 50%
5. At least 90% of discordant subjects will favor the MARVEL 2 features

   **Note: An evaluable beat is defined as an observable P-wave on the Holter ECG followed by at least 300 ms of drop-out free Holter telemetry data or a Micra ventricular event marker.*

Justification of Sample Size Assumptions

Figure 5 displays the AV synchronous pacing percentage observed in the MARVEL study by predominant rhythm. The average AV synchronous pacing percentage among the 33 subjects with a predominant rhythm of high-grade AV block was 80.0% during MARVEL adaptive mode (VDD pacing) compared to 37.5% during VVI pacing (P<0.001). Among the 33 subjects with a predominant rhythm of high-grade AV block, 72.7% of subjects (24 of 33) had an AV synchronous pacing rate exceeding 70% while in MARVEL adaptive mode compared to 6.1% (2 of 33) during MARVEL monitor mode (VVI pacing).

Figure 5: AV Synchronous Pacing Percentage Observed in the MARVEL Study by Predominant Rhythm



17.5.4 Analysis Methods

Following download of the investigational MARVEL 2 software, a Holter monitor will be placed on the subjects. The Holter monitor will record surface ECG, EGM, accelerometer signals, and device and MARVEL 2 algorithm markers. Specifically, the Holter will record whether the MARVEL 2 features senses an atrial contraction (A4 signal representing active ventricular filling detected on the accelerometer waveform), delivers a pacing spike, or inhibits a pacing spike based on a sensed intrinsic R-wave.

For each subject, the VVI pacing control period will occur shortly following investigational software download during the approximately 20-minute algorithm auto-setup phase where the MARVEL 2 programmable parameters are setup to enable optimal tracking of the A4 signal. The auto-setup phase will occur while the MARVEL 2 features are in monitor mode (i.e. VDI pacing, which is effectively VVI pacing). For purposes of evaluating the primary efficacy objective, the 20-minute resting period while the MARVEL 2 features are programmed to adaptive mode and providing VDD pacing will serve as each subject's treatment period.

Note that a randomized crossover design will *not* be used to compare AV synchronous pacing percentage between the MARVEL 2 pacing mode and VVI pacing for the following reasons: 1) knowledge of pacing mode is unlikely to influence AV synchronous pacing rate as such knowledge is unlikely to influence right atrial contractility, 2) the auto-setup phase will provide an opportunity to assess the AV synchronous pacing percentage during VVI pacing, 3) carryover effects are not possible since as soon as the MARVEL 2 features are programmed to adaptive mode atrial tracking will commence, and [redacted]

[redacted]

Similar to the original MARVEL study, 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 and MARVEL 2 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 MARVEL 2 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. If at least 70% of beats are considered synchronous during the VVI or MARVEL 2 adaptive pacing mode during resting, then the subject will be considered to have met the primary efficacy endpoint during the VVI or MARVEL 2 adaptive pacing mode during rest respectively. McNemar's test for paired proportions will be used to test the primary efficacy objective hypothesis.

The following pre-specified subgroups will be evaluated: sex, geography (US versus outside of US), and participation in the MARVEL study (yes versus no). A repeated measures logistic regression model utilizing generalized estimating equations will be used to evaluate the homogeneity of the MARVEL 2 adaptive pacing mode effect on the primary efficacy endpoint by subgroup. For this model, the response will be the primary endpoint status (1=met primary endpoint, 0=did not meet) and the independent variables will be the pacing mode (VVI pacing or MARVEL 2 adaptive mode), subgroup status, and a subgroup status by pacing mode interaction.

Additionally, the proportion of subjects meeting the primary efficacy endpoint will be summarized and compared between VVI pacing and MARVEL 2 adaptive pacing using the methods described above in the following subsets of subjects with normal sinus node function and persistent 3rd degree AV block:

1. Those subjects exhibiting low PVC burden
2. Those subjects exhibiting low PVC burden with a mitral valve doppler echo E/A ratio of 1.5 or less

17.5.5 Determination of Subjects and Data for Analysis

All subjects with normal sinus node function and persistent 3rd degree AV block during Holter monitoring with at least 500 evaluable beats during VVI pacing and at least 500 evaluable beats during MARVEL 2 adaptive pacing in which the device is providing VDD pacing[1] will be included in the primary analysis for this objective. For *de novo* subjects, only data collected during the 20-minute resting period at pre-hospital discharge will contribute to the analysis of the primary objective. (Note that ancillary objective number five will compare the atrioventricular synchronous pacing rates observed at pre-hospital discharge and at 1-month post-implant.) However, if a *de novo* subject does not have usable Holter data at pre-hospital discharge, their Holter data approximately 1-month post-implant will be used in the analysis, if available.

[1] Cardiac cycles during MARVEL 2 adaptive mode pacing that occur during an AV conduction test will not be considered evaluable as the pacing mode is set temporarily to VVI40 while the device checks for intrinsic AV conduction.

Loss of communication between the Holter and the implanted Micra device, called telemetry dropout, can lead to loss of the marker indicating a ventricular event was sensed or a ventricular pace was delivered. Therefore, beats with no ventricular sense or pace markers and indication of telemetry dropout in the first 300 ms after a P-wave will be discarded (i.e. they are not evaluable beats).

