Medtronic

Panel Pack

Micra™ Transcatheter Pacing System (TPS)

Prepared for the Circulatory Systems Devices Panel Meeting

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1. Executive Summary

The Micra™ Transcatheter Pacing System (TPS) is a miniaturized (0.8 cc), leadless, full featured single chamber ventricular pacemaker that is implanted directly in the right ventricle. It provides a treatment option for patients with Class I or Class II indication for bradycardia pacing therapy. The concept of an intracardiac leadless pacemaker first originated in 1970[1] in an effort to reduce complications associated with the subcutaneous pocket and the lead that are common for current transvenous pacemakers. Approximately 1 in 8 patients with a transvenous pacemaker has an early complication that include problems with the pocket (hematomas, infections, etc.), lead-insertion (e.g. pneumothoraxes), lead dislodgements and integrity issues, system infections, and vascular obstructions.[2] A fully intracardiac pacemaker has now become a reality due to technology advances enabling deep miniaturization and high density battery chemistries.

Micra TPS is comprised of a delivery system, an introducer, and the pacemaker device. The Micra is delivered to the heart via the femoral vein using an introducer and delivery tool. Micra is deployed from the delivery system, allowing its fixation tines to engage into the cardiac tissue. Micra provides rate responsive pacing as well as automated pacing capture threshold management to maximize battery longevity. Micra can be used in the MRI environment, allowing for full body scans at 1.5T and 3T. Importantly, the Micra pacemaker provides the option to be programmed to Device Off mode, permanently disabling pacing and sensing, allowing it to remain in the body beyond its useful life without inappropriate interaction with concomitant device therapy. Micra has a retrieval feature when percutaneous retrieval is needed.

In addition to extensive pre-clinical testing, Micra met all efficacy and safety endpoints in a prospective clinical trial from 56 centers in 19 countries on 5 continents. The clinical results include the safety outcomes from all 725 implant attempts and endpoint electrical data from the first 300 patients followed to 6 months. Micra was successfully implanted in 99.2% of patients by 94 implanters. The device met prespecified criteria for pacing efficacy with 98.3% of patients having low and stable pacing capture thresholds to 6 months, and the prespecified safety criteria was met with 96.0% of patients having experienced no major complications at 6 months. All other endpoints for the trial were met.

Micra safety performance was compared with 2667 patients who received contemporary transvenous pacemakers in a historical control cohort. Through 6 months follow-up, Micra patients experienced 51% fewer major complications, with a similar result after adjustment for differences in patient populations. Micra patients had significantly fewer hospitalizations (54%) and system revisions (87%), driven by the elimination of pneumothoraxes and absence of Micra dislodgements.

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[1] Spickler JW, Rasor NS, Kezdi P, Misra SN, Robins KE, LeBoeuf C. Totally self-contained intracardiac pacemaker. J Electrocardiol 1970;3:325-31.

[2] Udo EO, Zuithoff NP, van Hemel NM, et al. Incidence and predictors of short and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm 2012; 9: 728-35.

There may be patient preference for Micra due to the miniaturization (e.g. outward cosmetic appearance) and lack of device pocket which is associated with a scar. Additionally, the leadless pacemaker has no arm motion or weight-bearing restrictions and this can help people get back to work and limit disability or restrictions to lifestyle (e.g. carpenter, professions with weight-bearing requirements, golfing, swimming, etc.).

Further long term benefit with Micra is expected because it enables the preservation of veins (e.g. hemodialysis, the need for an indwelling catheter), as well as avoiding lead-associated problems such as stenosis of the subclavian vein or tricuspid valve injury. Another benefit is the absence of the device pocket and its associated replacement complications.[3]

Questions remain regarding end-of-service/deactivation considerations and regarding training strategy upon commercialization. In response to Medtronic's application for premarket approval, this panel pack discusses the following points:

1. *Clinical trial experience and lessons learned from U.S. as well as from the European experience (Section 3)*
   Medtronic Summary:
   - Both primary safety and efficacy objectives were met. Micra had zero dislodgements (i.e. device emboli).
   - Micra reduced major complications by 51% compared to traditional transvenous pacemaker systems.
2. *Perforation related adverse events, including types of events and severity (Section 3.3.7)*
   Medtronic Summary:
   - Micra patients with effusions were more likely to be female, elderly, with lower BMI, and have chronic lung disease than patients without effusions. These are known risk factors reported for traditional technology, suggesting these patients would be at high risk for effusion regardless of device type.
   - Micra patients had 1.6% effusion / perforation rate, which is not significantly different than the 1.1% rate from the transvenous pacemaker historical control group and is similar to other large pacemaker studies (1.2%, Mayo clinic[4]).
   - The overall safety profile for Micra compared favorably to transvenous systems across subgroups and no subgroup showed a higher risk of major complication.
3. *Training plans (Section 4)*
   Medtronic Summary:
   - Training for Micra will be based on the clinical study training program, which was successful with a high implant success rate (99.2%) and a low major complication rate (4%), regardless of the training venue (e.g. in a laboratory environment training center or locally at a hospital with a proctor). Medtronic will continue to offer multiple training approaches while maintaining consistent learning objectives.

[3] Poole JE et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. Circulation. 2010 Oct 19;122(16):1553-61.

[4] Mahapatra S, Bybee KA, Bunch TJ, Espinosa RE, Sinak LJ, McGoon MD, et al. Incidence and predictors of cardiac perforation after permanent pacemaker placement. Heart Rhythm 2005;2:907–11.

4. *Expected device failures over time (Section 5)*
   Medtronic Summary:
   - It is expected the long-term Micra device failure rate will be very low, and the potential device failure types would be similar to conventional pacemakers, excluding failures related to transvenous leads. The Micra Post-Market Study and market release product performance monitoring will be used to continually monitor performance over a longer term.
5. *Data on explants and end-of-life (EOL) of the device and what information will be provided to users on EOL options (labeling, instructions, etc.) (Section 6)*
   Medtronic Summary:
   - Micra was designed to provide options for managing various EOS and deactivation scenarios. In summary, it is expected:
     - The majority of Micra patients will require only one device in their lifetime
     - For those patients who need more than one device or need a device upgrade, most implanters will choose to leave Micra *in situ* and implant a second Micra or implant a transvenous system. At 0.8 cc in size (representing 0.5% volume of right ventricle), Micra was designed to remain in the body.
     - When necessary, percutaneous or surgical retrieval is an option using standard tools that are commercially available.
6. *Address 3draft panel questions (Sections 7-9)*

2. Device Description

2.1 Introduction

The Indications for Use of Micra are intended to be the same indications that currently apply for Medtronic single chamber pacemakers, consistent with all commercially available Medtronic single chamber pacemakers. This indication is consistent with the latest Heart Rhythm Society and the American College of Cardiology Foundation expert consensus statement on pacemaker device selection[5] and with the Centers for Medicare and Medicaid Services (CMS) decision memo for cardiac pacemakers[6].

> Micra Model MC1VR01 is indicated for use in patients who may benefit from rate-responsive pacing to support cardiac output during varying levels of activity. This device is indicated for use in patients who have experienced one or more of the following conditions:
>
> - symptomatic paroxysmal or permanent second- or third-degree AV block
> - symptomatic bilateral bundle branch block
> - symptomatic paroxysmal or transient sinus node dysfunctions with or without associated AV conduction disorders
> - bradycardia-tachycardia syndrome

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

[5] Gillis AM, Russo AM, Ellenbogen KA, et al. HRS/ACCF Expert Consensus Statement on Pacemaker Device and Mode Selection. Heart Rhythm. 2012 Aug;9(8):1344-65.

[6] https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=267

Figure 1: Micra Implantable Device

Despite the differences in size and shape, the Micra device is very similar to standard Medtronic pacemakers in regards to functionality and features. The VVIR pacing therapy delivered by the Micra device is comparable to that delivered by a conventional transvenous pacemaker. Both devices communicate to the standard Medtronic Model 2090 Programmer and no ECG patches are required for communication. Table 1 provides an overview of the size and features of Micra in comparison to a conventional pacemaker.

Table 1: Size and Features in Comparison to Conventional Pacemaker[7]

Attribute	Medtronic Adapta ADSR01	Medtronic Micra
Size		
Volume of device (cm^3)	9.7	0.8
Mass of device (g)	21.5	2.0
Total volume of material within body (cm^3)	10.56 (assumes Adapta device + 30 cm, 6 Fr lead)	0.8 (device with electrodes placed directly on the pacemaker capsule)
Features		
Battery chemistry/capacity	Lithium-iodine, 830 mA h	Lithium silver vanadium oxide/carbon monoflouride, 120 mA h
Threshold measurement and tracking	Measure 1/day Output = maximum of 2× threshold or 2.0 V	Measure 1/day, verify 1/h Output = threshold + 0.5 V
Capture management	Evoked response (all leads) Works at 0.4 ms	Evoked response (one pair of low polarization, 18 mm spaced electrodes) Works at 0.24 and 0.4 ms
Prolonged service period	3 months	6 months
Magnet mode	Yes	No
Rate response	SubQ accelerometer, (activity)	Cardiac three-axis accelerometer, (activity), individually selectable with one vector used
Ability to inactivate device at EOS	No	Device can be manually deactivated with programmer and automatically deactives at EOS
MRI conditional	No	Yes, by design
Electrodes	Lead dependent	Pacing electrodes placed directly on the pacemaker capsule: *Cathode*: 2.5 mm^2 TiN-coated and sintered, located at tip. *Anode*: 22 mm^2 TiN-coated, located on ring on body
Steroid elution	Lead dependent	Yes

2.2. Design Requirements

The Micra system leverages both existing and new technologies. Although the idea of a self-contained intracardiac pacemaker has existed since the 1970s, the new technology in the Micra system is made possible due to advances in miniaturization technologies (high density battery), catheter delivery systems, novel materials (nitinol), and placement of electrodes directly on the pacemaker capsule.

Table 2 describes the design requirements and solutions.

[7] Ritter P, Duray GZ, Zhang S, et al. The rationale and design of the Micra Transcatheter Pacing Study: safety and efficacy of a novel miniaturized pacemaker. Europace 2015; 17: 807-13.

