AccelAV Study (Accelerometer Sensing for Micra AV)

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[redacted]

[redacted]

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	[redacted], Senior Statistician [redacted], Senior Principal Statistician [redacted], Principal Scientist
2.0	Updated to fix broken links	[redacted], Senior Statistician
3.0	Section 7.1.5: Changed from using the P-P interval and P-R interval as recorded during the echocardiogram to using the implant Holter to determine each subject's predominant heart rhythm during the echocardiogram. The reason for this was that it was more difficult than originally thought to determine the predominant rhythm based on a single cardiac cycle. Section 7.9.3.7 Added an additional analysis to summarize AV synchrony percentage during rest at 1-month in subjects with normal sinus function and >40% ventricular pacing during rest regardless of AV conduction status. Section 7.9.5.4 and 7.9.5.6 Further clarified that primary analysis cohort for secondary objective #2 would include the subset of subjects included in the primary objective analysis cohort that also had at least 500 evaluable cardiac cycles during the ambulatory Holter monitoring period at the 1-month visit. The rationale was to further clarify the analysis cohort. Section 7.9.6.6 Added an additional analysis stating that point estimates for the mean difference in LVOT VTI between VDD and VVI pacing modes may also be determined for the subset of subjects with a predominant heart rhythm of persistent 3rd degree AV	[redacted], Senior Principal Statistician [redacted], Senior Statistician

Version	Summary of Changes	Author(s)/Title
	block and normal sinus function at both the echocardiogram visit and at the 1-month visit. The rationale for this was evaluate the difference in LVOT VTI in subjects persistently in this heart rhythm of interest.	
4.0	[redacted] Section 7.9.2.1 Changed section to indicate that an artificial intelligence algorithm to identify P-waves from Holter surface ECG rather than a human overread. Section 7.9.3.3 Added bullet indicated that P-waves occurring during VVI mode will be considered not evaluable during the resting and ambulatory periods for subjects with a predominant rhythm of 3rd degree AV block and normal sinus function. The reason for this addition is that each hour a pacing confirmation test is performed in which the device switches to VVI mode to confirm the threshold. Thus, these cycles would be dyssynchronous by definition for subjects with high degree AV block. Section 7.9.5.3: Deleted sentence indicating only the first 5-minutes of each hour would be truthed. The rationale for this is that human based P-wave truthing was very time intensive and with the artificial intelligence algorithm then entire ambulatory period can be examined for the presence of P-waves. [redacted]	[redacted], Senior Principal Statistician

Version	Summary of Changes	Author(s)/Title
	[redacted]	

2. List of Abbreviations and Definitions of Terms

Abbreviations and definitions are displayed in the table below.

Abbreviation	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)
ADC	Analog-to-digital converter
AE	Adverse event
ANOVA	Analysis of variance
AUROC	Area under receiver operating curve
AV	Atrioventricular
AVB	Atrioventricular block
BPM	Beats per minute
CEC	Clinical event committee
CIP	Clinical investigation plan
csv	Comma-separated values
DDD pacing mode	Sensing and pacing occurs in both the atrium and in the ventricle
ECG	Electrocardiogram
e-CRF	Electronic case report form
EGM	Electrogram
EQ-5D-3L	EuroQual-5D quality of life questionnaire
LVOT	Left ventricular outflow tract
PR interval	Time between P-wave and R-wave
PVC	Premature ventricular contraction
R	R programming language for statistical computing
SAP	Statistical analysis plan
SAS	SAS Institute (SAS software)
SD	Secure digital
TPS	Transcatheter pacing system
VDD pacing mode	Sensing occurs in the atrium and in the ventricle, while pacing is limited to the ventricle. In VDD, pacing is synchronized to atrial sensing. In the absence of atrial activity, VVI pacing behavior is seen. The ventricle is paced synchronously to the atrium up to the programmed maximum tracking rate.
VDI pacing mode	Sensing occurs in the atrium and in the ventricle, while pacing is limited to the ventricle. In VDI, pacing is not synchronized to atrial sensing. The behavior is similar to VVI pacing. The ventricle is paced asynchronously to the atrium up to the programmed maximum tracking rate.
VP	Ventricular pace
VS	Ventricular sense
VTI	Velocity time integral
VVI pacing mode	Sensing and pacing occur only in the ventricle.
VVIR pacing mode	Rate adaptive VVI pacing

3. Introduction

The Micra™ Transcatheter Pacing System (TPS), Model MC1VR01, hereafter referred to as Micra VR, was developed to provide pacing entirely within the right ventricle to eliminate the acute and chronic complications related to the leads and pocket-based generator of traditional transvenous systems[1].

The Micra Model MC1AVR1, hereafter referred to as Micra AV, provides all the functionality of the Micra VR system including VVI(R) pacing. Additionally, the Micra AV system provides a form of VDD pacing that is based on mechanical atrial sensing utilizing the device's 3-axis accelerometer, which provides rate response in the Micra VR[2]. This allows the potential benefits of leadless pacemakers for patients where there is a need to preserve atrioventricular synchrony, such as those with AV block (AVB)[3].

The MASS/MASS2 studies collected the intracardiac accelerometer signal from 39 subjects with an implanted Micra VR and intrinsic AV conduction during the study period. These studies showed that four distinct signals, including a signal associated with atrial contraction (designated A4) could be observed.[4] Accelerometer signals from these subjects were used to develop an algorithm to provide AV synchronous pacing. That algorithm was evaluated in the MARVEL study. The MARVEL study demonstrated improved atrioventricular synchronous pacing in humans using Micra VR's intracardiac accelerometer to mechanically detect atrial contraction[4]. The MARVEL study also demonstrated that VDD pacing based on mechanical atrial sensing was safe. A sub-study of the MARVEL study, MARVEL-Evolve, re-tested the MARVEL algorithm in patients from one center to compare the accelerometer signals and AV synchrony at two time-points. The MARVEL-Evolve study showed no evidence of a difference in the A4 amplitude or percentage of AV synchrony during rest between study visits[5].

The accelerometer signal is complex and currently is not well understood by clinicians. Therefore, it was desirable to reduce the clinical burden and expertise required to accurately set up the accelerometer detection algorithm. To accomplish this, Medtronic enhanced the MARVEL algorithm to automatically adjust the most often programmed detection parameters. In addition, two mode-switching algorithms were incorporated: 1) a mode-switch to VVI-40 for patients with paroxysmal AV block who often have intact AV conduction and 2) a mode-switch algorithm that switches to VVIR (rate adaptive pacing) if the sensor rate is significantly faster than the VDD pacing rate. The performance of the enhanced algorithms was the focus of the MARVEL 2 study, which showed the safety and ability of mechanical sensing of the atrium to provide atrioventricular synchronous pacing during rest leading to improved cardiac function in subjects with persistent 3rd degree AV block and normal sinus node function[6]. The MARVEL 2 clinical study was used as pivotal evidence to support market approval of the Micra AV system for expanding the use of transcatheter pacing systems into patients with AV block and normal sinus node function.

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

This Statistical Analysis Plan (SAP) will be used to support the final report and analysis of the AccelAV study. The SAP has been designed to document, before data is analyzed, the planned analyses for the final report and primary study manuscript. This SAP does not limit the analyses in reports, and additional analyses of the study data beyond this plan might be conducted. However, this document provides the basis for the statistical sections of the final report. Analyses not planned in the SAP and incorporated into the final report will be referred to as "Additional Analysis". Furthermore, if any analyses will be done differently than planned in the CIP or SAP, an explanation will be provided in the final report. The following document was used to create this Statistical Analysis Plan (SAP): CIP AccelAV Version 2, dated 24 January 2020.