17.5.6 Missing Data and Sensitivity Analyses

Missing Data

Given the relatively short duration of the study, missing data is not expected to be a serious issue. Since telemetry dropout may influence the number of evaluable beats for a subject during both VVI pacing and MARVEL 2 adaptive pacing, the total number of heart beats and total number of evaluable beats will be summarized.

If any subjects with normal sinus node function and persistent 3rd degree AV block do not have usable Holter data during the study, the reason the Holter data was not usable will be discussed. Additionally, to address concerns with missing data that may arise, sensitivity analyses will be performed to assess the robustness of the observed statistical inference with respect to the missing data.

The first sensitivity analysis will be to include all subjects with normal sinus node function and persistent 3rd degree AV block that had some usable Holter data during both 20-minute resting period (MARVEL 2 adaptive pacing) and VVI pacing control period (i.e. auto-setup phase) regardless of the number of evaluable beats in each phase.

The second sensitivity analysis will include all subjects who had the MARVEL 2 software downloaded and had a Holter monitor placed on them that were classified as having a predominant rhythm of persistent 3rd degree AV block with normal sinus function or who did not have their rhythm classified. This sensitivity analysis will incorporate a tipping point methodology. Specifically, all subjects with missing data will be included as meeting the primary efficacy endpoint during MARVEL 2 adaptive pacing and not meeting it during VVI pacing (i.e. discordant in favor of MARVEL 2 adaptive pacing) and then iteratively changed to not meeting the endpoint during MARVEL 2 adaptive pacing and meeting it during VVI pacing (i.e. discordant in favor of VVI pacing pacing). The tipping point will be defined as the number of subjects of the total with missing data that would have to shift from being discordant in favor of MARVEL 2 pacing to discordant in favor of VVI pacing to change the statistical inference. Stochastic methods may be used to aid in interpreting the likelihood of meeting or exceeding the tipping point.

Other Sensitivity Analyses

Since *de novo* subjects may have more than one visit in which both the AV synchronous pacing percentage is evaluated in both VVI and MARVEL 2 adaptive mode, the primary efficacy endpoint will also be compared utilizing usable Holter data from all study visits for subjects with normal sinus node function and persistent 3rd degree AV block. Specifically, a logistic regression model utilizing GEE to account for correlation in outcomes within subject will be used to estimate the effect of MARVEL 2 adaptive pacing on the primary efficacy endpoint. Specifically, the response for this model will be the primary efficacy endpoint status (1=met primary efficacy endpoint, 0=did not meet primary efficacy endpoint) and the independent variable will be pacing mode (VVI or MARVEL 2 adaptive mode). An exchangeable working correlation matrix will be employed with subjects considered repeated across study visit.

[redacted]

17.6 Primary Safety Objective

Demonstrate that the MARVEL 2 features provide pacing as intended.

17.6.1 Hypothesis

H_o: $\pi_{AV} \leq 87\%$, vs

H_a: $\pi_{AV} > 87\%$

where π_{AV} is the percentage of subjects meeting the primary safety endpoint during the MARVEL 2 pacing mode.

17.6.2 Performance Requirement

The percentage of subjects meeting the primary safety endpoint is significantly greater than 87% (i.e. the lower two-sided 95% confidence interval for the estimate exceeds 87%). For example, in a sample size of 70 subjects with usable Holter datasets, this objective would be met if at least 67 of the 70 subjects (96%) meet the primary safety endpoint. Further, with a sample size of 70 subjects with usable Holter datasets the lower two-sided 95% confidence interval will be 94.9% if all 70 subjects meet the primary safety objective.

17.6.3 Sample Size

A sample size of 70 subjects with usable Holter telemetry data during the MARVEL 2 study procedures provides at least 90% power to test the primary safety hypothesis given the following assumptions:

1. One-sided type I error rate = 0.025
2. Single test of a proportion after all enrolled subjects have had an opportunity to complete the MARVEL 2 study procedures and have had their Holter data evaluated.

3. The proportion of subjects meeting the primary endpoint in the MARVEL 2 pacing mode will exceed 98%.

Justification of Sample Size Assumptions

It is expected that all (100%) subjects will meet the primary safety endpoint. Specifically, in the MARVEL study, no pauses exceeding two cardiac cycles (as defined by the lower pacing rate interval) and no oversensing induced tachycardia exceeding three minutes were observed.

17.6.4 Analysis Methods

A Holter monitor will be placed on all study subjects during the MARVEL 2 study procedures. The Holter continuously records ECG and data telemetered from the implanted Micra device. The telemetered data includes ventricular electrograms reflecting ventricular activation and marker channel. The marker channel includes the ventricular sensed and paced event markers as well as markers unique to the MARVEL 2 features including whether the MARVEL 2 features sense an atrial beat (A4 signal). In addition, the Holter records supplemental marker data including V-V interval, pacing rate, pacing mode, pacing amplitude, pacing pulse width, R-wave amplitude, and sensor counts.