Table 2: Micra Design Requirements

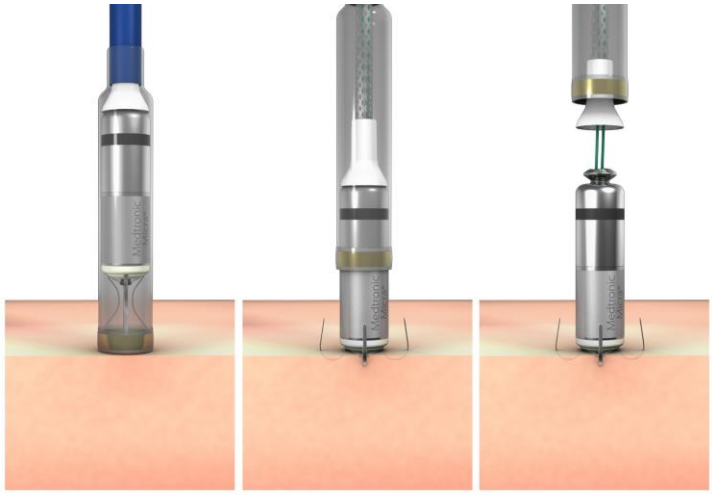
Design Requirements	Solutions
1 **Secure Fixation**	4 Nitinol Tines
2 **Transcatheter Delivery System**	23Fr catheter
3 **Miniaturization**	High-Density Battery
4 **Adequate Longevity**	Pacing Efficiencies: – Efficient pulse width (0.24ms) – Hourly Capture Management
5 **Rate Response within Heart**	3-Vector accelerometer
6 **Chronic Device Management**	- OFF feature allows for compatibility with future device(s) - Proximal Retrieval Feature

2.2.1 Secure Fixation

Medtronic developed a fixation mechanism comprised of 4 self-expanding nitinol tines (Figure 2) in order to:

- mitigate the risk of device dislodgement
- enable low, stable pacing thresholds
- facilitate device repositioning, retrieval, and extraction

Figure 2: Device Deployment (Tines)



Medtronic conducted multiple studies to select this fixation method and to ensure the reliability of the tine fixation approach. Sophisticated engineering modeling techniques indicate high

confidence in the reliability of the tines and protection against dislodgement.[8] This evaluation includes inputs from a variety of sources, including reanimated human hearts, bench testing, chronic animal studies, and the Micra Global Trial. These combined studies have provided a comprehensive understanding of the safety profile and reliability of the tines and secure fixation.

The Micra fixation mechanism provides a secure holding force in order to mitigate dislodgement risk. Engagement of a minimum of two tines with the myocardium is recommended for successful fixation and two tines have 15 times the holding force necessary to maintain the device in place. Two tines therefore provide a holding force well in excess of what is required while also providing redundancy.

The tines provide a fixation mechanism that is separated from the pacing cathode. This minimizes tissue damage at the electrode-tissue interface, facilitating low, stable pacing thresholds and a longevity comparable to conventional devices.

Lastly, the tines are constructed of nitinol, a shape memory alloy. The material is flexible to allow for repositioning or retrieval without tearing tissue. Nitinol material is also utilized in other Medtronic products such as the CoreValve Transcatheter Aortic Valve Replacement System.

2.2.2 Transcatheter Delivery System

The Micra device is placed through a dedicated catheter delivery system.

Micra Introducer

The Micra Introducer is a 23 Fr (inner diameter, 27 Fr outer diameter) hydrophilic coated sheath intended to provide a flexible and hemostatic conduit for the insertion of the Micra device (Figure 3The introducer system is comprised of 2 components: a dilator which accommodates a 0.035 in (0.89 mm) guide wire and an introducer sheath.

Figure 3: Micra Introducer

Transfemoral Delivery Catheter

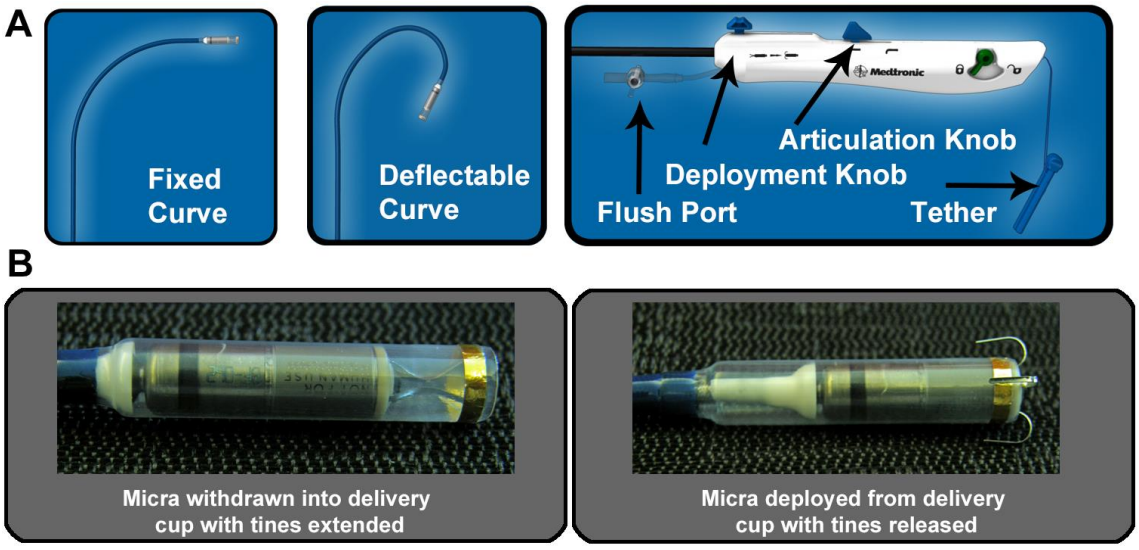
The single use Micra transfemoral delivery catheter contains the Micra at the distal end and consists of a handle, a long shaft with a fixed and articulating curve, and a cup containing the Micra device at the distal end.

[8] Eggen M, Grubac V, Bonner M. Design and Evaluation of a Novel Fixation Mechanism for a Transcatheter Pacemaker. IEEE Trans Biomed Eng. 2015 Sep;62(9):2316-23

Figure 4: Transfemoral Delivery Catheter

The Micra device sits inside a cup at the distal end of the catheter and is deployed by activating a button on the handle (Figure 5). When deployed, the Micra fixation tines are released to engage the myocardium. The Micra device is locked to the delivery system by means of a tether that goes through the proximal end of the device, through the braided shafts to the handle, and can be released (or locked) by means of a button on the handle.

Figure 5: Transfemoral Delivery Catheter: Articulation and Deployment



2.2.3 Miniaturization

In order to develop a device 93% smaller than conventional pacemakers, extensive miniaturization efforts were required, specifically for the battery which is the largest single component of the Micra device. Medtronic created new electronics and, using proprietary chemistry, a downsized hybrid high-energy density battery. The result is a device 2.8mm in diameter and 25.9mm long that is self-contained in a hermetically enclosed capsule.

2.2.4 Pacing Efficiencies to Maximize Battery Longevity

To achieve battery longevity in Micra that is similar to conventional pacemakers, Micra pacing efficiency was optimized.

First, Micra pacing is delivered at the chronaxie (0.24ms) pulse width which optimizes the balance between pacing duration (i.e. pulse width) and energy output (i.e. pacing amplitude). This is feasible due to the stability demonstrated by the Micra fixation coupled with the minimal tissue damage beneath the pacing cathode due to its distance from the fixation.

Second, the capture management algorithm was enhanced. Micra's capture management automatically conducts hourly safety margin confirmation checks in addition to nightly threshold checks. Micra nominally sets the output voltage to 0.5 V above the highest threshold measured in the last 2 weeks for the safety margin versus a nominal 2X the threshold (with a minimum output of 2 V) with conventional pacemakers. These automatic safety margin checks ensure pacing outputs remain at safe levels while adapting outputs to maximize battery longevity.

2.2.5 Rate Response Within the Heart

In order for Micra to deliver rate response therapy, a new accelerometer was developed. The Micra activity sensor is now located within the heart versus the subcutaneous pocket where a traditional pacemaker would reside, yet still uses body motion as the indicator of activity. The device differentiates cardiac motion from body motion occurring during activity. In addition, Micra offers a three-axis accelerometer sensor to allow the physician to select an alternate axis to sense activity in cases where the default axis provides suboptimal performance.

2.2.6 Chronic Device Management (Ability to Turn Device OFF)

Traditional pacemakers require a change-out when the battery reaches the end of its service. Micra was designed to provide options for managing a variety of clinical scenarios including End of Service (EOS) and elective device deactivation.

- Micra can be programmed to Device Off mode such that the device does not pace or sense and hence cannot interfere with the pacing and sensing operation of other pulse generators.
- At less than 1 cubic centimeter, Micra is small enough to allow multiple devices (e.g. another Micra or transveous leads) to be placed in the heart.
- The Micra design allows for retrieval of the device pre-encapsulation with commercially available off the shelf tools.

3. Global Clinical Experience

IDE Trial Summary:

- Prospective, single arm, worldwide clinical study (19 countries, 56 sites)
- 744 patients enrolled, with 725 implant attempts by 94 implanters
- Safety
    - There was a 96.0% freedom from major complications related to the Micra system or procedure through 6-months follow-up (95% CI: 93.9% to 97.3%; P<0.0001 versus a pre-specified performance goal of 83%). There were zero dislodgements (i.e. device emboli).
    - Micra patients experienced significantly fewer major complications compared to the historic control group through 6-months post-implant (hazard ratio: 0.49; 95% CI: 0.33 to 0.75; P=0.001) despite Micra patients being older with more co-morbidities.
- Efficacy
    - 98.3% of patients with low and stable pacing thresholds through 6-months (95% CI, 96.1% to 99.5%; P<0.0001 versus a pre-specified performance goal of 80%)

3.1 Pivotal Study Overview

The pivotal study is a prospective, single arm, worldwide clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Micra system and to assess long-term device performance. Patients who met class I or II guideline-based indications for pacing and were considered suitable candidates for single-chamber pacing were eligible for participation. Study participation did not exclude any co-morbid disease states, provided the patient had a life expectancy of at least 12-months. Patients were evaluated for device function and adverse events at hospital discharge and at follow-up assessments at 1, 3, and 6 months and every 6 months thereafter.