4. Study Objectives

4.1.1. Primary Objective

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

4.1.2. Secondary Objectives

4.1.2.1. Secondary Objective #1

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

4.1.2.2. Secondary Objective #2

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

4.1.2.3. Secondary Objective #3

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

[redacted]

[redacted]

5. Investigation Plan

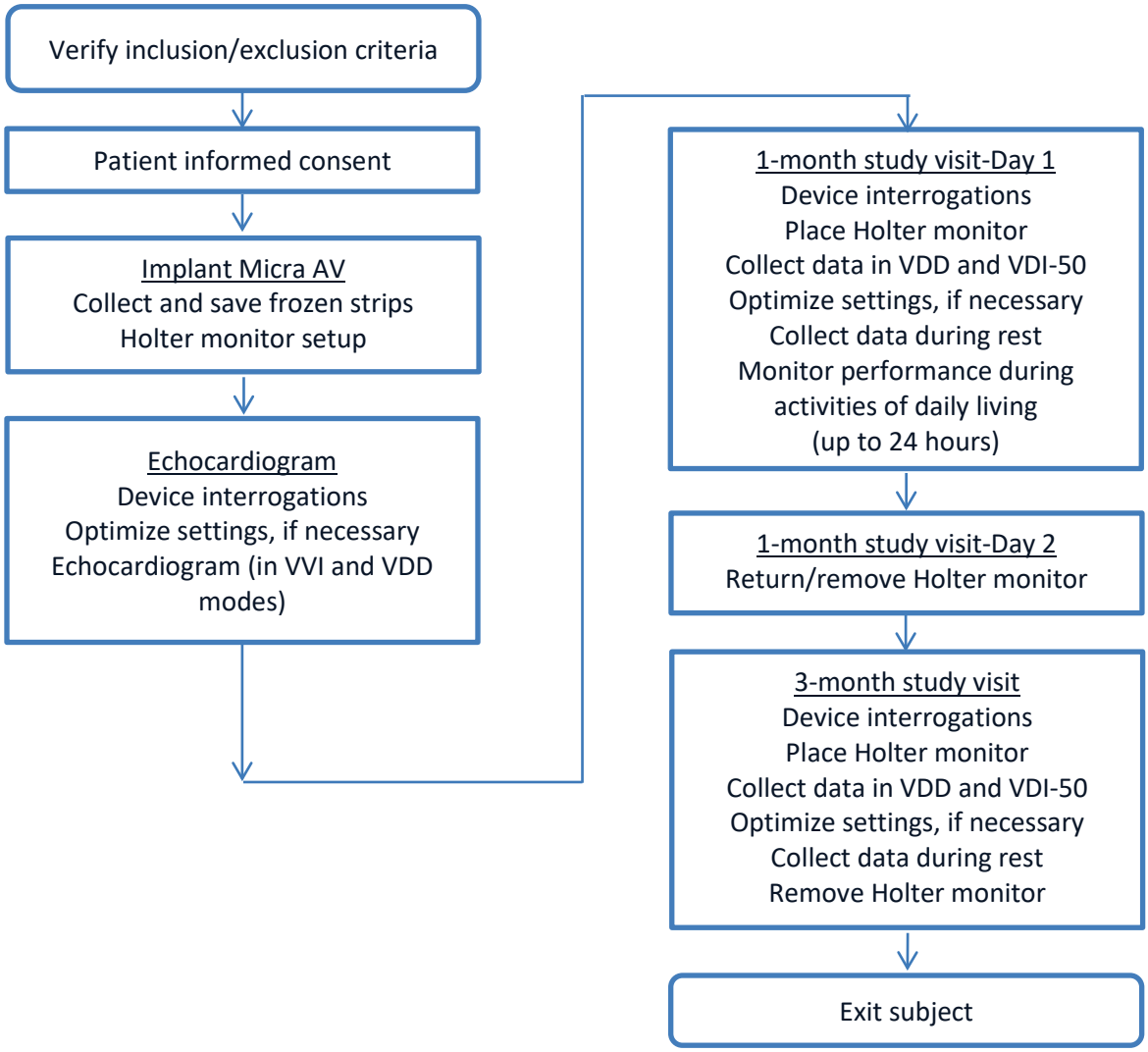
5.1 Study Design

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

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

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

Figure 1. AccelAV Study Flow



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

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

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

5.2 Study Population

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

5.3 Study Procedures

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

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

One month after the Micra AV implant, the subject will come into an in-clinic setting for the 1-month post-implant visit. A Holter monitor will be placed on the subject to record accelerometer, EGM, and ECG waveforms and device-specific markers. The atrial sensing will be reviewed and optimized, if necessary. Overall, approximately 30 minutes of data will be collected during the in-clinic visit with approximately 20 minutes collected at rest. The subject will then be given an activity log to be filled out

and will wear the Holter monitor for approximately 24 hours. The Holter can be returned in-person or sent back in a pre-addressed package.

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

A summary of the data collected for this study is displayed below in Table 1.

Table 1: AccelAV Data Collection Summary

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

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

6. Determination of Sample Size

A sample size of approximately 150 subjects with usable Holter recordings is required to evaluate the study's objectives. Based on the predicate MARVEL and MARVEL 2 studies it is expected that approximately half, or 75, of these subjects will have a predominant rhythm of persistent 3rd degree AVB and normal sinus node function during the 1-month visit. A sample size of 75 subjects with persistent 3rd degree AVB and normal sinus node function will allow the percentage of AV synchrony during rest to be measured with a precision (distance from point estimate to lower 2-sided 95% CI) of approximately ≤3.5%. Since not all subjects may have usable Holter datasets, up to 175 subjects may be enrolled. See section 7.9.3.4 for a detailed sample size calculation.

7. Statistical Methods

7.1 General Considerations

7.1.1 Analysis Timing

There might be up to two formal statistical analyses. A first formal analysis may happen once all enrolled subjects have completed their 1 month visit and will be related to the primary study objective only. A final formal analysis will then happen once all subjects have had the opportunity to complete their 3 months visit and will be related to the secondary, [redacted] objectives of the study. In case the first analysis is not performed, the final analysis will be related to all study objectives. Both analyses will be produced once the study databases have been frozen for analyses.

7.1.2 Type I Error Control

The goal of the AccelAV study is to estimate the rate of AV synchrony in the real-world population rather than test a formal hypothesis with specific type I error control. Therefore, no type I error control is needed.

7.1.3 Usable Holter Datasets

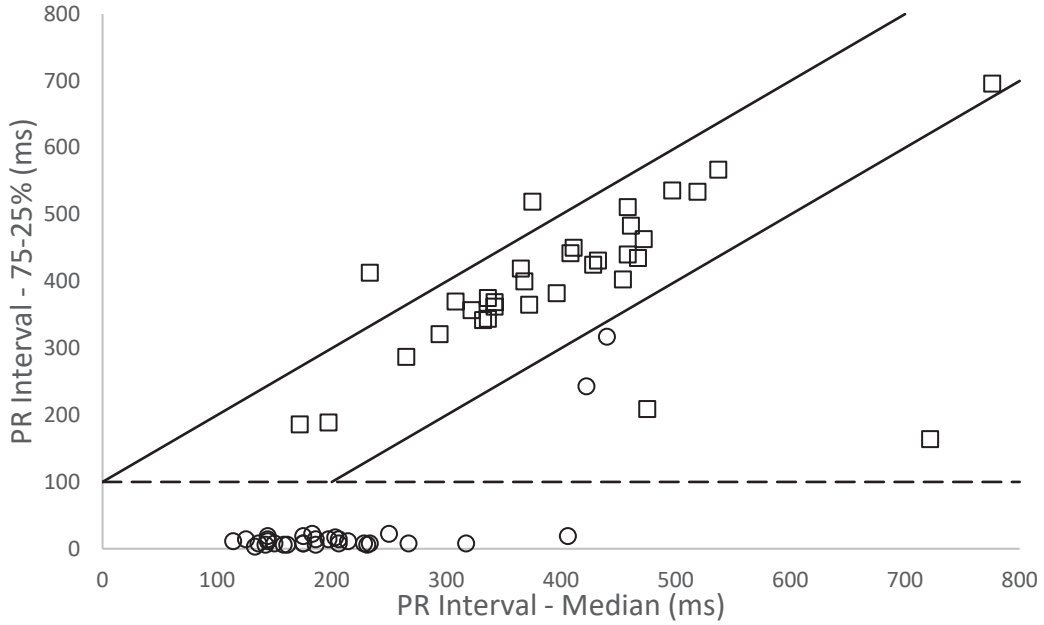
A Holter dataset (i.e., device data telemetered to the Holter flash memory and surface ECG recordings) will be considered usable if there is readable telemetry signal as determined by the presence of visible device and algorithm marker channel. Additionally, to be included in the analysis of study objectives that require assessment of AV synchrony (i.e., primary efficacy objective, secondary objective #1, secondary objective #2, [redacted]) visible P-waves must be present on the ECG recordings.