Each Holter dataset will be reviewed by Medtronic personnel experienced in the review of Holter recordings to determine the recording time, quality of the recording, and confirm correct MARVEL 2 feature operation. Holter datasets will be further analyzed manually and using programmed scripts to extract information related to:

- Ventricular sensing (including V-V interval)
- A4 detection

All available Holter recordings (including multiple recordings for subjects evaluated at multiple visits following initial Micra implant) will be used to determine if a subject meets the primary safety endpoint. First, the ventricular markers from the Micra device will be searched for long intervals. For each of these identified long intervals, the surface ECG signal will be manually reviewed to determine if they are true pauses or due to telemetry dropout. For any true pauses, the surface ECG signal, accelerometer signal, and device markers will be examined to determine if the pause was related to the MARVEL 2 algorithm or for another reason (e.g. T-wave oversensing). To identify any potential oversensing induced tachycardia the ventricular markers from the Micra will be searched for indication of a heart rate above 100 BPM exceeding 3 minutes. If high heart rates exceeding this criterion are identified, the surface ECG, the accelerometer signal, and MARVEL 2 markers will be examined to determine if the high heart rates were due to MARVEL 2 algorithm oversensing. Subjects free from pauses and oversensing induced tachycardia exceeding 3 minutes related to the MARVEL 2 algorithm will be considered to have met the primary safety endpoint.

An exact binomial test will be used to test the primary safety hypothesis. Specifically, the numerator will be the number of subjects meeting the primary safety endpoint. The denominator will be the number of subjects with Holter recordings with usable telemetry while the MARVEL 2 algorithm is programmed to adaptive mode (i.e. atrial tracking mode).

The following pre-specified subgroups will be evaluated if there are two or more subjects who do not meet the primary safety objective: sex, geography (US versus outside of US), and predominant heart

rhythm during Holter recording (normal sinus node function and persistent 3rd degree AV block, intact AV conduction, or other predominant rhythm). Fisher's exact test will be used to identify differences between subgroups.

17.6.5 Determination of Subjects and Data for Analysis

All subjects with Holter recordings with usable telemetry during MARVEL 2 adaptive mode will be included in the analysis.

17.6.6 Missing Data and Sensitivity Analyses

The primary source of missing data for this objective is anticipated to be Holter usability status and telemetry dropout during MARVEL adaptive mode pacing. Note that both sources of missing data can plausibly be assumed independent of primary safety endpoint status as Holter usability status is primarily related to electrode contact. However, to quantify the amount of missing data, the number of unusable Holter files and the proportion of beats during MARVEL 2 adaptive pacing with telemetry dropout will be computed.

If the level of missing data is an issue, tipping point methodology will be employed to evaluate the sensitivity of the statistical inference to the missing data. Additionally, stochastic methods may be employed to aid in interpreting the likelihood the tipping point would be met or exceeded.

17.7 Secondary Objective

Demonstrate an increase in stroke volume, as measured by left ventricular outflow tract velocity time integral, with the MARVEL 2 software relative to VVI pacing in subjects with normal sinus node function and persistent 3rd degree AV block.

17.7.1 Hypothesis

H_o: $\mu_{AV} = \mu_{VVI}$, vs

H_a: $\mu_{AV} \neq \mu_{VVI}$

where μ_{AV} population mean LVOT VTI in the MARVEL 2 pacing mode and μ_{VVI} is the population mean LVOT VTI in VVI mode.

17.7.2 Performance Requirement

The sample mean LVOT VTI during MARVEL 2 adaptive pacing (VDD pacing)is significantly different and greater at the 0.05 level than the sample mean LVOT VTI during VVI pacing.

Meeting the performance requirement for the secondary objective will demonstrate that the MARVEL 2 features can increase cardiac stroke volume compared to VVI pacing in the population with normal sinus node function and persistent 3rd degree AV block.