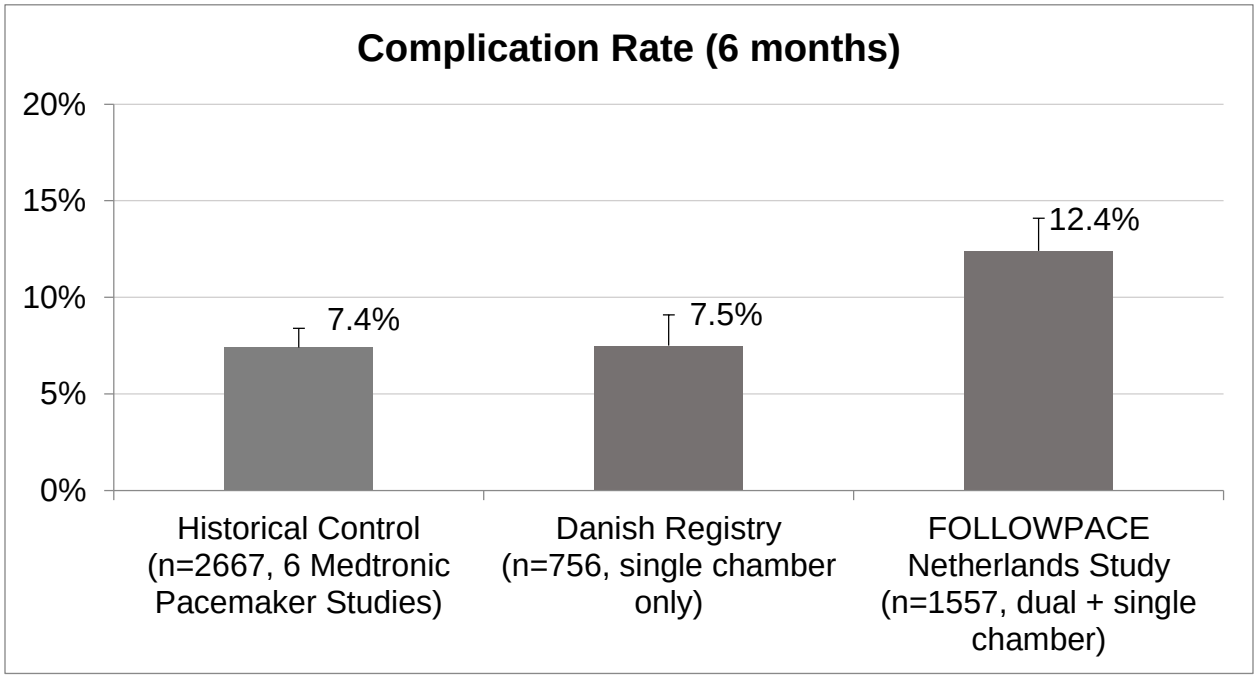
The study was designed to compare Micra performance to traditional pacemaker technology. Traditional pacemakers have complication rates which range from 7.4%-12.4% at 6 months (Figure 6). [9, 10, 11]

[9] Udo EO, Zuithoff NP, van Hemel NM,et al. Incidence and predictors of short and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm 2012; 9: 728-35.

[10] Kirkfeldt RE, Johansen JB, Nohr EA,Jørgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Eur Heart J 2014; 35: 1186-94.

[11] Ritter P, Duray GZ, Zhang S, et al. The rationale and design of the Micra Transcatheter Pacing Study: safety and efficacy of a novel miniaturized pacemaker. Europace 2015; 17: 807-13.

Figure 6: Traditional Pacemaker Safety Profile



3.2 Primary Endpoints

The study had two primary endpoints that were assessed at 6-months post-implant. The primary efficacy endpoint was a combination of low (≤2 V at a pulse width of 0.24 ms) and stable (increase of ≤1.5 V from implant) pacing capture thresholds at the 6-month visit.

The primary safety endpoint was freedom from system or procedure related major complications through 6-months post implant. Major complications were defined as events resulting in at least one of the following: (1) death, (2) permanent loss of device function as a result of mechanical or electrical dysfunction (e.g. deactivation), (3) hospitalization, or (4) prolonged hospitalization by at least 48 hours.

For a comparison of safety performance relative to current traditional pacemaker systems, a patient-level dataset of 2667 *de novo* dual-chamber pacemaker patients from 6 trials completed between 2000-2012 was assembled as a pre-defined historic control group. In this dataset, all events related to the right atrial lead were excluded to approximate a single chamber dataset.[12] The historical control performance was similar to single chamber performance described in the literature (Figure 6).

The study was considered successful when the primary safety and efficacy objectives were met:

[12] Ritter P, Duray GZ, Zhang S, et al. The rationale and design of the Micra Transcatheter Pacing Study: safety and efficacy of a novel miniaturized pacemaker. Europace 2015; 17: 807-13.

Primary Safety Objective: The primary safety objective was considered met if the freedom from major complications related to the Micra system or procedure at 6-months is significantly greater than 83% (i.e. the lower boundary of the confidence interval must exceed 83%).

Primary Efficacy Objective: The primary efficacy objective was considered met if the percentage of patients meeting the primary efficacy end point is significantly greater than 80% (i.e. the lower boundary of the confidence interval must exceed 80%).

The study protocol allowed the primary objectives to be analyzed once 300 patients completed the 6-month visit. The study also features a long-term safety objective that will be evaluated after all implanted patients have the opportunity to complete the 12 month follow-up visit.

3.3 Study Results

The clinical trial experience and study results from the Micra transcatheter pacing study have been described (see Appendix A: Reynolds D, Duray GZ, Omar R, et al. A leadless intracardiac transcatheter pacing system. N Engl J Med. DOI: 10.1056/NEJMoa1511643). The patient flow diagram is provided in the NEJM supplement, see Figure S3.

3.3.1 Enrollment and Baseline Data

The first enrollment was in December 2013. Enrollment was completed in May 2015 with 744 patients from 56 centers in 19 countries from North America, Europe, Asia, Australia, and Africa. Nineteen patients exited before implant attempt due to withdrawal of consent (n=11) or eligibility criteria not being met (n=8). A total of 725 patients underwent an implant attempt. Study follow-up remains ongoing to allow evaluation of the study's long-term safety objective described above. The primary indications among the 725 patients undergoing attempted Micra implantation were bradycardia associated with persistent or permanent atrial tachyarrhythmia (64.0%), sinus-node dysfunction (17.5%), atrioventricular block (14.8%), and other reasons (3.7%). The reasons for the selection of VVI pacing included indications associated with atrial tachyarrhythmia (65.0%), an expectation that pacing would not be frequent (29.7%), the patient's advanced age (18.2%), and patient preference for new technology (12.3%).

Of the 725 attempted implants, 719 patients (99.2%) were successfully implanted by 94 operators and were followed for an average of 4 months, ranging from implant to 14 months. At the time of the analysis, 301 patients had completed the 6-month study visit. Key baseline and medical history information for the 725 patients with an implant attempt are shown in Table 3. Of note, the Micra study cohort reflects a very broad exposure across numerous countries and ethnicities, with a wide variety of implanted patients:

- average weight 79 kg (range: 37 – 155 kg)
- average height 169 cm (range: 134 – 203 cm)
- average BMI 27.6 (range: 14 – 57)
- average age 76 years (range: 19 – 94)

Table 3: Baseline Characteristics of the Study Patients

Subject Characteristics	Patients with Attempted Implant (N = 725)
Age (years)	
Mean ± Standard Deviation	75.9 ± 10.9
Minimum – Maximum	19.0 - 94.0
Number of Subjects With Measure Available (N,%)	725 (100.0%)
Sex n(%)	
Male	426 (58.8%)
Female	299 (41.2%)
LVEF (%)	
Mean ± Standard Deviation	58.8 ± 8.8
Minimum – Maximum	25.0 - 91.0
Number of Subjects With Measure Available (N,%)	613 (84.6%)
Co-morbidities n(%)	
Diabetes	207 (28.6%)
COPD	90 (12.4%)
Renal Dysfunction	145 (20.0%)
LBBB	98 (13.5%)
Vascular Disease	53 (7.3%)
CAD	203 (28.0%)
AF	526 (72.6%)
CHF	123 (17.0%)
Hypertension	570 (78.6%)
Valvular Disease	306 (42.2%)

Abbreviations: LVEF: Left Ventricular Ejection Fraction; COPD: Chronic Obstructive Pulmonary Disease; LBBB: Left Bundle Branch Block; CAD: Coronary Artery Disease; AF: Atrial Fibrillation; CHF: Congestive Heart Failure

Compared to the historical control, Micra subjects were older and had significantly more co-morbidities (diabetes, COPD, renal dysfunction, etc.), see Table 4.

Table 4: Comparison of Demographics and Key Medical History Between Micra Subjects and Historical Control Subjects

Subject Characteristics	Patients with Attempted Implant (N = 725)	Historical Control (N = 2667)	P-value[1]
Age (years)			
Mean ± Standard Deviation	75.9 ± 10.9	71.1 ± 12.1	<0.001
Minimum – Maximum	19.0 - 94.0	9.0 - 99.9	
Number of Subjects With Measure Available (N,%)	725 (100.0%)	2667 (100.0%)	
Sex n(%)			
Male	426 (58.8%)	1469 (55.1%)	0.08
Female	299 (41.2%)	1198 (44.9%)	
LVEF (%)			
Mean ± Standard Deviation	58.8 ± 8.8	58.1 ± 10.0	0.18
Minimum – Maximum	25.0 - 91.0	15.0 - 86.0	
Number of Subjects With Measure Available (N,%)	613 (84.6%)	804 (30.1%)	
Diabetes n(%)	207 (28.6%)	395 (21.9%)	<0.001
Number of Subjects With Measure Available	725 (100.0%)	1805 (67.7%)	
COPD n(%)	90 (12.4%)	53 (7.2%)	0.001
Number of Subjects With Measure Available	725 (100.0%)	735 (27.6%)	
Renal Dysfunction n(%)	145 (20.0%)	26 (9.8%)	<0.001
Number of Subjects With Measure Available	725 (100.0%)	266 (10.0%)	
LBBB n(%)	98 (13.5%)	191 (12.0%)	0.31
Number of Subjects With Measure Available	725 (100.0%)	1597 (59.9%)	
Vascular Disease n(%)	53 (7.3%)	170 (10.1%)	0.032
Number of Subjects With Measure Available	725 (100.0%)	1689 (63.3%)	
Other Co-morbidities n(%)			
CAD	203 (28.0%)	1025 (38.4%)	<0.001
AF	526 (72.6%)	977 (36.6%)	<0.001
CHF	123 (17.0%)	400 (15.0%)	0.20
Hypertension	570 (78.6%)	1792 (67.2%)	<0.001
Valvular Disease	306 (42.2%)	512 (19.2%)	<0.001

[1] *P-value from from T-test (continuous variables) or Fisher's Exact test (categorical variables).*
Abbreviations: LVEF: Left Ventricular Ejection Fraction; COPD: Chronic Obstructive Pulmonary Disease; LBBB: Left Bundle Branch Block; CAD: Coronary Artery Disease; AF: Atrial Fibrillation; CHF: Congestive Heart Failure

3.3.2 Primary Safety Objective

The study's primary safety objective was met:

- Safety: 96.0% freedom from major complications related to the Micra system or procedure through 6-months (95% CI: 93.9% to 97.3%; P<0.0001 versus a pre-specified performance goal of 83%), with 28 major complications in 25 of 725 patients with implant attempts. When rates of major complications were compared between Micra and the historical control group in a post-hoc analysis against the pre-defined control group, Micra patients experienced significantly fewer major complications through 6-months post-implant (hazard ratio: 0.49; 95% CI: 0.33 to 0.75; P=0.001) despite Micra patients being older with more co-morbidities.