7.1.4 Determination of Predominant Heart Rhythm During Holter Monitoring

Holter data from the approximately 30-minute atrial sensing setup during implant and the approximately 5-minute data collection in VDI mode at the 1-month and 3-month follow-up visits will be used to determine each subject's predominant heart rhythm during a Holter monitoring session. The sinus node function will be categorized as normal sinus, sinus node dysfunction (sinus bradycardia, sinus tachycardia, other) or atrial arrhythmia. Subjects without visible P-waves and without evidence of atrial arrhythmias will be classified as having an indeterminate rhythm (e.g. noisy signal, poor electrode placement). The AV conduction status will be categorized as persistent 3rd degree AV block, intact AV conduction, or other (e.g. 2nd degree AVB). Note that subjects with a predominant rhythm of persistent 3rd degree AV block with normal sinus node function will be included in the analysis of the primary efficacy objective.

The AV conduction status will be determined based on the distribution of PR intervals during the 30-minute atrial sensing setup during implant and the approximately 5-minute data collection in VDI mode at the 1-month and 3-month follow-up visits while the Micra AV algorithm is in VDI mode (i.e., no atrial tracking). For each subject, the median PR interval and PR interval interquartile range will be computed. Subjects with intact AV conduction will have a consistent PR interval. Therefore, subjects with an interquartile range of their PR interval <100 ms will be classified as having intact AV conduction (Figure 2, values below dotted line). Subjects with 3rd degree AV block tend to have more uniformly distributed PR intervals. Therefore, for the remaining subjects, i.e., those with a median PR interval exceeding 100 ms, if the median PR interval is within 100 ms of their interquartile PR interval range, they will be classified as having persistent 3rd degree AV block (Figure 2, values between solid lines). For example, a subject with a median PR interval of 300 ms with an interquartile PR interval range lying between 200 and 400 ms would be classified as having persistent 3rd degree AV block. AV conduction status for subjects with a PR interval distribution that falls outside these two criteria or who have a high PVC burden will be determined manually from the ECG Holter recording.

Figure 2: Example of PR Interval Interquartile Range vs Median – Data from MARVEL Study



Notes: Circles indicate MARVEL subjects classified as having intact AV node conduction. Squares indicate MARVEL subjects having persistent 3rd degree AV block.

The sinus node function will be determined based upon the duration of the P-P intervals during both the atrial sensing setup and subsequent VDD mode operation during implant and both the VDD and VDI resting phases at the 1-month and 3-month follow-up visits. P-P intervals greater than the lower rate interval (i.e., 1200 ms at a lower rate of 50 bpm), or P-P intervals less than 600 ms (corresponding to a sinus rate > 100 bpm) will be identified. If these long or short intervals comprise less than 5% of the total P-P intervals during these two procedure steps, then the subject will be classified as having normal sinus node function. If these long or short intervals comprise 5% or more of the P-P intervals, then the ECG will be manually reviewed to classify the subject as having normal sinus node function or sinus node dysfunction. A manual review may also be triggered if the subject has been identified during the study as having an atrial arrhythmia, such as atrial flutter or atrial fibrillation, where the P-waves may not have been identified during the P-wave truthing process.

7.1.5 Classification of Predominant Heart Rhythm During Echo

Holter data from the atrial sensing setup procedure during the implant visit will be used to determine each subject's predominant heart rhythm during the echocardiogram which is required to be performed within 48 hours of implant. The sinus node function will be categorized as normal sinus, sinus node dysfunction (sinus bradycardia, sinus tachycardia, other) or atrial arrhythmia. Subjects without visible P-waves and without evidence of atrial arrhythmias will be classified as having an indeterminate rhythm

(e.g. noisy signal, poor electrode placement). The AV conduction status will be categorized as persistent 3rd degree AV block, intact AV conduction, or other (e.g. 2nd degree AVB). The AV conduction status and sinus node function will be determined using the methods described in section 7.1.4.

7.1.6 Atrial Sensing Programming Optimization

Changes to the atrial sensing parameters prior to performing the echocardiogram and the resting periods at the 1-month and 3-month visits will be recorded on the e-CRFs. The number and proportion of subjects requiring optimization of their atrial sensing parameters prior to their echocardiograms and resting periods at the 1-month and 3-month visits will be summarized by predominant rhythm and specific parameter.

7.2 Study Subjects

7.2.1 Disposition of Subjects

The number of enrolled subjects, number of successfully implanted subjects, and number of subjects with usable Holter data at the 1-month visit and 3-month visit will be reported by study center and country.

The number and percentage of enrolled subjects exiting the study will be summarized by the subject status term on the Study Exit e-CRF.

A narrative of any subject deaths occurring during the study period will be provided in the final study report.

Furthermore, flow diagrams describing the subjects contributing to each of the primary and secondary objectives may be made.

7.2.2 Clinical Investigation Plan (CIP) Deviations

Deviations from the clinical investigation plan will be collected as deviations on the Study Deviation e-CRF. Deviations will be summarized in the final report in a table by coded category. Deviation coding will be performed by Medtronic, and the coding will be collected on the MDT Study Deviation e-CRF. The number of deviations per category, and the number and percentage of subjects with a deviation in this category will be reported.

A summary of deviations resulting from the COVID 19 pandemic may also be reported.

7.2.3 Analysis Sets

For each study objective, the subjects that contribute to the statistical analysis for that objective are defined in section 7.9.

7.3 Center Pooling

This study is expected to be conducted in approximately 20 centers in the USA and Hong Kong. Study results are not expected to differ by study center, therefore data from all centers will be pooled. There will be no minimum limit that each investigator must enroll. The maximum number of enrolled subjects per center is 30 subjects (or approximately 20% of the target sample size).

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

For each study objective, details of statistical analyses for handling possible missing data are provided in Section 7.9.

7.5 Adjustments for Multiple Comparisons

Since there are no formal hypotheses tested in this study, no adjustments for multiple comparisons will be made.

7.6 Demographic and Other Baseline Characteristics

Standard baseline and relevant medical history will be collected on the e-CRFs for all enrolled subjects. Baseline and medical history variables to be summarized include, but are not limited to: age, sex, cardiovascular history, arrhythmia history, and cardiovascular medications.

Baseline variables will be summarized for all enrolled subjects, all subjects with a successful Micra AV implant, and all subjects contributing to the primary objective (i.e., those subjects with a predominant rhythm of 3rd degree AV block and normal sinus node function during the 1-month visit).

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

7.7 Treatment Characteristics

There are no treatment requirements for this study and subjects will be implanted with the market released Micra AV (Model MC1AVR1).[redacted]

7.8 Interim Analyses

No interim analysis of the study objectives is planned for this study. However, the primary study objective may be evaluated once all subjects complete their 1-month visit.