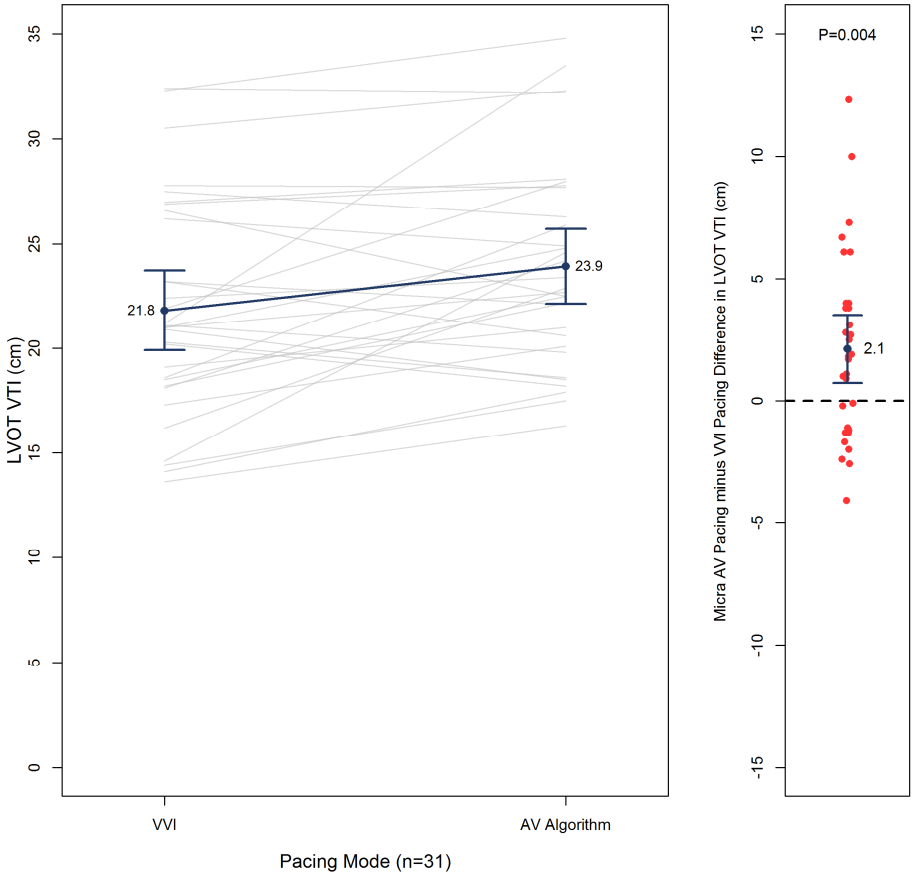
17.7.3 Power Calculation

Background

The MARVEL study demonstrated a mean increase in LVOT VTI of 2.1 (cm) [95% CI: 0.7 – 3.5 cm] with associated standard deviation of 3.8 cm in MARVEL 2 adaptive pacing relative to VVI pacing in 31 subjects with high-grade AV block and with paired echocardiogram data. Specifically, as displayed in Figure 6, mean LVOT VTI increased from an average of 21.8 cm to 23.9 cm. The left panel of Figure 6 displays the LVOT VTI values for individual subjects (gray lines) and on average (dark blue lines) for the 31 subjects with high-grade AV block subjects in MARVEL with paired echo assessments in both pacing modes. The right-hand plot in Figure 6 displays the absolute change in LVOT VTI for MARVEL 2 adaptive pacing relative to the VVI pacing mode for individual subjects (red circles) and on average (blue circle). The right-hand plot also indicates that the lower 95% confidence interval for the mean change in LVOT VTI exceeded zero.

The increase of 2.1 cm in LVOT VTI observed in the MARVEL study with MARVEL adaptive mode relative to VVI pacing is consistent with historical studies during the 1980s evaluating cardiac output between DDD and VVI pacing modes. See for example, Labovitz, et al[9], who observed a mean increase in LVOT VTI of approximately 2 cm with DDD pacing relative to VVI pacing in 26 patients with paired echocardiogram data in both DDD and VVI pacing modes.

Figure 6: LVOT VTI (cm) During VVI Mode and MARVEL Adaptive Mode (MARVEL Study)



Note: Error bars represent 95% confidence intervals for mean LVOT VTI by pacing mode (right panel) or in mean paired LVOT VTI value differences during MARVEL adaptive pacing relative to VVI pacing.

Power Calculation

As the sample size for the primary efficacy objective determines the number of subjects with normal sinus node function and persistent 3rd degree AV block with usable Holter data that are required for the study (at least 35 subjects), the power to reject the null hypothesis for the secondary objective was determined for a number of sample sizes as the protocol does not preclude study investigators from enrolling a higher number of subjects with normal sinus node function and persistent 3rd degree AV block nor account for the potential of missing echocardiogram data due to reasons such as improper

echocardiogram image acquisition, equipment malfunction, or subject refusal. The following assumptions were made for all power calculations:

1. Two-sided type I error rate = 0.05
2. Single analysis after all enrolled subjects have had an opportunity to complete the MARVEL 2 study procedures and have had their Holter data evaluated
3. Each subject will have paired echocardiogram available for analysis in both the MARVEL 2 adaptive mode and in VVI mode.
4. The paired difference in LVOT VTI is normally distributed with a mean of 2.1 cm and a standard deviation of 3.8 cm in the population of potential patients with normal sinus node function and persistent 3rd degree AV block.
5. A paired t-test will be the primary test statistic.

Table 9 displays the study power for both the paired t-test and for the Wilcoxon Signed-Rank test when there are 30, 35, and 40 subjects with normal sinus node function and persistent 3rd degree AV block observed during Holter monitoring. Although the pre-specified analytical method to evaluate the null hypothesis will be the paired t-test, the Wilcoxon Signed-Rank test may be used as a sensitivity analysis if there is strong evidence the difference in LVOT VTI is not normally distributed.

Table 9: Power to Reject the Null Hypothesis for the Secondary Objective

Sample Size[1]	Statistical Method[2]	Power (%)
30	Paired t-test	83.3
	Wilcoxon Signed-Rank	80.5
35	Paired t-test	88.8
	Wilcoxon Signed-Rank	86.8
40	Paired t-test	92.6
	Wilcoxon Signed-Rank	91.3

[1]Number of subjects with paired LVOT VTI data available for analysis.
[2]Power for Wilcoxon Singed-Rank test based on the population LVOT VTI having an underlying normal distribution.