Among the 725 patients with a Micra implant attempt, 25 patients experienced a total of 28 major complications related to the Micra system or procedure (Table 5). There were no device dislodgements (i.e. device emboli).

Figure 7 shows that the Kaplan-Meier estimate for the 6-month freedom from major complications related to the system or procedure was 96% (95% CI: 93.9% - 97.3%) which greatly exceeded the performance goal of 83% (P<0.001).

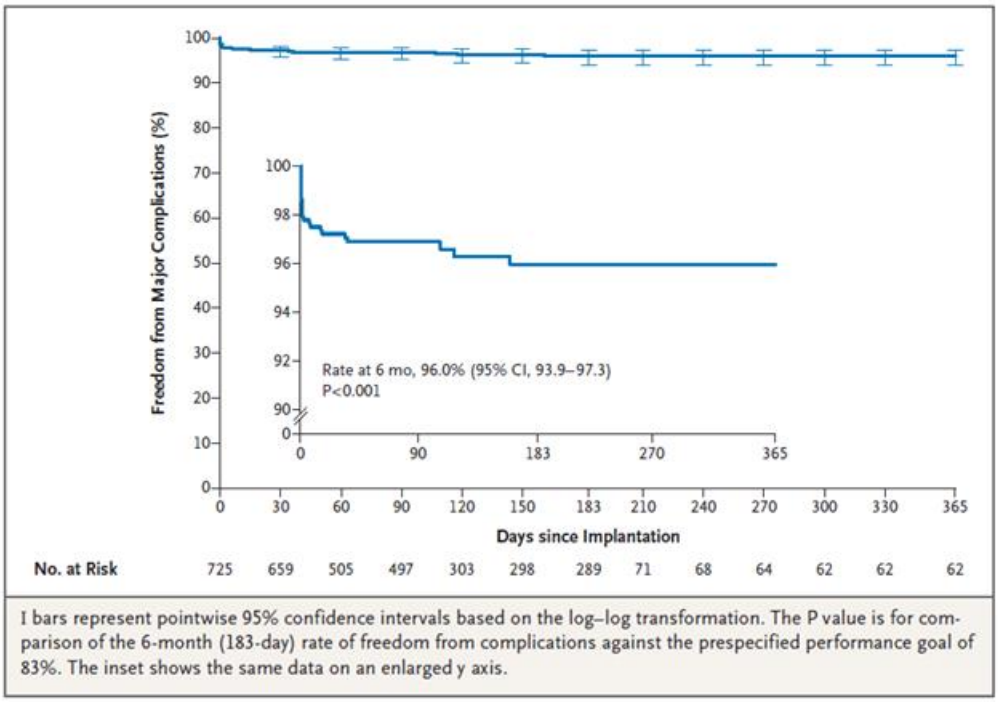
Table 5: Major Complications in 725 Patients with a Micra Implant Attempt[13]

Adverse Event	No. of Events Associated with Major Complication Criterion*						No. of Patients (%)†
	Death	Loss of Device Function	Hospitalization	Prolonged Hospitalization‡	System Revision	Total Events	
Embolism and thrombosis	0	0	1	1	0	2	2 (0.3)
Deep vein thrombosis	0	0	0	1	0	1	1 (0.1)
Pulmonary thromboembolism	0	0	1	0	0	1	1 (0.1)
Events at groin puncture site: atrioventricular fistula or pseudoaneurysm	0	0	2	3	0	5	5 (0.7)
Traumatic cardiac injury: cardiac perforation or effusion	0	0	3	9	0	11	11 (1.6)
Pacing issues: elevated thresholds	0	1	2	1	2	2	2 (0.3)
Other events	1	0	5	4	1	8	8 (1.7)
Acute myocardial infarction	0	0	0	1	0	1	1 (0.1)
Cardiac failure	0	0	3	2	0	3	3 (0.9)
Metabolic acidosis	1	0	0	0	0	1	1 (0.1)
Pacemaker syndrome	0	0	1	0	1	1	1 (0.2)
Presyncope	0	0	0	1	0	1	1 (0.1)
Syncope	0	0	1	0	0	1	1 (0.1)
Total	1	1	13	18	3	28	25 (4.0)

* A single event could meet more than one major-complication criterion. The total numbers and 6-month Kaplan–Meier percentages of patients with adverse events fulfilling each criterion were as follows: death, 1 patient (0.1%); loss of device function, 1 (0.1%); hospitalization, 12 (2.3%); prolonged hospitalization, 16 (2.6%); and system revision, 3 (0.4%). In total, 25 patients (4.0%) had major complications.
† The percentages are 6-month Kaplan–Meier estimates.
‡ Complications resulting in prolonged hospitalization of 48 hours or longer were associated with the hospitalization for the implantation procedure or a hospital admission for another reason.

[13] Reynolds D, Duray GZ, Omar R, et al. A leadless intracardiac transcatheter pacing system. N Engl J Med. DOI: 10.1056/NEJMoa1511643

Figure 7: Freedom from Major Complications Related to the Micra System or Procedure[14]



I bars represent pointwise 95% confidence intervals based on the log–log transformation. The P value is for comparison of the 6-month (183-day) rate of freedom from complications against the prespecified performance goal of 83%. The inset shows the same data on an enlarged y axis.

3.3.3 Primary Efficacy Objective

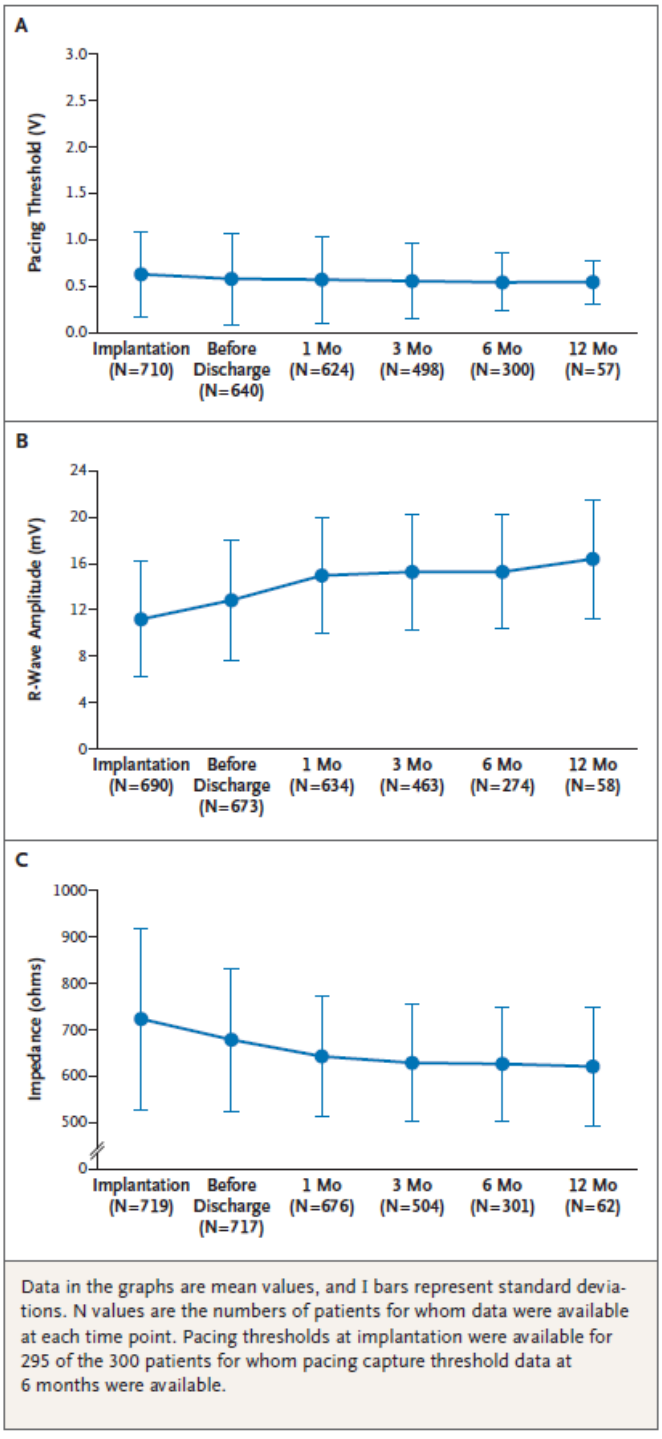
The study's primary efficacy objective was met:

- Efficacy: 98.3% of patients with low and stable pacing thresholds through 6-months (95% CI, 96.1% to 99.5%; P<0.0001 versus a pre-specified performance goal of 80%) in 292 of 297 patients with complete data available for analysis.

Of the 297 patients who were included in the primary analysis, 292 (98.3%; 95% CI: 96.1% - 99.5%) met the primary end point at 6-months demonstrating low (≤2 V at 6-months at 0.24 ms) and stable (increase from implant ≤1.5 V) pacing capture threshold. This greatly exceeded the pre-specified performance goal of 80% (P<0.001). Among the patients with a successful Micra implant and for whom follow-up data were available, the pacing capture threshold tended to decrease shortly after implant and remain stable thereafter; the mean pacing capture threshold was 0.63 V at implant and 0.54 V at 6-months at a pulse duration of 0.24 ms (Figure 8A). The mean R-wave amplitude was 11.2 mV at implant and 15.3 mV at 6-months (Figure 8B) and mean pacing impedance was 724 ohms at implant and decreased to 627 ohms at the 6-month visit (Figure 8C).