7.9 Evaluation of Objectives

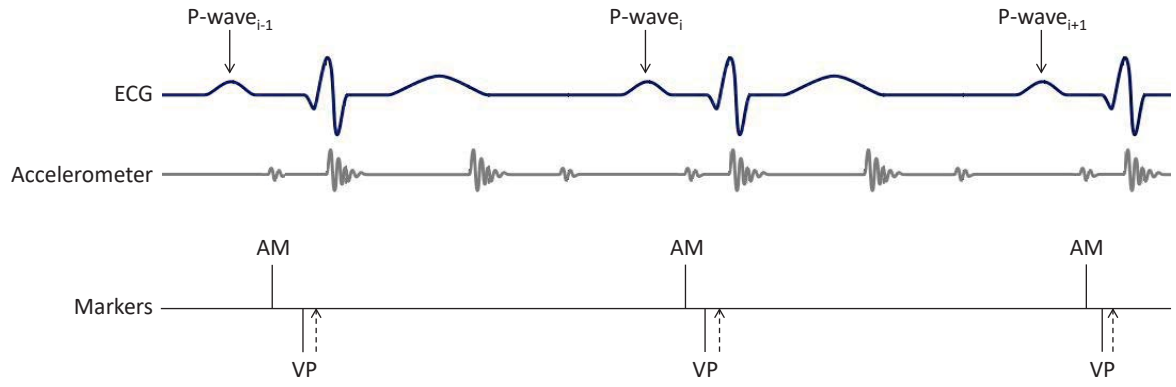
7.9.1 Holter Data Preprocessing

A Holter monitor will be placed on the subjects at the implant, 1-month follow-up, and 3-month follow-up study visits. The Holter monitor continuously records surface ECG, EGM, accelerometer signals, and device and Micra AV algorithm markers that are telemetered from the implanted Micra AV device. The marker channel includes the ventricular sensed and paced event markers as well as a marker indicating that the Micra AV sensed an atrial beat (A4 signal). In addition, the Holter records supplemental marker data from the Micra AV including the V-V interval, pacing mode, pacing amplitude, and atrial sensing specific settings and measurements, including A4 amplitude and mode switch status.

Figure 3 shows an example Holter recording for three cardiac cycles indexed by P-wave. The top line shows the ECG, the middle line displays the accelerometer signal, and the bottom line displays the Micra AV pacing markers including the AM (atrial sense) and VP (ventricular pace) markers. The supplemental markers are sent to the Holter monitor separately from the pacing markers and are indicated by a dashed arrow after the VP marker. The time from the P-wave on the ECG to the ventricular event marker can be used to determine if a ventricular beat is synchronous or not (i.e., ventricular event follows P-wave by no more than 300 ms); the presence of an atrial sense marker following a P-wave can be used to determine if an atrial contraction (A4) was detected. The pacing mode is uplinked to the Holter in the supplemental markers and indicates the pacing mode on the ventricular beat following the one associated with the supplemental marker. Therefore, it is necessary to look back to the supplemental marker prior to the P-wave to assess the ventricular pacing mode associated with the current P-wave. Measurements of the accelerometer signals (A3 and A4 amplitudes and times) are uplinked in the supplemental marker following the P-wave.

Loss of communication between the Holter monitor and the implanted Micra AV, called telemetry dropout, can lead to loss of the pacing markers, supplemental markers, or both. The times from the P-wave to the preceding marker and supplemental marker will be computed. Telemetry dropout can also be determined by a signature in the EGM and accelerometer waveforms. Telemetry dropout is implied if time to these preceding markers exceeds the time to the preceding P-wave.

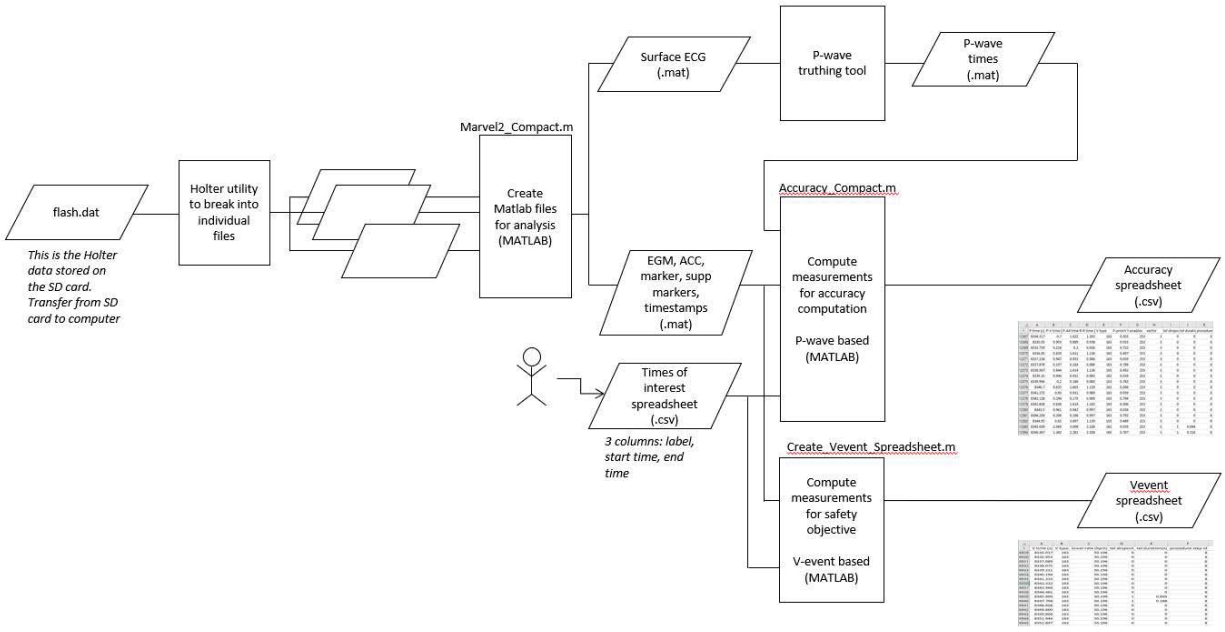
Figure 3: Example Holter Recording Showing Three Cardiac Cycles



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 Micra AV feature operation.

The Holter data is preprocessed to generate two spreadsheets that are used for the analyses of many of the study objectives (Figure 4). These preprocessing steps are described in subsequent sections.

Figure 4: Block Diagram Illustrating Holter File Processing



7.9.2 Holter Data Processing

Each Holter recording is stored on an SD card in a single file named flash.dat. A PC-based utility (HolterManager, NorthEast Monitoring, Inc., Maynard, MA) will be used to separate the various data types recorded on the Holter into individual files. A custom Matlab program will read these files and create two separate Matlab data files containing a collection of variables for further processing. The two channels of surface ECG will be stored in one file for P-wave truthing (note that this file does not contain Micra AV pacing or supplemental markers). Surface ECG, EGM, accelerometer signals, and Micra AV pacing and supplemental markers will be stored in the other file.

7.9.2.1 P-Wave Truthing

[redacted]

7.9.2.2 Timeline Generation

A timeline spreadsheet will be manually generated that identifies the start and end times of various AccelAV procedure steps, such as the resting period or the atrial sensing setup. This spreadsheet will be in a .csv format, and starting with row 4 will contain the name of the procedure step in column A, the start time of the procedure step in column B, and the end time of the procedure step in column C. The start and end times are in seconds from the start of the Holter recording. There will be a separate timeline spreadsheet for each of the three visits where there is Holter recording. An example spreadsheet for a 1-month follow-up visit is displayed in Figure 5.

The approximate start times of procedure steps are recorded in an e-CRF. These times will be used to identify the region in the Holter recording corresponding to the procedure steps. These times will be further refined to exactly identify the times of the procedure steps in the Holter recording by examining data in the Holter recording itself. For example, the atrial sensing setup times can be determined from supplemental markers indicating the status of the atrial sensing setup; the approximate time of the resting period can be determined from the e-CRF and then adjusted by looking at times of programming changes, minimal activity, and a stable heart rate.

The locations of P-waves will not be used in the generation of the timeline.