17.7.4 Analysis Methods

Echocardiograms will be collected for each subject during MARVEL 2 adaptive pacing and during VVI pacing. 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 medium. Specifically, a random 5-digit number ("echo id") will be assigned to label the echo recording medium and link the echo core lab results to an individual study subject. Additionally, study sites will be randomized to perform the echo while the MARVEL 2 algorithm is programmed to Adaptive mode first followed by Monitor Mode second

or while the MARVEL 2 algorithm is programmed to Monitor mode first followed by Adaptive mode. 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, a paired t-test will be used to test the null hypothesis.

The following pre-specified subgroups will be evaluated using an analysis of variance (ANOVA) model: sex, geography (US versus outside of US), and participation in the original MARVEL study (yes versus no). For each ANOVA model the response will be the change in LVOT VTI between MARVEL 2 adaptive pacing and VVI pacing. The independent variable will be an identifier for subgroup.

If graphical assessments (e.g. Q-Q plots) of the distribution of change in LVOT VTI strongly suggest a deviation from normality, the Wilcoxon Signed-Rank test may be used as a sensitivity analysis.

17.7.5 Determination of Subjects and Data for Analysis

All subjects with normal sinus node function and persistent 3rd degree AV block during Holter monitoring and with paired LVOT VTI measurements during MARVEL 2 adaptive pacing and VVI pacing will be included in the analysis. Note that so long as a subject's predominant rhythm can be determined from the Holter recording, the subject may be included in this analysis as determination of predominant rhythm does not require device marker channel.

For *de novo* subjects, only echocardiogram data collected at pre-hospital discharge will contribute to the analysis of the secondary objective. However, if a *de novo* subject is missing paired echocardiogram on the day following their Micra procedure but have paired LVOT VTI data from their 1-month visit, the 1-month data will be used in the analysis if available.

17.7.6 Missing Data and Sensitivity Analyses

Missing Data

Given the relatively short duration of the study, 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.

If the level of missing data is an issue, tipping point methodology will be employed to evaluate the sensitivity of the statistical inference to the missing data. Additionally, stochastic methods may be employed to aid in interpreting the likelihood the tipping point would be met or exceeded.

Additional Sensitivity Analysis

Since *de novo* subjects may have more than one visit in which echocardiograms are obtained, the secondary objective will also be evaluated utilizing all available echocardiogram data. Specifically, a mixed effects linear regression model will be used account for correlation in outcomes within subject to determine the effect of MARVEL 2 pacing on change in LVOT VTI. For this model, change in LVOT VTI will be the response and the model will incorporate an intercept and a random effect for subject. The fixed effects for the intercept term will be used to quantify the effect of MARVEL 2 adaptive pacing on LVOT VTI.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

18 Ethics

18.1 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 are implemented in this study by means of the informed consent process, Ethics Board approval, study training, clinical trial registration, and risk benefit assessment.

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.

The MARVEL 2 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 before initiating a study, continuing review of an ongoing study by an Ethics Board and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The MARVEL 2 study is designed to reflect the GCP principles outlined in ISO 14155:2011 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2011, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. Adverse Event and Device Deficiency handling in the MARVEL 2 study is ISO 14155:2011 compliant for all participating geographies.

Ultimately, all sites in all geographies will follow 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

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 will be conducted under an FDA IDE in compliance with 21 CFR Parts:

- 50: Protection of Human Subjects
- 56: Institutional Review Boards
- 812: Investigational Device Exemptions

In EMEA, the study will be conducted in compliance with:

- ISO 14155:2011
- Active Implantable Medical Device Directive (AIMDD)
- Declaration of Helsinki version 2013.

In Hong Kong and Malaysia, the study will be conducted in compliance with:

- ISO 14155:2011, with exception of a formal site initiation visit / visit report (All activation related requirements will be conducted / collected in separate parts).
- Declaration of Helsinki 2013.

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
- Geography-specific regulatory authorities (if regulatory approval is required)
- 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.

19 Study Administration

19.1 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.

19.2 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, and Echo data delivered to Medtronic will be downloaded or saved to a secure network drive prior to being processed Direct Access to Source Data/Documents.

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

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 office visits will be sent to Medtronic. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

19.3 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, patient medical records, echo data, Holter data, programmer printouts, and interrogation files, must be created and maintained by the investigational site team.

The investigator will clearly mark clinical record to indicate that the subject is enrolled in this clinical investigation (geographies following ISO14155). 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 investigation 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 section 19.2, Data Management.

19.4 Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. See section 19.2 for further information.

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). In Malaysia, the informed consent form and the process for conducting this study will be in compliance with the Personal Data Protection Act 2010. 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.

19.5 Liability

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

19.5.1 Insurance (EMEA)

Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee and/or a Competent Authorities (CA).

19.5.2 Insurance (Malaysia)

Medtronic Malaysia Sdn Bhd is a wholly owned subsidiary of Medtronic, plc, 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 study insurance statement/certificate will be provided to the Ethics Board and/or a Competent Authority.