[14] Reynolds D, Duray GZ, Omar R, et al. A leadless intracardiac transcatheter pacing system. N Engl J Med. DOI: 10.1056/NEJMoa1511643

Figure 8: Micra Electrical Parameters by Study Visit[15]

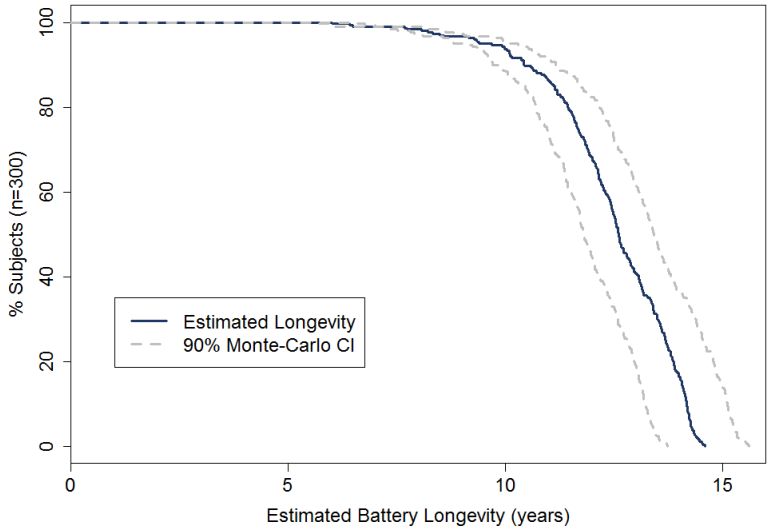


Data in the graphs are mean values, and I bars represent standard deviations. N values are the numbers of patients for whom data were available at each time point. Pacing thresholds at implantation were available for 295 of the 300 patients for whom pacing capture threshold data at 6 months were available.

[15] Reynolds D, Duray GZ, Omar R, et al. A leadless intracardiac transcatheter pacing system. N Engl J Med. DOI: 10.1056/NEJMoa1511643

Based on actual device use conditions through 6-months for patients completing the 6-month visit, the mean projected battery longevity is 12.5 years (range: 6 – 14.6 years, with 94% having an estimated longevity >10 years, Figure 9).

Figure 9: Projected Battery Longevity Based on Device Use Conditions Through 6-months



Note: Based on pacing capture threshold (median 0.5V), percent pacing (median 49%), impedance (median 573Ω), actual programmed pulse width (nominal 0.24 ms), and actual programmed safety margin (nominal 0.5V) through the 6-month visit. One of the 301 patients completing 6-month visit did not have device interrogation data available for analysis.

3.3.4 System / Procedure Related Deaths

There were no deaths related to the device. There was one death (0.1%) that was adjudicated as related to the procedure. A 77 year old female patient had a concomitant procedure (AV nodal ablation) performed during the Micra implantation, which resulted in prolonged procedure duration. Of note, the patient had end stage renal disease and was scheduled for dialysis that day (it had been 3 days since the last dialysis session). No arterial blood gases were monitored during the procedure and no autopsy was conducted; however, the Investigator felt the most likely cause of death was metabolic acidosis due to prolonged procedure time with underlying end stage renal disease. There was no perforation as confirmed by echo, but the patient became hypotensive post procedure. The 0.1% rate of death associated with pacemaker implantation compares similarly to

traditional pacemakers, where related deaths are reported to range from 0.01%[16], 0.1%[17], 0.3%[18] to 0.9% in patients aged >75 years[19].

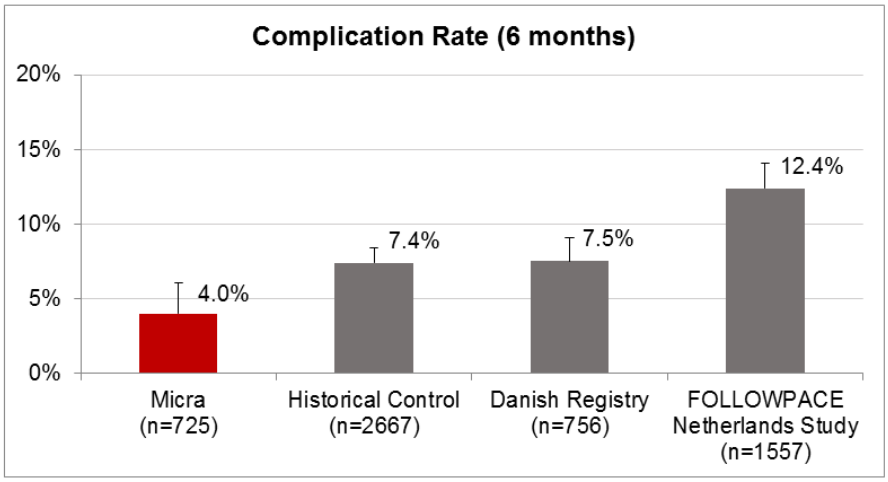
3.3.5 Dislodgements / Device Emboli

There were zero (0) dislodgements (i.e. device emboli) observed.

3.4 Safety Comparison to Traditional Pacemakers

As previously mentioned, the safety profile of traditional pacing systems was used to benchmark the performance of the Micra system. Figure 10 displays the safety profile of the Micra system relative to the safety profile of traditional transvenous systems obtained from six previous Medtronic studies and two large population based registries reported in the literature. The Micra 4% rate of major complications compares favorably to the traditional technology which ranges from 7%-12% (Figure 10).

Figure 10: Complication Rates (6 months)[20, 21, 22]



[16] Kirkfeldt RE, Johansen JB, Nohr EA, Moller M, Arnsbo P, Nielsen JC. Risk factors for lead complications in cardiac pacing: a population-based cohort study of 28,860 Danish patients. Heart Rhythm. 2011;8(10):1622–8. doi:10.1016/j.hrthm.2011.04.014.

[17] Sweeney MO, Bank AJ, Nsah E, et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *N Engl J Med*. 2007;357(10):1000–8. doi:10.1056/NEJMoa071880.

[18] Lee MA, Weachter R, Pollak S, et al. The effect of atrial pacing therapies on atrial tachyarrhythmia burden and frequency: results of a randomized trial in patients with bradycardia and atrial tachyarrhythmias. J Am Coll Cardiol. 2003;41(11):1926–32.

[19] Armaganijan LV, Toff WD, Healey JS, et al. Are Elderly Patients at Increased Risk of Complications Following Pacemaker Implantation? A Meta-Analysis of Randomized Trials. Pace 2012;35:131-34.

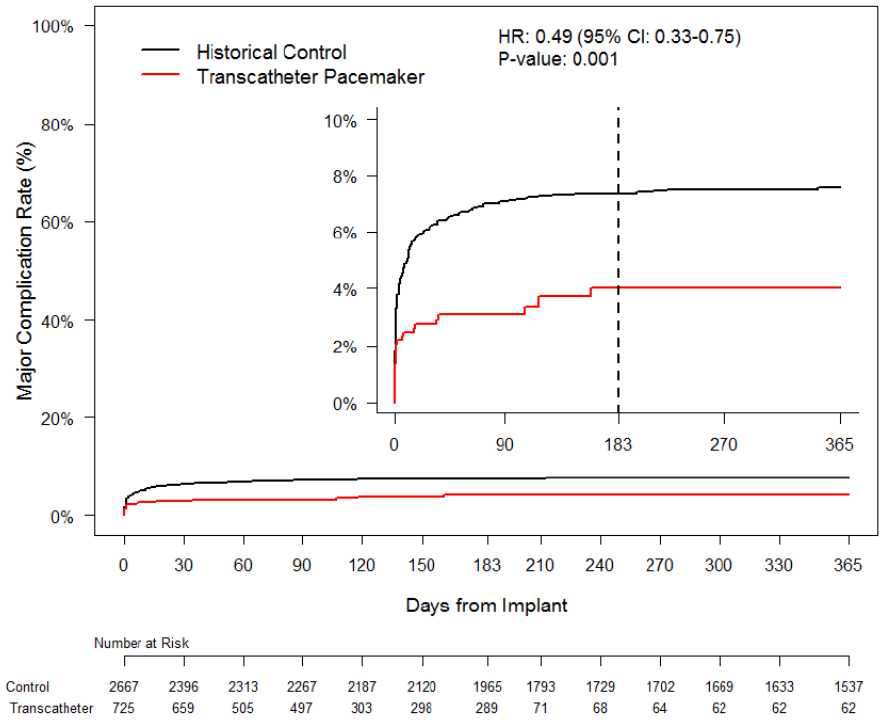
[20] Udo EO, Zuithoff NP, van Hemel NM,et al. Incidence and predictors of short and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm 2012; 9: 728-35.

[21] Kirkfeldt RE, Johansen JB, Nohr EA,Jørgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Eur Heart J 2014; 35: 1186-94.

[22] Ritter P, Duray GZ, Zhang S, et al. The rationale and design of the Micra Transcatheter Pacing Study: safety and efficacy of a novel miniaturized pacemaker. Europace 2015; 17: 807-13.

The rate of major complications at 6-months for the Micra system was also lower than the 6-month major complication rate observed in the historical control cohort of 2667 patients from the six previous Medtronic pacing studies where the same definitions and evaluation time point (6-months post-procedure) were employed. Specifically, the risk of major complications was reduced by 51% through 6-months post-implant in patients with Micra compared to the historical control (P=0.001, Figure 11). A similar result was obtained in the analysis with adjustment for differences in the patient population, in which the propensity-matched control subgroup was used (hazard ratio, 0.46; 95% CI, 0.28 to 0.74).

Figure 11: Major Complication Rate (Micra vs Historical Control)



Micra was able to reduce major complications primarily through elimination of device pocket and lead-related complications, see Figure 12.