Figure 5: Example Timeline File

	A	B	C	D	E	F	G	H
1	1234502	-	-	Holter rec	20:43			
2		start time	end time		worksheet time		Visit	
3		(sec)	(sec)					
4	Atrial sensing setup scheduled	0	0				Implant	
5	Atrial sensing setup in progress - histogram	0	0				Implant	
6	Atrial sensing setup in progress - VDI	0	0				Implant	
7	Atrial sensing setup in progress - VDD	0	0				Implant	
8	Initial VDD	126	426		20:44	20:50	1 and 3 month	
9	VDI	428	735		20:50	20:55	1 and 3 month	
10	Resting	850	2050		20:57	21:17	1 and 3 month	
11	Ambulatory	2052	86335		0:00		1 month	
12	Implant - left implant room	0	0		0:00		Implant	
13	Implant - arrive recovery room	0	0		0:00		Implant	
14	Transportation total - worksheet	0	0		0:00		Implant	
15	Transportation 1 - worksheet	0	0		22:00	22:35	1 month	automobile
16	Transportation 1 - activity log	0	0		0:00		1 month	
17	Transportation 1 - adjudicated	0	0				1 month	
18	Transportation 2 - worksheet	0	0		0:00		1 month	add type here
19	Transportation 2 - activity log	0	0		0:00		1 month	
20	Transportation 2 - adjudicated	0	0				1 month	
21	Sleep - activity log	0	0		0:00		1 month	
22	Sleep - adjudicated	0	0				1 month	

7.9.2.3 Accuracy Spreadsheet

A Matlab program will collate 1) the identified P-waves, 2) times corresponding to distinct study procedure steps from the timeline spreadsheet, 3) pacing markers, and 4) Micra AV pacing and supplemental markers into a .csv format spreadsheet, referred to below as an "accuracy spreadsheet." The accuracy spreadsheet uses the P-wave as the fiducial marker and contains one row of information per truthed P-wave that occurred during the Holter recording. An example of the use of this spreadsheet is to compare the time from a P-wave to the next ventricular event (Column B) to 300 ms to determine if a beat was synchronous. This can be further selected to specific procedure steps (Columns K and L) to characterize the AV synchrony for a specific procedure step, such as the resting period.

Loss of communication between the Holter and the implanted Micra AV, called telemetry dropout, can lead to loss of the pacing markers, supplemental markers, or both. Presence of telemetry dropout and the duration of the dropout is provided in the spreadsheet. In addition, an indication of telemetry in the first 300 ms after a P-wave is provided so that beats with no ventricular sense or pace markers and evidence of telemetry dropout in the first 300 ms after a P-wave can be excluded from analyses. Furthermore, some analyses may rely on valid Micra AV pacing or supplemental markers from the

previous pacing cycle. The times of the preceding markers is provided in the spreadsheet and if these exceed the previous P-P interval, telemetry dropout is implied.

Figure 6 displays an example accuracy spreadsheet. The columns of the accuracy spreadsheet are defined as follows:

1. (A): Time of P-wave in seconds relative to the beginning of the Holter recording
2. (B): Time in seconds from P-wave to next ventricular event (VS or VP)
3. (C): Time in seconds from P-wave to next A4 detection
4. (D): Time in seconds between the ventricular event preceding and following the P-wave (i.e., the R-R interval)
5. (E): Marker code associated with the ventricular event following the P-wave. Codes of 160, 172, or 173 mean a VS and codes of 163 or 164 mean a VP
6. (F): Time in seconds from ventricular event preceding the P-wave to the P-wave
7. (G): Bit encoding for Micra AV algorithm settings at last supplemental marker before the current P-wave. Note Micra AV algorithm settings are decoded in columns (P) and (Q).
8. (H): Selected accelerometer vector at last supplemental marker before the current P-wave
9. (I): Presence (1) or absence (0) of telemetry dropout in the interval from the current P-wave to the next P-wave
10. (J): Duration of telemetry dropout in seconds in the interval from the current P-wave to the next P-wave
11. (K): Procedure step identifier (row of the procedure step from the timeline spreadsheet
12. (L): Procedure step decoded name (alphanumeric) corresponding to procedure step identifier
13. (M): Identifier for presence (1) or absence (0) of ventricular event (VS or VP) in the current P-wave to next P-wave cycle. Note that this is redundant with Column A (i+1) – A(i) < B(i) but simplifies calculations
14. (N): Presence (1) or absence (0) of telemetry dropout in the first 300 ms after the P-wave
15. (O): Time in seconds from the ventricular supplemental marker prior to the P-wave to the P-wave. If this interval exceeds the P-P interval then the Micra AV supplemental marker was lost to telemetry dropout.
16. (P): Micra AV algorithm mode at last supplemental marker before the current P-wave (1 = VDD/Adaptive, 3 = VDI/Monitor)
17. (Q): Pacing mode at last supplemental marker before the current P-wave (0=OOO, 1=VOO, 2=VVI, 3=OVO, 4=ODO, 5=VDI, 6=VDD, 10=VVIR, 13=VDIR, 130=VVI40)
18. (R): Time in seconds from current P-wave to the next ventricular supplemental marker following the P-wave

19. (S): A4 maximum amplitude in ADC counts
20. (T): Time in seconds to A4 maximum from prior ventricular event
21. (U): A3 maximum amplitude in ADC counts
22. (V): Time in seconds to A3 maximum from prior ventricular event

Figure 6: Example Holter Data (Accuracy Spreadsheet)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V
1	P time (s)	P-V time (	P-A4 time	R-R time (	V type	P-priorV t	enables	vector	tel dropo	tel durati	procedure	procedure	VSVP in P	tel_dropo	prior Vsup	prior Mar	prior paci	P-Vsupp t	A4 max an	A4 max tir	A3 max an	A3 max time
12367	8334.317	0.7	1.622	1.203	163	0.503	253	3	0	0	8	Resting	1	0	0.467	1	6	0.719	21	0.781	51	0.578
12368	8335.05	0.903	0.889	0.936	163	0.033	253	3	0	0	8	Resting	0	0	0.014	1	6	0.922	52	0.914	45	0.555
12369	8335.739	0.214	0.2	0.936	163	0.722	253	3	0	0	8	Resting	1	0	0.703	1	6	0.233	52	0.914	45	0.555
12370	8336.45	0.639	1.611	1.136	163	0.497	253	3	0	0	8	Resting	1	0	0.478	1	6	0.678	21	0.711	49	0.563
12371	8337.128	0.947	0.933	0.986	163	0.039	253	3	0	0	8	Resting	0	0	1.156	1	6	0	21	0.711	49	0.563
12372	8337.878	0.197	0.183	0.986	163	0.789	253	3	0	0	8	Resting	1	0	0.75	1	6	0.247	49	0.977	43	0.555
12373	8338.567	0.644	1.614	1.136	163	0.492	253	3	0	0	8	Resting	1	0	0.442	1	6	0.681	21	0.773	57	0.57
12374	8339.25	0.944	0.931	0.983	163	0.039	253	3	0	0	8	Resting	0	0	0.003	1	6	0.967	38	0.961	44	0.57
12375	8339.994	0.2	0.186	0.983	163	0.783	253	3	0	0	8	Resting	1	0	0.747	1	6	0.222	38	0.961	44	0.57
12376	8340.7	0.633	1.603	1.139	163	0.506	253	3	0	0	8	Resting	1	0	0.483	1	6	0.669	21	0.727	50	0.57
12377	8341.372	0.95	0.931	0.989	163	0.039	253	3	0	0	8	Resting	0	0	0.003	1	6	0.964	47	0.984	36	0.555
12378	8342.128	0.194	0.175	0.989	163	0.794	253	3	0	0	8	Resting	1	0	0.758	1	6	0.208	47	0.984	36	0.555
12379	8342.828	0.636	1.614	1.142	163	0.506	253	3	0	0	8	Resting	1	0	0.492	1	6	0.664	22	0.766	40	0.563
12380	8343.5	0.961	0.942	0.997	163	0.036	253	3	0	0	8	Resting	0	0	0.008	1	6	0.992	39	0.992	33	0.563
12381	8344.256	0.206	0.186	0.997	163	0.792	253	3	0	0	8	Resting	1	0	0.764	1	6	0.236	39	0.992	33	0.563
12382	8344.95	0.65	3.697	1.139	163	0.489	253	3	0	0	8	Resting	1	0	0.458	1	6	0.664	26	0.766	51	0.672
12383	8345.639	2.069	3.008	2.108	163	0.039	253	3	1	0.094	8	Resting	0	0	0.025	1	6	2.097	23	0.758	31	0.57
12384	8346.367	1.342	2.281	2.108	163	0.767	253	3	1	0.316	8	Resting	0	1	0.753	1	6	1.369	23	0.758	31	0.57
12385	8347.061	0.647	1.586	2.108	163	1.461	253	3	1	0.285	8	Resting	1	1	1.447	1	6	0.675	23	0.758	31	0.57
12386	8347.744	0.914	0.903	0.95	163	0.036	253	1	1	0.188	8	Resting	0	1	0.008	1	6	0.928	40	0.953	69	0.555
12387	8348.467	0.192	0.181	0.95	163	0.758	253	1	0	0	8	Resting	1	0	0.731	1	6	0.206	40	0.953	69	0.555
12388	8349.161	0.639	1.625	1.142	163	0.503	253	1	0	0	8	Resting	1	0	0.489	1	6	0.667	22	0.781	46	0.578
12389	8349.833	0.972	0.953	1.006	163	0.033	253	1	0	0	8	Resting	0	0	0.006	1	6	0.992	44	0.977	33	0.555
12390	8350.578	0.228	0.208	1.006	163	0.778	253	1	0	0	8	Resting	1	0	0.75	1	6	0.247	44	0.977	33	0.555
12391	8351.289	0.656	1.589	1.139	163	0.483	253	1	0	0	8	Resting	1	0	0.464	1	6	0.692	24	0.711	69	0.555
12392	8351.983	0.914	0.894	0.953	163	0.039	253	1	0	0	8	Resting	0	0	0.003	1	6	0.933	47	0.953	56	0.555
12393	8352.7	0.197	0.178	0.953	163	0.756	253	1	0	0	8	Resting	1	0	0.719	1	6	0.217	47	0.953	56	0.555
12394	8353.372	0.661	1.608	1.136	163	0.475	253	1	0	0	8	Resting	1	0	0.456	1	6	0.7	22	0.758	59	0.563