19.5.3 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/certificate will be provided to the Ethics Committee.

19.5.4 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/certificate will be provided to the Ethics Board.

19.6 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 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 Regulatory Authorities (FDA, Competent Authority) and governing Ethics Boards, according to applicable regulations. All amendments to the CIP shall be agreed between Medtronic and the principal investigator(s). Approval by regulatory agencies and 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 or investigational software or investigational software use, Medtronic will review this proposal and decide whether the modification(s) will be implemented.

19.7 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.

19.7.1 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 after the date on which the investigation is terminated:

- Correspondence between the IRB/EC, sponsor, monitor, regulatory authority 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, ICF and Investigator's Brochure
- 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.
- Regulatory authority notification, correspondence and approval, where required per local law.

List of investigation 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 & Enrollment Log
- Device accountability logs and internal tracking of investigational products
- Current curriculum vitae (signed and dated) of principal investigators and key members of investigation site team (for EMEA only)
- Current curriculum vitae of principal investigators (US and Malaysia)
- Documentation of delegated tasks
- Study training records for investigation site team
- Insurance certificates
- Any other records that FDA and local regulatory agencies required to be maintained (e.g. Ethics Committee Roster, study equipment calibration information)
- Final Study Report including the statistical analysis

19.7.2 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an 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 15.3.2 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 10: 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.

Table 11: Investigator reports applicable to EMEA per ISO 14155

Report	Submit to	Description/Constraints
Progress Report	Sponsor and Ethics Board	Provide if required by local law or Ethics Board.
Study Deviations	Sponsor and Ethics Board	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, ethics committees, competent authorities or the appropriate regulatory bodies should be informed. *(ISO 14155:2011)*
Failure to obtain informed consent	Sponsor and Ethics Board	Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical study. *(ISO 14155:2011)*

Table 12: Investigator reports applicable to the United States per FDA regulations

Report	Submit to	Description/Constraints
Withdrawal of Ethics Board approval (either suspension or termination)	Sponsor	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. *(21 CFR 812.150(a)(2))*
Progress report	Sponsor and Ethics Board	The investigator must submit this report to the sponsor and Ethics Board at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (a)(3))*.
Study deviations	Sponsor and Ethics Board	Notice of deviations from the CIP to protect the life or physical wellbeing 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. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the Ethics Board, and the FDA/applicable regulatory authorities. If the deviation does not affect these issues, then only Medtronic must approve it. *(21 CFR 812.150(a)(4))*
Failure to obtain informed consent prior to investigational device use	Sponsor and Ethics Board	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final report	Sponsor, Ethics Board, Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	Ethics Board and FDA	An investigator shall, upon request by a reviewing Ethics Board, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

19.7.3 Sponsor records

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

- Correspondence which pertains to the MARVEL 2 Study
- Executed Clinical Trial Agreement
- Current curriculum vitae (signed and dated) of principal investigators and key members of investigation site team (EMEA only)
- Current curriculum vitae of principal investigators (US and Malaysia)
- 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
- List of names, addresses, and professional position of the clinical investigators and coordinating clinical, if appointed.
- Names and addresses of the institutions in which the MARVEL 2 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/contact addresses of monitors
- Monitoring reports (interim monitoring visit reports, follow-up letters and close-out visit reports)
- Site qualification visit reports
- Statistical analyses and underlying supporting data
- Final report of the MARVEL 2 study
- The approved Clinical Investigation Plan, Investigator's Brochure and study related reports, and revisions
- Documentation of delegated tasks
- Study training records for site personnel and Medtronic personnel involved in the study
- Sample of CRFs
- Any other records that local regulatory agencies require to be maintained

19.7.4 Sponsors reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Board, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Table 7 of the Adverse Event section.

Table 13: Sponsor Reports for EMEA

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical study	Investigators, Ethics Board, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155:2011)*
Withdrawal of Ethics Board approval	Investigators, Head of Institution, Ethics Board and relevant authorities	Investigators, Ethics Board will be notified only if required by local laws or by the Ethics Board.
Withdrawal of CA approval	Investigators, Head of Institution, Ethics Board, and relevant authorities	Investigators, Ethics Board and relevant authorities will be notified only if required by local laws or by the Ethics Board.
Progress Reports	Ethics Board and regulatory authorities	This will be submitted to the Ethics Board and regulatory authorities only if required by the Ethics Board, regulatory authorities or local law.
Final report	Investigators, Ethics Board, and Regulatory authorities upon request	For studies with sites complying to ISO 14155: • The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The signature of the principal Investigator in each center should be obtained. *(ISO 14155:2011)*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical study. *(ISO 14155:2011)* Site specific study deviations will be submitted to investigators periodically.