Figure 12: Elimination of Traditional Pacemaker Complications

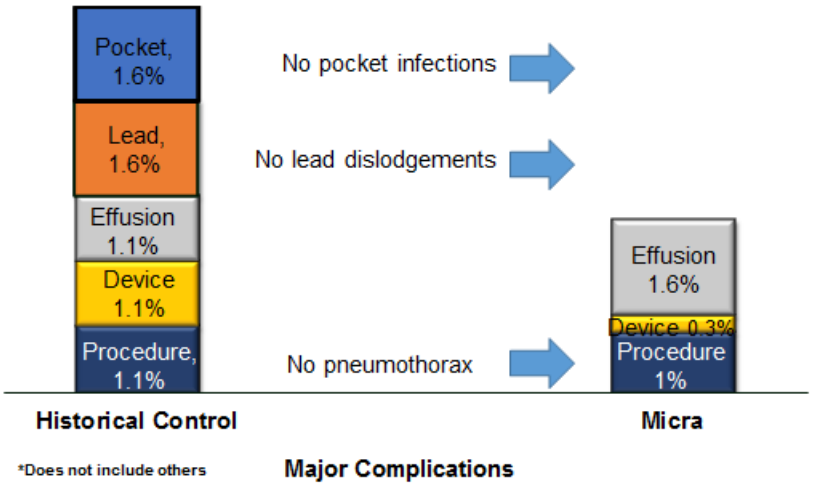
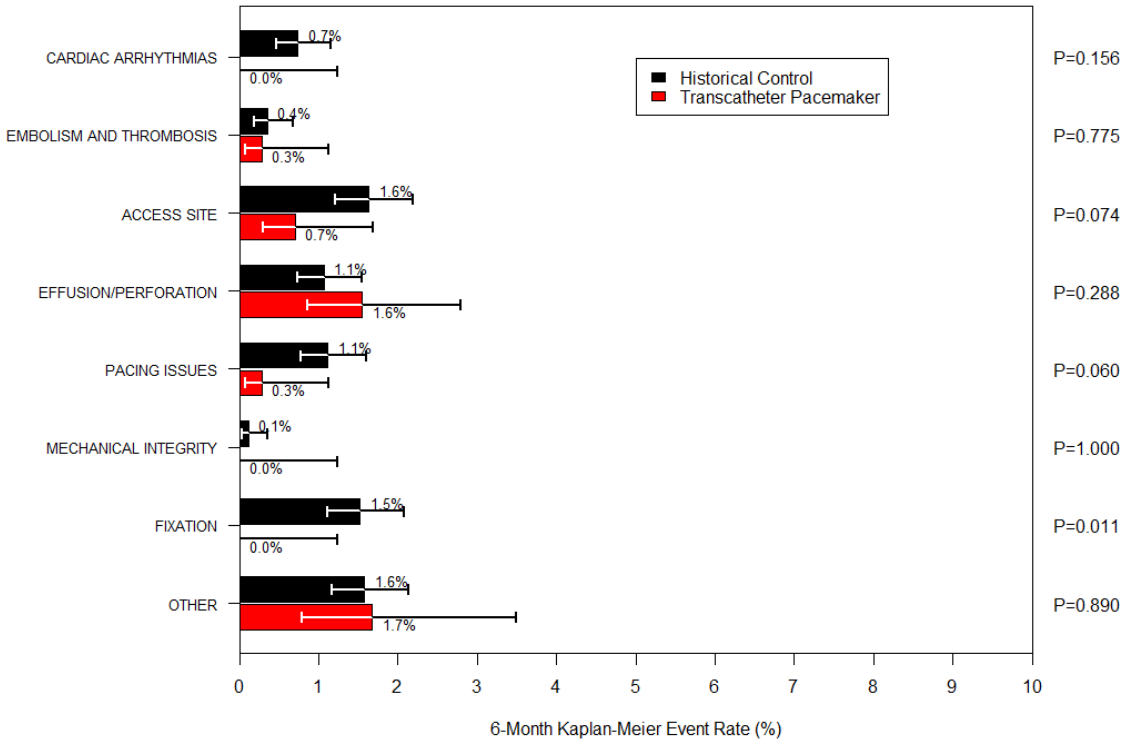


Figure 13 displays the Kaplan-Meier estimates at 6-months post-implant of each category of major complication for Micra (red bars) and the historical control dataset (black bars). Micra appeared the same or lower than traditional technology in nearly all categories of major complications.

Figure 13: Categories of Major Complications: Historical Control vs. Micra



There were two categories where Micra experienced significantly lower complications than traditional pacing:

- Fixation (Lead Dislodgements): Micra eliminated the lead dislodgements associated with traditional systems.

- Access (Groin) Site: Micra had few events at the groin puncture site compared to numerous pocket site complications associated with traditional systems including pneumothoraxes and pocket hematomas. There were no infections and no erosions.

3.4.1 Healthcare Utilization

Healthcare utilization was decreased as there were 54% fewer hospitalizations and 87% fewer system revisions with Micra compared to traditional transvenous pacemakers (Table 6).

Table 6: Healthcare Utilization

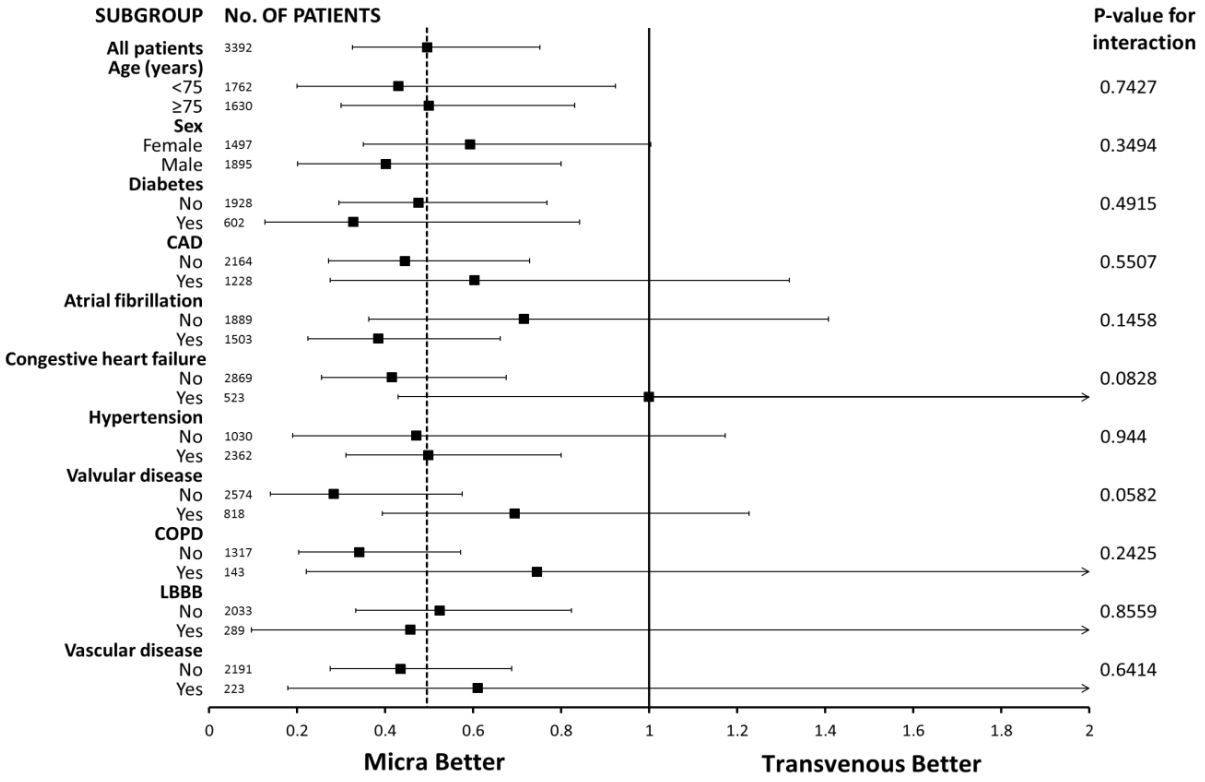
6-Month Kaplan-Meier Estimates	Micra (n=725)	Historical Control (n=2667)	Relative Risk Reduction
Total Major Complications	4.0%	7.4%	51%
Death	0.1%	0%	NS
New Hospitalization	2.3%	3.9%	54%
Prolonged Hospitalization	2.6%	2.4%	NS
System Revision	0.4%	3.5%	87%
Loss of device function	0.1%	0%	NS

Not mutually exclusive as a single event may meet more than one major complication criteria.
NS = Not significant

3.4.2 Subgroups

There are no subgroups where Micra shows a higher risk than traditional pacemakers. Micra appeared to reduce the risk of major complication through 6-months compared to transvenous systems in nearly all subgroups of patients as shown in Figure 14. This forest plot evaluates the risk for major complication through 6-months in the 725 Micra patients (on the left) and 2667 patients from the 6 previous Medtronic transvenous pacemaker studies (on the right). Micra provided a consistently lower risk of major complication through 6-months compared to traditional transvenous systems.

Figure 14: Major Complications Across Subgroups: Micra vs Traditional Pacemakers



3.5 Perforation/ Cardiac Effusion

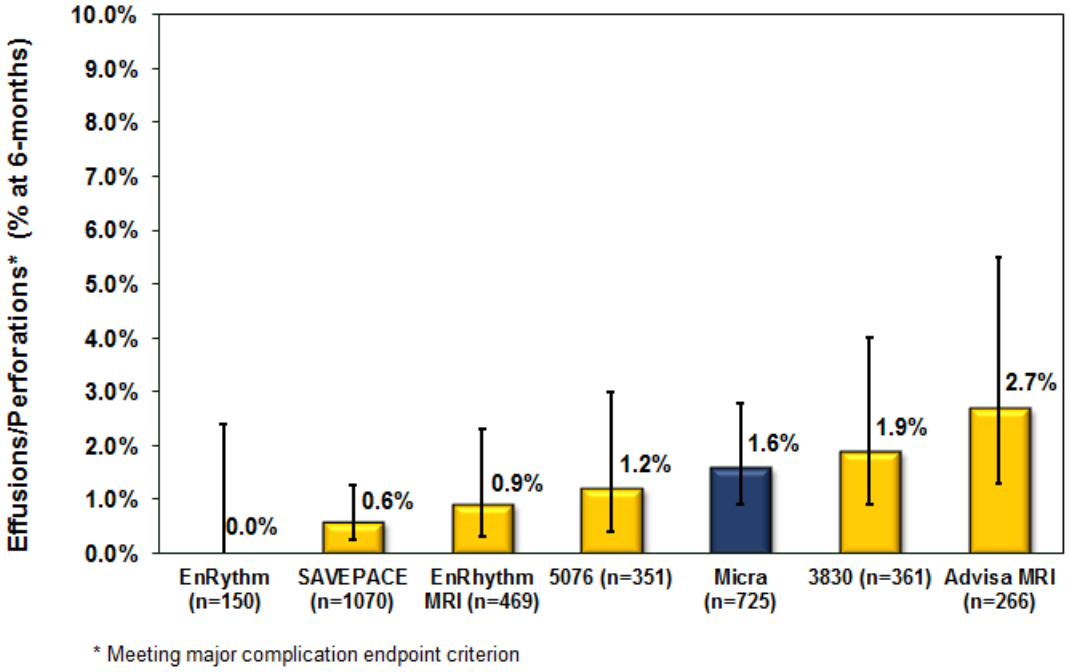
There were 13 total cardiac effusion/ perforation events related to Micra. None of these events resulted in death and 9 of the 13 patients were successfully implanted with Micra. Eleven of the 13 events were adjudicated as major complications; each of these adjudications met major complication criteria due to the event resulting in a hospitalization (3) or prolonged hospitalization (9). One event resulted in both a new hospitalization and a prolonged hospitalization. Two of the 13 events were adjudicated as minor complications/observations.