7.9.2.4 Ventricular Event Spreadsheet

Holter datasets will be further analyzed to extract information related to ventricular sensing (including V-V interval). Specifically, a Matlab program will collate each ventricular event, times corresponding to distinct study procedures, and other device markers and information in a .csv file, referred to below as an "VEvent spreadsheet" that will contain one row per ventricular event (i.e., ventricular pace or sense). This contrasts with the accuracy spreadsheet where each row contains information for a P-wave.

Similar to the discussion of the accuracy spreadsheet creation, loss of communication between the Holter and the implanted Micra AV, called telemetry dropout, can lead to loss of the Micra and Micra AV supplemental markers. Note that since this spreadsheet is created from ventricular pacing markers, the loss of a pacing marker can only be inferred from a long interval between ventricular events with evidence of telemetry dropout. Some analyses may rely on Micra AV pacing and supplemental markers from the previous pacing cycle. The times of the preceding markers are provided in the spreadsheet, and if these exceed the previous V-V interval, telemetry dropout is implied.

Figure 7 shows an example VEvent spreadsheet. The VEvent spreadsheet uses the ventricular event as the fiducial marker and contains one record per ventricular event that occurred during the Holter recording. The columns of the VEvent spreadsheet are defined below:

1. (A): Time of ventricular event in seconds relative to the beginning of the Holter recording
2. (B): Marker code associated with the ventricular event. Codes of 160, 172, or 173 mean a VS and codes of 163 or 164 mean a VP
3. (C): Programmed lower rate in bpm
4. (D): Time in seconds from the ventricular supplemental marker prior to the V-Event to the V-Event. The Micra AV algorithm mode and pacing mode are derived from the ventricular supplemental marker. The ventricular supplemental marker is uplinked separately after each V-Event
5. (E): Micra AV algorithm mode at last supplemental marker before the current V-Event (1=VDD/Adaptive, 3=VDI/Monitor)
6. (F): Pacing mode at last supplemental marker before the current V-Event (0=OOO, 1=VOO, 2=VVI, 3=OVO, 4=ODO, 5=VDI, 6=VDD, 10=VVIR, 13=VDIR, 130=VVI40)
7. (G): Time of nearest activity supplemental marker to current V-Event. The lower rate, sensor rate, target rate, and activity counts are derived from the activity supplemental marker. The activity supplemental marker is uplinked on a 2-second interval asynchronous to the ventricular event
8. (H): Sensor rate in bpm
9. (I): Target rate in bpm
10. (J): Activity counts
11. (K): Presence (1) or absence (0) of telemetry dropout in the interval from the current ventricular event to the next ventricular event
12. (L): Duration in seconds of telemetry dropout in the interval from the current ventricular event to the next ventricular event
13. (M): Procedure step identifier (row of the procedure step from the timeline spreadsheet
14. (N): Procedure step decoded name (alphanumeric) corresponding to procedure step identifier

Figure 7: Example Ventricular Event Data (VEvent Spreadsheet)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	V time (s)	V type	lower rate	prior Vsupp time	prior Mar	prior pacing	ta marker time	sensor rate	target rate	activity count	tel dropout	tel duration	procedure s	procedure step	
8929	8335.017	163	49.87	1.167	1	6	8335.158	49.87	50	15	0	0	8	Resting	
8930	8335.953	163	49.87	0.917	1	6	8335.158	49.87	50	15	0	0	8	Resting	
8931	8337.089	163	49.87	1.117	1	6	8337.156	49.87	50	12	0	0	8	Resting	
8932	8338.075	163	49.87	0.947	1	6	8337.156	49.87	50	12	0	0	8	Resting	
8933	8339.211	163	49.87	1.086	1	6	8339.186	49.87	50	17	0	0	8	Resting	
8934	8340.194	163	49.87	0.947	1	6	8341.15	49.87	50	16	0	0	8	Resting	
8935	8341.333	163	49.87	1.117	1	6	8341.15	49.87	50	16	0	0	8	Resting	
8936	8342.322	163	49.87	0.953	1	6	8343.147	49.87	50	16	0	0	8	Resting	
8937	8343.464	163	49.87	1.128	1	6	8343.147	49.87	50	16	0	0	8	Resting	
8938	8344.461	163	49.87	0.969	1	6	8345.144	49.87	50	13	0	0	8	Resting	
8939	8345.6	163	49.87	1.108	1	6	8345.144	49.87	50	13	1	0.695	8	Resting	
8940	8347.708	163	49.87	2.094	1	6	8347.206	49.87	50	15	1	0.188	8	Resting	
8941	8348.658	163	49.87	0.922	1	6	8349.139	49.87	50	15	0	0	8	Resting	
8942	8349.8	163	49.87	1.128	1	6	8349.139	49.87	50	15	0	0	8	Resting	
8943	8350.806	163	49.87	0.978	1	6	8351.136	49.87	50	15	0	0	8	Resting	
8944	8351.944	163	49.87	1.119	1	6	8351.136	49.87	50	15	0	0	8	Resting	
8945	8352.897	163	49.87	0.917	1	6	8353.167	49.87	50	15	0	0	8	Resting	
8946	8354.033	163	49.87	1.117	1	6	8353.167	49.87	50	15	0	0	8	Resting	
8947	8354.994	163	49.87	0.922	1	6	8355.131	49.87	50	15	0	0	8	Resting	
8948	8356.133	163	49.87	1.125	1	6	8357.128	49.87	50	15	0	0	8	Resting	
8949	8357.125	163	49.87	0.961	1	6	8357.128	49.87	50	15	0	0	8	Resting	

7.9.3 Primary Objective

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

7.9.3.1 Endpoint Definition

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

7.9.3.2 Performance Requirements

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

7.9.3.3 Analysis Methods

At the 1-month study visit, a Holter monitor will be placed on the subject. Each subject's Holter monitor will record surface ECG and Micra AV markers. Specifically, the Holter will record whether the Micra AV senses an atrial contraction (A4 signal representing active ventricular filling detected by the accelerometer), delivers a pacing spike, or inhibits a pacing spike based on a sensed intrinsic R-wave. Holter files will be processed as described in Section 7.9.2.