Table 14. Sponsor Reports for Malaysia

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical study	Investigators, Ethics Board, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155:2011)*
Withdrawal of Ethics Board approval	Investigators, Head of Institution, Ethics Board and relevant authorities	Investigators, Ethics Board will be notified only if required by local laws or by the Ethics Board.
Withdrawal of CA approval	Investigators, Head of Institution, Ethics Board, and relevant authorities	Investigators, Ethics Board and relevant authorities will be notified only if required by local laws or by the Ethics Board.
Progress Reports	Ethics Board and regulatory authorities	This will be submitted to the Ethics Board and regulatory authorities only if required by the Ethics Board, regulatory authorities or local law.
Final report	Investigators, Ethics Board, and Regulatory authorities upon request	For studies with sites complying to ISO 14155: • The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The signature of the principal Investigator in each center should be obtained. *(ISO 14155:2011)*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical study. *(ISO 14155:2011)* Site specific study deviations will be submitted to investigators periodically.

Table 15. Sponsor Reports for Hong Kong

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical study	Investigators, Ethics Board, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). *(ISO 14155:2011)*
Withdrawal of Ethics Board approval	Investigators, Head of Institution, Ethics Board and relevant authorities	Investigators, Ethics Board will be notified only if required by local laws or by the Ethics Board.
Withdrawal of CA approval	Investigators, Head of Institution, Ethics Board, and relevant authorities	Investigators, Ethics Board and relevant authorities will be notified only if required by local laws or by the Ethics Board.
Progress Reports	Ethics Board and regulatory authorities	This will be submitted to the Ethics Board and regulatory authorities only if required by the Ethics Board, regulatory authorities or local law.
Final report	Investigators, Ethics Board, and Regulatory authorities upon request	For studies with sites complying to ISO 14155: • The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The signature of the principal Investigator in each center should be obtained. *(ISO 14155:2011)*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical study. *(ISO 14155:2011)* Site specific study deviations will be submitted to investigators periodically.

Table 16: Sponsor Reports for United States

Report	Submit to	Description/Constraints
Withdrawal of Ethics Board approval	Investigators, Ethics Board, FDA, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(2))*
Withdrawal of FDA approval	Investigators, Ethics Board, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(3))*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	Ethics Board and FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*
Recall and device disposition	Investigators, Head of Institution, Ethics Board, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators, Ethics Board, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and Ethics Board within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*

Table 16: Sponsor Reports for United States (cont.)

Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical study. Site specific study deviations will be submitted to investigators periodically.
Other	IRB and FDA	Accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(b)(10))*

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.

19.8 Publication and Use of Information

Results may be submitted for publication. If results from the MARVEL 2 study will be published, they will be handled according to Medtronic Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

19.8.1 Publication Committee

Medtronic may form the MARVEL 2 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 this appendix, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary, secondary and ancillary study results, 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet at a regular interval, as needed.

19.8.2 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.

19.8.3 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 MARVEL 2 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.

19.8.4 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

19.9 Suspension or Early Termination

Medtronic or 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 investigation 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 investigation 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 investigation 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 investigation site suspension or termination subjects will be followed-up as per standard of care.

19.9.1 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.

19.9.2 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/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)

19.9.3 Procedures for termination and 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

For regions following ISO only: the investigator will promptly inform the regulatory authorities

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

For regions following ISO only: the sponsor (and investigator, if required by local law) will promptly inform the regulatory authorities

20 References

1 Reynolds D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, Narasimhan C, Steinwender C, Brugada J, Lloyd M, Roberts PR, Sagi V, Hummel J, Bongiorni MG, Knops RE, Ellis CR, Gornick CC, Bernabei MA, Laager V, Stromberg K, Williams ER, Hudnall JH, Ritter P; Micra Transcatheter Pacing Study Group. A Leadless Intracardiac Transcatheter Pacing System. N Engl J Med. 2016 Feb 11;374(6):533-41. Doi: 10.1056/NEJMoa1511643. Epub 2015 Nov 9.

2 Duray GZ, Ritter P, El-Chami M, Narasimhan C, Omar R, Tolosana JM, Zhang S, Soejima K, Steinwender C, Rapallini L, Cicic A, Fagan DH, Liu S, Reynolds D; Micra Transcatheter Pacing Study Group. Long-term performance of a transcatheter pacing system: 12-Month results from the Micra Transcatheter Pacing Study. Heart Rhythm. 2017 May;14(5):702-709. Doi: 10.1016/j.hrthm.2017.01.035. Epub 2017 Feb 10.

3 Roberts PR, Clementy N, Al Samadi F, Garweg C, Martinez-Sande JL, Iacopino S, Johansen JB, Vinolas Prat X, Kowal RC, Klug D, Mont L, Steffel J, Li S, Van Osch D, El-Chami MF. A leadless pacemaker in the real-world setting: The Micra Transcatheter Pacing System Post-Approval Registry. Heart Rhythm. 2017 Sep;14(9):1375-1379. Doi: 10.1016/j.hrthm.2017.05.017. Epub 2017 May 11.

4 Lloyd M, Reynolds D, Sheldon T, Stromberg K, Hudnall JH, Demmer WM, Omar R, Ritter P, Hummel J, Mont L, Steinwender C, Duray GZ. Rate adaptive pacing in an intracardiac pacemaker. Heart Rhythm. 2017 Feb;14(2):200-205. Doi: 10.1016/j.hrthm.2016.11.016. Epub 2016 Nov 15.