The rate of Micra effusion / perforation resulting in major complication was in-line with the rates observed within the individual six Medtronic studies of currently approved pacing systems in the historical control as shown in

Figure 15. This is also similar to the literature, where 1.2% of 4280 Mayo Clinic patients implanted with permanent pacemakers developed significant effusion and symptoms consistent with perforation.[23]

[23] Mahapatra S, Bybee KA, Bunch TJ, Espinosa RE, Sinak LJ, McGoon MD, et al. Incidence and predictors of cardiac perforation after permanent pacemaker placement. Heart Rhythm 2005;2:907–11.

Figure 15: Effusions/ Perforations Compared to Individual Studies in Historical Control



3.5.1 Patient Risk Factors for Effusion /Perforation

The literature[24, 25, 26] reports the risk for cardiac effusion/ perforation with traditional technology is increased in certain subgroups, such as:

- Elderly age (>75 years)
- Chronic lung disease
- Female sex
- Prior percutaneous coronary artery intervention
- Low BMI (<25)

As shown in Table 7, these are the same risk factors observed in Micra patients who experienced cardiac effusion / perforation. Table 7 shows that the 13 patients with a Micra system or procedure related cardiac effusion / perforation (regardless of severity) tended to be older, have lower BMI, be female, have a history of myocardial infarction, and have a history of chronic lung disease including COPD. The Micra patients who experienced cardiac effusion/perforation each had 1 or more of these risk factors and most had several risk factors (Table 8). The patients in the Micra study were older and more likely to have COPD compared to the historical control population.

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[24] Udo EO, Zuithoff NP, van Hemel NM,et al. Incidence and predictors of short and long-term complications in pacemaker therapy: the FOLLOWPACE study. Heart Rhythm 2012; 9: 728-35.

[25] Hsu et al. Cardiac Perforation From Implantable Cardioverter-Defibrillator Lead Placement: Insights From the National Cardiovascular Data Registry. Circ Cardiovasc Qual Outcomes. 2013;6:582-590

[26] Mahapatra et al. Incidence and predictors of cardiac perforation after permanent pacemaker placement. Heart Rhythm 2005;2:907-11

Table 7: Characteristics of Micra Patients With and Without Cardiac Effusion/Perforation

Patient Characteristics	No Cardiac Effusion (n = 712)	Yes Cardiac Effusion (n = 13)	p-value
Age (years)			
Mean ± Standard Deviation	75.8 ± 11.0	81.7 ± 8.6	0.053
Median	78.0	85.0	
Minimum - Maximum	19.0 - 94.0	64.0 - 91.0	
BMI			
Mean ± Standard Deviation	27.6 ± 5.3	24.5 ± 4.0	0.032
Median	26.8	24.8	
Minimum - Maximum	14.2 - 56.9	18.3 - 30.9	
Sex			
Male n (%)	422 (59.3%)	4 (30.8%)	0.048
Female n (%)	290 (40.7%)	9 (69.2%)	
Cardiovascular Disease History n (%)			
Cardiomyopathy	76 (10.7%)	1 (7.7%)	1.00
Congestive heart failure	119 (16.7%)	4 (30.8%)	0.25
Coronary artery disease	199 (27.9%)	4 (30.8%)	0.76
Hypertension	561 (78.8%)	9 (69.2%)	0.49
Myocardial infarction	72 (10.1%)	4 (30.8%)	0.038
Pulmonary hypertension	77 (10.8%)	3 (23.1%)	0.16
Tricuspid valve dysfunction	176 (24.7%)	6 (46.2%)	0.10
Coronary artery intervention	108 (15.2%)	4 (30.8%)	0.13
Other Comorbidities n (%)			
COPD	85 (11.9%)	5 (38.5%)	0.015
Chronic lung disease	203 (28.5%)	8 (61.5%)	0.025
Diabetes	203 (28.5%)	4 (30.8%)	1.00
Renal dysfunction	143 (20.1%)	2 (15.4%)	1.00

Patient details for each of the events are outlined in the table below.

Table 8: Detailed Listing of Cardiac Effusions / Perforations

Age/ Sex/	BMI	# Repositions	# Risk Factors[1]	Final Micra Location	# for Implanter	Pericardio-centesis?	Surgical Repair?
Major Complications (n = 11)							
74/F	27.9	3	2	NA; traditional	21	Yes	Yes
91/F	20.7	2	3	NA; traditional	19	Yes	Yes
84/F	22.8	0	5	NA; traditional	10	Yes	No
88/M	23.5	1	4	Apex	4	Yes	No
83/F	24.8	0	4	Apex	28	Yes	No
85/F	25.2	0	3	Apex	4	Yes	No
88/M	26.9	2	1	NA; traditional	1	Yes	No
90/F	30.9	17	3	Apex	5	Yes	No
64/F	18.4	0	2	Apex	30	No	No
67/F	28.6	1	2	Septum	3	No	No
85/M	22.1	2	3	Apex	11	No	No
Minor Complication/Observation (n = 2)							
86/M	18.3	7	4	Mid-septum	2	Yes	No
77/F	28.0	0	2	Apex	5	No	No

[1]*Risk factors: female, age >75 years, chronic lung disease, prior percutaneous artery intervention, and BMI <25.*

Thus, the increased incidence of effusion / perforation with Micra is a function of patient co-morbidity, suggesting these patients would be at high risk regardless of device type. Furthermore, when comparing to the overall safety profile to the transvenous pacemaker cohort, Micra patients consistently faired favorably, and no subgroup showed a higher risk of major complication (see Figure 14).

Perforation / Effusion Major Complication Criterion Comparison

In an effort to assess severity of events, this table summarizes the criteria resulting in major complication designation for all cardiac effusions/perforations.

Table 9: Effusion Major Complication Criterion Comparison

	Micra N=13 cardiac effusions/perforations (from 725 implant attempts)	**Historical Control N=50 cardiac effusions perforations (from 2667 implant attempts)**
Not a major complication	15% (N=2)	36% (N=18)
Death	0% (N=0)	0% (N=0)
Hospitalization	69% (N=9)	34% (N=17)
Prolonged Hospitalization (≥48 hours)	23% (N=3)	18% (N=9)
System revision	0% (N=0)	22% (N=11)

*not mutually exclusive as an event could contribute to more than one category

Intervention Comparison

This table summarizes the intervention in Micra versus the historical control for all cardiac effusions/perforations regardless of event severity.

Table 10: Intervention Comparison (Effusions in Micra versus Historical Control)

	Micra N=13 cardiac effusions/perforations (from 725 implant attempts)	**Historical Control N=50 cardiac effusions/perforations (from 2667 implant attempts)**
Surgical Repair *(with or without pericardiocentesis)*	15% (N=2)	4% (N=2)
Pericardiocentesis	54% (N=7)	20% (N=10) *(with or without lead revision)*
Lead Revision	0% (N=0)	22% (N=11)
No intervention	31% (N=4)	54% (N=27)
Death	0% (N=0)	0% (N=0)

3.6 Total Experience, Including Commercial Implants

The Micra total experience to date includes approximately 1300 patients:

- IDE trial (725 implants)- 1st enrollment December 2013
- U.S. Continued Access study (~75 implants)- 1st enrollment June 2015
- Commercial Experience Outside of the U.S. (~500)- 1st implant June 2015

The IDE study represents the bulk of the Micra experience to date, as the U.S. Continued Access study and the commercial experience have only recently been initiated. The clinical experience obtained outside the IDE study is in line with the findings reported within the IDE study.

3.7 Lessons Learned from Worldwide Experience

Micra was successfully implanted in the IDE study across a wide variety of patient populations, implanted by 94 physicians representing 56 centers and 19 countries.

Throughout the study, as best practices were determined, they were shared with all of the Micra implanters and Medtronic field support. Table 11 identifies the most significant lessons learned and how these were addressed within the training program and through communications with investigators.

Table 11: Lessons Learned During Clinical Study and Subsequent Training Updates

Clinical Observations	Lessons Observed	Training Updates
1. Potential for sub-optimal rate response with various postures observed with holter analysis	• Sub-optimal Rate Response	• Evaluate for postural sensitivity by conducting a posture test and hall-walk prior to hospital discharge or prior to initiating VVIR mode
2. Cases reported of complete or intermittent AV block during procedure	• Complete AV Block	• Reminder to implanters to recognize risk of complete heart block in patients with LBBB and consider whether insertion of a temporary pacing wire before Micra implantation is warranted
3. Cases reported of effusion/perforation	• Minimize risk of cardiac perforation/effusion	• To ensure good visualization of location, consider using a small amount of contrast • Reminder to implanters to utilize multiple fluoroscopic views
4. Cases where repositioning attempts exceeded 10 which prolonged the procedure time	• Prolonged Procedure Time	• Consider using heparin IV bolus to avoid clot formation resulting in prolonged procedure time • Steering committee recommended implanters limit their repositioning attempts to 10 or less. The training for repositioning attempts is documented in the implant procedure tip card as follows: • >3-5 deployments with unacceptable electricals: o Ensure adequate tip pressure o Consider contrast injection to visualize device cup against endocardial wall o Remove delivery system tool and check for clots o Consider an R-wave as low as 2mV o Consider accepting a higher pacing threshold (up to 3V or more) depending on patient pacing/longevity needs (consult table on projected longevity) • >10 deployments • Consider abandonment of system and reverting to traditional approach
5. Cases of AV fistula and pseudoaneurysm	• Vascular Injury	• Reminder to implanters to consider the use of ultra sound for venous access
6. Cases of Difficult Tine Visualization	• Difficult Tine Visualization	• Assess in multiple fluoroscopic views • Zoom in on tines fluoroscopically (magnified cine) • Record cine frame by frame (loop at ≥15 frames per second) • Assess fixation by all available sources (e.g. fluoro visualization, EGM waveform, initial electrical measurements)

4. Training Plans

4.1 Introduction

Medtronic has a long history of providing robust training programs to physicians prior to the market release of novel technologies.

Training for Micra will be based on the clinical study training program, which was successful with a high implant success rate (99.2%) and a low major complication rate (4%), regardless of the training venue (e.g. laboratory setting versus local hospital training). Medtronic will continue to offer multiple training approaches while maintaining consistent learning objectives.

The purpose of this training program is to ensure that all Micra implanting physicians receive appropriate preparation on device implantation as well as managing a patient with the device to ensure safe and effective outcomes for Micra recipients.

4.2 Background: Clinical Study Implanter Training Strategy

During the clinical study, positive outcomes were achieved through two different implanter training learning paths:

- A hospital's first implanter was trained in a lab environment training center (Implanter 1)
- A hospital's second implanter was trained locally on site at the hospital and proctored by Implanter 1 (Implanter 2)

This table summarizes the clinical study training methods for Implanter 1 and 2.