The accuracy spreadsheet derived from each Holter file (see section 7.9.2.3) will be used to determine the synchrony status (yes or no) for each P-wave. Each accuracy spreadsheet will be imported into SAS

and/or R and the P-P interval computed for each P wave *i* (where *i*>1) as the time in seconds in Column 1 (A) for the i^{th} P-wave minus the time in seconds in Column 1 (A) for the i^{th}-1 P-wave. Each P-wave in the accuracy spreadsheet file will be classified as being evaluable or not evaluable. P-waves that are not evaluable include:

1. P-waves with no ventricular sense or pace markers and indication of telemetry dropout in the first 300 ms after the P-wave. These are identified from the accuracy spreadsheet where column 13 (M) = 0 and column 14 (N) = 1.
2. P-waves that occur during an AV conduction mode switch for subjects with a predominant rhythm of persistent 3rd degree AV block and normal sinus node function. During an AV conduction mode switch the pacing mode is set temporarily to VVI40 while the device checks for intrinsic AV conduction. These are identified from the accuracy spreadsheet where a supplemental marker in the preceding P-P interval (column 15 (O) < P-P interval), and the pacing mode in the supplemental marker is VVI40, indicating a mode switch (column 17 (Q) = 130). Note that for the pacing mode, the supplemental marker indicates the pacing mode on the next ventricular event, which is why a look-back to the preceding supplemental marker is necessary to determine if the current ventricular event is in a mode-switched state.
3. P-waves that occur during VVI mode during the resting and ambulatory periods for subjects with a predominant rhythm of persistent 3rd degree AV block and normal sinus node function. The device may be permanently programmed to VVI or switches to VVI mode temporarily each hour to perform a pacing threshold confirmation check and once per day to perform a pacing capture threshold test. While the device is in VVI mode AV synchronous pacing is not expected to occur in these subjects. These cycles are identified from the accuracy spreadsheet where a supplemental marker in the preceding P-P interval (column 15 (O) < P-P interval), and the pacing mode in the supplemental marker is VVI40, indicating a mode switch (column 17 (Q) = 2).

All other P-waves in the accuracy spreadsheet will be considered evaluable. Evaluable P-waves will be considered synchronous if they occur within 300 ms of the following ventricular event. Thus, evaluable P-waves will be considered synchronous if column 2 (B) ≤ 0.3 and asynchronous if column 2 (B) > 0.3.

For the analysis of the primary objective, P-waves with records in the accuracy spreadsheet for each subject's 1-month Holter file corresponding to resting period (i.e., columns 11 (K) and 12 (L) indicate resting phase) will be selected.

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

term and consider observations repeated across subjects with an exchangeable working correlation structure.

A sample SAS PROC GENMOD statement for computing the overall point estimate for the algorithm's ability to provide AV synchrony and its two-sided confidence interval across all subjects is displayed below:

```
proc genmod data = AVsynchData descending;
   class pt;
   model AVsynch = / dist = binomial link = logit;
   repeated subject = pt / type = exch;
   estimate 'probability of success' int 1/ alpha = 0.05;
   output out = pred p = phat;
run;
```

In the SAS code above, "pt" is the subject identifier and "AVsynch" is an identifier for whether a ventricular beat (ventricular pace or sensed event) is within 300 ms following an ECG confirmed P-wave (1=yes, 0=no). The ESTIMATE statement requests the mean probability of success and its 95% confidence interval across all subjects and beats.

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

7.9.3.4 Sample Size

The MARVEL 2 study reported an average AV synchrony rate during rest of 89.2% (95% CI: 84.8% - 92.5%) with a median of 94.3% across the 40 subjects with a predominant heart rhythm of 3rd degree AV block and normal sinus node function and P-waves visible on their Holter ECG channel. The remaining subjects included 17 subjects with intact AV conduction, and 7 subjects with other predominant rhythms. Based on the distribution of predominant rhythms in the MARVEL 2 study together with the enrollment strategy described in section 5, it is expected that approximately half of the subjects with usable Holter recordings will have a predominant rhythm of 3rd degree AV block and normal sinus node function at their 1-month visit.

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

unsuccessful Micra AV implant attempts, and study attrition, approximately 175 subjects may be enrolled.

Since the number of subjects that will have a predominant rhythm of 3rd degree AV block at the 1-month visit is somewhat unknown, Table 2 displays the relationship between the number of subjects that will contribute to the primary efficacy analysis and the distance between the point estimate and lower 95% confidence interval for sample sizes ranging from 40 to 90 subjects.

Table 2: Relationship Between Sample Size and Confidence Interval Width

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

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

7.9.3.5 Determination of Subjects and Data for Analysis

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

7.9.3.6 Missing Data

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

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

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

Additionally, a sensitivity analysis will be performed to assess the sensitivity of the observed AV synchrony percentage estimate with respect to the missing data. The analysis will consist of including in the statistical model all subjects that had some usable Holter data during the 20-minutes resting period at the 1-month visit regardless of the number of evaluable beats. Other stochastic based methods to investigate the sensitivity of the results to the number of unevaluable beats due to telemetry lost may be utilized if necessary.

7.9.3.7 Other Planned Analyses

As described in section 7.1.4, subjects may have different predominant heart rhythms at their 1-month and 3-month visits. For example, a subject may have intact AV conduction at their 1-month visit but have persistent 3rd degree AV block and normal sinus node function at their 3-month visit. Thus, for subjects with different predominant heart rhythms at their 1-month and 3-month visits, an estimate of percent AV synchrony will also be computed using the methods described in section 7.9.3.3 using each subject's first visit Holter recording where they have at least 500 evaluable beats and have a predominant rhythm of persistent 3rd degree AV block and normal sinus node function.

The AV synchrony percentage will also be computed using the methods described in section 7.9.3.3 for subjects not included in the primary objective analysis cohort including those subjects with intact AV conduction and other predominant rhythms.

The AV synchrony percentage during rest will also be computed using the methods described in section 7.9.3.3 among the subset of subjects with normal sinus function at 1-month with >40% ventricular pacing during the resting period regardless of AV conduction status.

7.9.4 Secondary Objective #1

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

7.9.4.1 Endpoint Definition

The endpoint for secondary objective #1 will be the same as for the primary objective (see section 7.9.3.1) with the exception that ECG confirmed P-waves that occur during the 20-minute resting period at both the 1-month and 3-month visits will be included in the analysis.

7.9.4.2 Performance Requirements

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

7.9.4.3 Analysis Methods

A Holter monitor will be placed on each subject at the 1-month and 3-month visits. Each Holter file will be processed as described in section 7.9.2 and the AV synchrony during the 20-minutes resting periods at the 1-month and 3-months visits will be compared using a generalized linear model incorporating generalized estimating equations. The response for this model on an individual heartbeat basis will be AV synchrony endpoint met as defined in section 7.9.3.1 (i.e., 1= yes, 0=no). The model will also incorporate an intercept term and indicator for visit (1-month or 3-month visits) and utilize an exchangeable working correlation structure to account for the fact that the atrioventricular synchrony may be correlated within subject. The difference in the least squared means between visits on the linear scale (i.e., when utilizing the identity link function with the binomial distribution) and its related 95% confidence interval will be used to assess the stability of the AV synchronous pacing rate between study visits.

A sample SAS PROC GENMOD statement for comparing the percentage of AV synchronous pacing between study visits is displayed below:

```
proc genmod data = AVsynchData descending;
   class pt visit;
   model AVsynch = visit / dist = binomial link = id;
   repeated subject = pt / type = exch;
   lsmeans visit / cl;
   estimate 'Difference' visit -1 1/ alpha = 0.05;
run;
```

7.9.4.4 Determination of Subjects and Data for Analysis

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

7.9.4.5 Missing Data

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

Additionally, a sensitivity analysis will be performed to assess the sensitivity of the estimated difference in AV synchrony percentage with respect to the missing data. Specifically, the analysis will include in the

statistical model all subjects with persistent 3rd degree AV block and normal sinus node function and at least one evaluable cardiac cycle at the 1-month and 3-month visits respectively.