5 Gillis AM, Russo AM, Ellenbogen KA, Swerdlow CD, Olshansky B, Al-Khatib SM, Beshai JF, McComb JM, Nielsen JC, Philpott JM, Shen WK. HRS/ACCF expert consensus statement on pacemaker device and mode selection. J Am Coll Cardiol. 2012 Aug 14;60(7):682-703. Doi: 10.1016/j.jacc.2012.06.011. Epub 2012 Jul 30.

6 Chinitz L, Ritter P, Khelae SK, Iacopino S, Garweg C, Grazia-Bongiorni M, Neuzil P, Johansen JB, Mont L, Gonzalez E, Sagi V, Duray GZ, Clementy N, Sheldon T, Splett V, Stromberg K, Wood N, Steinwender C. Accelerometer-based atrioventricular synchronous pacing with a ventricular leadless pacemaker: Results from the Micra atrioventricular feasibility studies. Heart Rhythm. 2018 May 11. Pii: S1547-5271(18)30470-3. Doi: 10.1016/j.hrthm.2018.05.004.

7 Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, Sheldon T, LamasGA; Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACe) Trial. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. N Engl J Med. 2007 Sep 6;357(10):1000-8.

8 Toff WD, Camm AJ, Skehan JD; United Kingdom Pacing and Cardiovascular Events Trial Investigators. Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. N Engl J Med. 2005 Jul 14;353(2):145-55.

9 Labovitz AJ, Williams GA, Redd RM, Kennedy HL. Noninvasive assessment of pacemaker hemodynamics by Doppler echocardiography: importance of left atrial size. J Am Coll Cardiol. 1985 Jul;6(1):196-200.

21 Appendices

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

Electronic Case Report Forms for the MARVEL 2 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: FORESEEABLE ADVERSE EVENT LIST

The information provided in this section pertains to foreseeable adverse events that may be observed in the MARVEL 2 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 Marvel 2 software as well as risk minimization are discussed within Section 14. Treatment required for MARVEL 2 software 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 participation in the MARVEL 2 study include:

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

Table 17 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 17: 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%)

Number of Events (Number, % Subjects) (Denominator = 726 Subjects with Implant Attempt)			
Adverse Event Keyterm	**Event**	**Serious Event**	**Complication**
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%)

It is expected that approximately 10 subjects may enroll in the study at the time of their Micra implant. Thus, Table 18 provides a summary of procedure related adverse events by MedDRA keyterm that occurred during the Micra IDE clinical study.

Table 18: 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%)
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%)**

Number of Events (Number, % Subjects) (Denominator = 726 Subjects with Implant Attempt)			
Adverse Event Keyterm	**Event**	**Serious Event**	**Complication**
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 D: PARTICIPATING INVESTIGATORS AND INSTITUTIONS

At the time of MARVEL 2 CIP Version 2.0 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. Approval of the MARVEL 2 CIP will be documented by signing the Clinical Trial Agreement or a separate investigator agreement.

APPENDIX E: ETHICS COMMITTEE

At the time of MARVEL 2 CIP Version 2.0 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 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 MARVEL 2 investigational software will be distributed and installed via a USB drive with an attached uniquely identified key tag. The key tag will be labelled according to local requirements with the statements "Investigational Software for MARVEL 2 Study", "For use with Medtronic Carelink programmer only," "Investigational Device," "Exclusively for clinical investigations," "Software to be installed by Medtronic personnel only." In addition, literature and labeling will be provided according to local law, which may require translation to the local language.

Once the MARVEL 2 investigational software is installed on a Medtronic Carelink Programmer, the Medtronic Carelink Programmer will be labeled per local requirements to indicate that it contains investigational software. Labeling will be placed on the Medtronic Carelink Programmer for the duration of the study and contain the following "PROGRAMMER is used for MARVEL 2 Study. Investigational Software installed *(in addition to other software that is commercially available).* The Investigational software is limited by law to investigational use only. For questions please contact the Investigator."

The Model ER220 Extended Range Holter Monitor is investigational in certain geographies and will be labelled according to local requirements with the statements "Investigational Device," Exclusively for clinical investigations."

APPENDIX G: PRE-CLINICAL TESTING

A summary of results of pre-clinical testing with the MARVEL 2 feature is provided in the MARVEL 2 Investigator's Brochure.

APPENDIX H: PREVIOUS CLINICAL STUDIES

A summary of results from previous clinical studies related to the MARVEL 2 clinical study is provided in the MARVEL 2 Investigator's Brochure.

APPENDIX I: ADDITIONAL INFORMATION FOR SITES BY COUNTRY

Regulations for the conduct of clinical trials vary by country. Other required information for sites in each country, such as detailed sponsor contact information, names of monitors, detailed CRF instruction, etc. not outlined in the Clinical Investigation Plan will be provided under separate cover.

22 Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable	Nicole Wood, Principal Clinical Research Specialist Kurt Stromberg, Sr Prin Statistician

2.0	Changed Version number and date. Section 19.3 Direct Access to Source Data/Documents. added (geographies following ISO14155) and removed the clause “For EMEA only”	Nicole Wood, Principal Clinical Research Specialist Kurt Stromberg, Sr. Prin Statistician