7.9.4.6 Other Planned Analyses

The AV synchrony during the 20-minutes resting periods at the 1-month and 3-months visits will be compared for subjects with predominant rhythms other than persistent 3rd degree AV block and normal sinus node function including those with intact AV conduction and other predominant rhythms, using the methods described in section 7.9.4.3.

7.9.5 Secondary Objective #2

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

7.9.5.1 Endpoint Definition

The endpoint for secondary objective #2 will be the same as for the primary objective (see section 7.9.3.1) with the exception that ECG confirmed P-waves that occur during the ambulatory period during the 1-month Holter recording will be used in the analysis.

7.9.5.2 Performance Requirement

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

7.9.5.3 Analysis Methods

At the 1-month visit, a Holter monitor will be placed on the subject and following the in-clinic study procedures the subject will wear the Holter monitor for approximately 24 hours as they go about their activities of daily living. The Holter files will be processed as described in section 7.9.2. A logistic regression model using generalized estimating equations will be used to construct a single estimate and 95% confidence interval for algorithm performance across all subjects using the methods described in section 7.9.3.3. For analysis purposes, the ambulatory period will be defined as starting at the end of the 20-minute resting period.

7.9.5.4 Determination of Subjects/Data for Analysis

All subjects included in the primary objective analysis cohort that have a usable Holter recording available during the ambulatory period will be included in the analysis of this objective.

7.9.5.5 Missing Data

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

beats). The total number of heart beats and total number of evaluable beats will be summarized for each subject.

7.9.5.6 Other Planned Analyses

An estimate of AV synchrony will also be computed for all subjects with a predominant rhythm of persistent 3rd degree AV block and normal sinus function at the 1-month visit with usable Holter recordings during the ambulatory period. This analysis will only be performed if there are subjects with a predominant rhythm of persistent 3rd degree AV block and normal sinus function at the 1-month visit that were excluded from the primary objective analysis cohort (e.g. had fewer than 500 evaluable beats during the 20 minute resting period), but have usable Holter data during the ambulatory period.

The AV synchrony percentage will also be estimated during the 1-month ambulatory period for predominant rhythms other than persistent 3rd degree AV block and normal sinus node function including those with intact AV conduction and other predominant rhythms, using the methods described in section 7.9.3.3.

7.9.6 Secondary Objective #3

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

7.9.6.1 Endpoint Definition

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

7.9.6.2 Performance Requirements

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

7.9.6.3 Analysis Methods

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

For each pacing mode (VDD or VVI) within each subject, up to 6 LVOT VTI and two heart rate measurements will be collected. LVOT VTI and heart rate measurements will be averaged within each subject and pacing mode combination. Subjects with at least 3 LVOT VTI measurements and one heart rate measurement in each pacing mode will be included in the analysis.

Since subject is the experimental unit, the mean difference in LVOT VTI during the VDD and VVI pacing will be estimated and tested using a paired t-test. The estimated mean difference in LVOT VIT between the two pacing modes will be reported along with its 95% confidence interval.

A sample SAS PROC TTEST statement for estimating and testing the difference in LVOT VTI during the VDD and the VVI pacing modes is displayed below:

```
proc ttest data=echo sides=2 alpha=0.05 h0=0;
      paired LVOTvtiVVI * LVOTvtiVDD;
run;
```

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.

7.9.6.4 Determination of Subjects/Data for Analysis

All subjects with persistent 3rd degree AV block and normal sinus node function at the time of their echocardiogram with at least 3 LVOT VTI measurements and one heart rate measurement in both VDD and VVI mode and where the absolute difference in the average heart rate between the VDD and VVI modes is ≤ 15 bpm will be included in the analysis.

7.9.6.5 Missing Data

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

If the level of missing data is an issue, tipping point methodology may be employed to evaluate the sensitivity of the statistical inference to the missing data. Specifically, all subjects with missing data will be imputed to have the mean change and standard deviation in LVOT VTI in the observed data then iteratively set to a smaller mean change value until the statistical inference changes (i.e., P-value exceeds 0.05). Additionally, stochastic methods may be employed to aid in interpreting the likelihood the tipping point would be met or exceeded by determining how likely the mean value for subjects with missing data would exceed the tipping point.

7.9.6.6 Other Planned Analyses

Point estimates for the mean difference in LVOT VTI between VDD and VVI pacing and its corresponding 95% confidence interval will also be constructed for subjects not included in the analysis cohort using the methods described in section 7.9.6.3 including those with intact AV conduction and other heart rhythms as well as those with persistent 3rd degree AV block and normal sinus function, but with absolute differences in heart rate between VDD and VDI modes exceeding 15 bpm.

Additionally, point estimates for the mean difference in LVOT VTI between VDD and VVI pacing and its corresponding 95% confidence interval may also be constructed for subjects with a predominant rhythm of persistent 3rd degree AV block and normal sinus function and normal sinus function during the echocardiogram visit and at 1-month post-implant.

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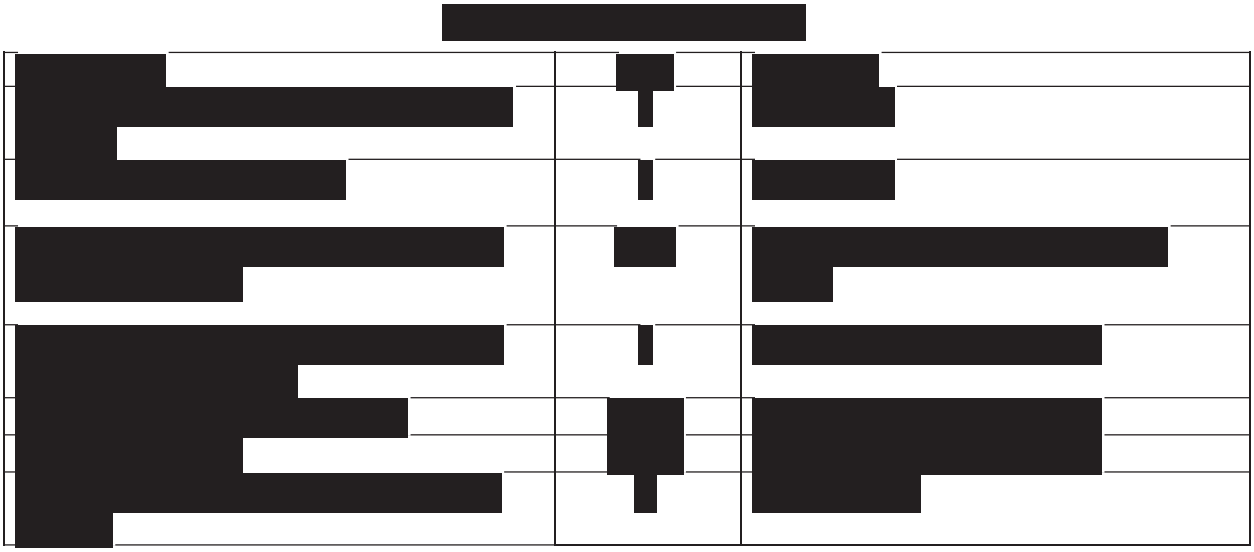
8. Validation Requirements

To ensure the quality of the statistical results and datasets created for the study, the following validation requirements will be implemented.

Programs that contribute directly or indirectly to results pertaining to the primary objective will be validated level I or level II by a statistician or a statistical programmer. Level II or Level III validation (self-validation) will be acceptable for programs, which do not pertain to the primary objective. The table below specifies the validation requirements for data extraction, mapped datasets, analysis datasets, TLGs (Tables, Listings, and Graphs) and study objectives. Mapped datasets are considered as datasets that map case report forms. Analysis datasets are datasets that contain derived variables relevant for the statistical analysis.



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