Table 12: Clinical Study Implanter Training Pathways

<table>
<tr><th>Implanter Training</th><th>First Case</th><th>Subsequent Implants</th></tr>
<tr><td>Implanter 1:
Venue: Lab environment
1. Didactic Session
2. Hands-On procedural training session (e.g.: implant simulator, cadaver and animal models, videos, Micra demonstration models)</td><td>Implanter 1:
1. Prior to implant, procedure review by Medtronic Micra Technical Expert
2. Medtronic Micra Technical Expert support during implant</td><td rowspan="2">Additional training (as needed)
Medtronic Micra Technical Support (as needed)</td></tr>
<tr><td>Implanter 2:
Venue: Locally on-site (at hospital)
1. Didactic Session
2. Hands-On Session (e.g.: implant simulator, videos, demonstration models)</td><td>Implanter 2:
1. Prior to implant, procedure review by Medtronic Micra Technical Expert
2. Medtronic Micra Technical Expert support during implant
3. Proctoring by Implanter 1</td></tr>
</table>

4.3 Clinical Study Implanter Training Pathway Outcomes

The clinical study data showed both Implanter 1 and Implanter 2 training pathways achieved similar outcomes with acceptable safety profiles.

Implant Success Rate

- Micra had a 99.2% implant success rate. Success rates were similar between Implanter 1 and Implanter 2 (98.6% and 100%).

Major Complication Rate

- There was no significant difference between the major complication rate within 30 days between Implanter 1 and Implanter 2 (OR: 1.62, 95% CI: 0.53 – 4.91).

Procedure Duration

- The median procedure time (introducer in/ introducer out) was 27 minutes for both Implanter 1 and Implanter 2, respectively. The procedure duration was reduced to 22 minutes after physicians had completed their first 10 implants. This is comparable to the 37 minute average procedure time for traditional single chamber implants in the German pacemaker registry[27].

4.4 Proposed Market Release Implanter Training Program and Learning Objectives

The Micra implanter training program is designed to provide a comprehensive, standardized educational path to safeguard patient outcomes for this novel device and procedure. All Micra implanting physicians will be required to complete Micra training. Hospitals will only receive product after a physician has completed training and this completion will be tracked by Medtronic. Once approved to receive shipment, it is the responsibility of the hospital to ensure product is utilized only by trained physicians.

To successfully implant the Micra system, physicians must be able to demonstrate that they can:

- Gain access via the femoral vein
- Navigate the delivery catheter to the right ventricle
- Deliver the device
- Appropriately ensure fixation of device and/or recapture device if necessary
- Free device from delivery system
- Manage device interrogation and patient follow up
- Manage end of device life and subsequent implant considerations

Learning objectives are based on these competencies.

Micra implant training was successful in the clinical study regardless of the training venue. Medtronic will continue to offer a similar approach with a combination of settings (e.g.

[27] Markewitz, A. (2013). [Annual Report 2011 of the German pacemaker and defibrillator register: Section pacemakers and AQUA-Institute for Applied Quality Improvement and Research in Health Care].. *Herzschrittmachertherapie & Elektrophysiologie*, *24*(4), 249-274.

laboratory setting or local hospital training). The market release physician training pathway will consist of four general areas:

Topics covered in each area are noted here:

1. Clinical Pre-Requisite:
   - Gaining access via the femoral vein is not included in the training course. This skill is a clinical pre-requisite and is the responsibility of the hospital to ensure the prerequisite is met.
2. Standardized Pre-Work
   - This pre-work will leverage content from the clinical study training curriculum, including an e-learning which contains a video library of cases, an implant procedure simulation, and interactive testing.
   - Pre-Work topics include:
     - Device technology
     - Delivery system technology
     - Implant procedure
     - Device programming
3. In-Person Training
   - Didactic Session
     - Implant preparation/pre-implant considerations
     - Clinical data review (study results, lessons learned, patient selection and consideration of adverse event risk profile)
   - Troubleshooting Hands-On Session
     - Implant simulator or delivery system and device demonstration model
     - Video case observations (for troubleshooting, peer-sharing, etc.)
4. Implant Support:
   - First Implant: Additional training (as needed, such as topic-specific review, demonstration of device delivery)
   - Subsequent Implants: It will be recommended that all physicians will have a Micra trained Medtronic staff member (called the Micra Technical Expert) present for at least their first 5-10 Micra implants, where hospital policy allows presence of Medtronic personnel within the procedure room.
5. Follow-Up
   - Micra follow-up is managed in a similar fashion to standard single chamber pacemakers and will be incorporated in the standard Medtronic pacemaker training program for follow-up.

4.5 Training Beyond Initial Launch Phase (e.g. Hospital Accreditation Programs)

Longer term, as we have seen with the introduction of other procedures such as Cardiac Resynchronization Therapy, it is expected governing societies will provide guidelines for

training and practices related to transcatheter pacemaker implantation. Hospitals will be responsible for ensuring accredited physicians are implanting and following society recommended guidelines. Medtronic anticipates cooperating fully with such recommendations.

In summary, the Micra implanter training provides a comprehensive education program built on the successful training model from the clinical study with positive clinical results to enable safe patient outcomes.

5. Expected Device Failures Over Time

5.1 Introduction

This section addresses the risk assessment and potential failures as compared to traditional systems.

The conventional single chamber pacemaker risk profile is summarized in Table 13, alongside of the potential risks for the Micra system. Because of the fundamental differences between the systems, Micra inherently eliminates some of the known risks associated with pacemaker systems (e.g. risks associated with access, lead fixation and the use of a pacemaker pocket). For those risks which the two systems share (device-related risks) it is expected that the two systems will have similar levels of risk. There are a few potential new risks, which are noted in italics.

Table 13: Risk Profile of Transvenous Pacemakers and Micra

	Existing Risks: Single Chamber Pacemaker	Potential Risk with Micra TPS
ACCESS	• Pneumothorax • Subclavian vein thrombosis/occlusion	~~• Pneumothorax~~ ~~• Subclavian vein thrombosis/occlusion~~ *NEW: Femoral Vein Complication*
LEAD (FIXATION)	• Lead dislodgement • Loose header connection • Insulation Breach • Lead fracture • Perforation/ effusion • Temporary arrhythmias • Capture/Sense Failure	~~• Lead dislodgement~~ ~~• Loose header connection~~ ~~• Insulation Breach~~ ~~• Lead fracture~~ • Perforation/ effusion • Temporary arrhythmias • Capture/Sense Failure *NEW: Tine Fixation Complication*
POCKET	• Pocket Hematoma • Infection • Twiddler's Syndrome	~~• Pocket Hematoma~~ ~~• Infection~~ ~~• Twiddler's Syndrome~~
DEVICE	• Battery Malfunction • Electrical Component • Early Battery Depletion • Software Malfunction • Mechanical Integrity	• Battery Malfunction • Electrical Component • Early Battery Depletion • Software Malfunction • Mechanical Integrity *NEW: Device Embolization*
END OF SERVICE	• Lead extraction • Device removal from pocket	~~• Lead extraction~~ ~~• Device removal from pocket~~ *NEW: Device Extraction, if attempted*

Risks Eliminated by Micra

The Micra system inherently eliminates risks associated with the lead to device connection, lead body failure modes, the device pocket, subclavian vein access, and lead extraction. These risks represent a significant portion of the risk associated with conventional pacemaker systems, and are eliminated when Micra is implanted.

Risks Similar for Micra

Some conventional pacemaker system device and lead tip risks are also potential risks associated with the Micra TPS system, such as device electrical and battery failure modes. The long-term failure rates associated with conventional pacemakers are very low, as reported in the periodic Medtronic CRHF Product Performance Report, and the failure rates for the Micra TPS device are expected to be equally low.

Potential New Risks for Micra

New aspects of the Micra TPS system compared to conventional pacemaker systems introduce the potential for new risks. Potential new risks include: the femoral access implant procedure, the novel Micra fixation, the potential risk for device embolization, and the potential risk around device extraction.

5.2 Overall Safety Profile

Based on the results of the Micra study, it has been demonstrated the overall complication rate of Micra is significantly reduced as compared to conventional pacemaker systems through the implant procedure, and the first 6 months of device implant as displayed in Figure 10 and Figure 11. Since it is expected the long-term Micra device failure rate will be very low, as it is with conventional pacemakers, it is expected the overall complication rate of Micra will remain significantly reduced as compared to conventional pacemaker systems throughout the device implant life. The Micra Post-Market Study and market release product performance monitoring will be used to continually monitor performance over a longer term.

6. End-of-Service (EOS) and Deactivation

6.1 Introduction

Managing end-of-service (EOS) and deactivation for cardiac implantable electrical devices (CIED) is a common occurrence due to battery depletion, need for alternate therapy (i.e. device upgrade), and system complication (lead dislodgement, infection, etc.). The decision to leave the device in place or to remove all or a portion of it percutaneously or surgically involves multiple factors that include the patient's life expectancy, comorbidities, risk of infection or surgical complication, and the likelihood of encapsulation of the implanted system. Encapsulation of transvenous leads makes extraction difficult and can lead to tearing of the superior vena cava.

Micra was designed to provide options for managing these various EOS and deactivation scenarios. In summary, it is expected:

- The majority of Micra patients will require only one device in their lifetime
- For those patients who need more than one device or need a device upgrade, most implanters will choose to leave Micra *in situ* (program Micra OFF) and implant a second Micra or implant a transvenous system
- When necessary, percutaneous or surgical retrieval is an option

Projections based on the use conditions of the 300 Micra patients followed to 6 months in the global clinical trial suggest an estimated battery longevity of 12.5 years, with 94% lasting more than 10 years; a similar battery longevity to transvenous pacing systems[28,29] and one that would service over 75% of adult patients needing VVIR pacing for their lifetime. The decision to leave Micra in the body requires different considerations compared to conventional CIEDs. Micra has a programmable Device Off mode which has the unique capability to permanently deactivate pacing and sensing (OOO) even in the event of an electrical reset ("power on reset") or upon reaching battery replacement status. Although conventional CIEDs can program therapy off, they are subject to reverting to a therapy On mode upon "power on reset" or reaching EOS; thus inappropriate therapy is a risk when abandoning conventional devices. Micra eliminates this risk as it is the first Medtronic CIED with the Device Off mode feature. Furthermore, device telemetry remains functional and can be differentiated by the programmer from subsequent Micra devices or CIEDs.

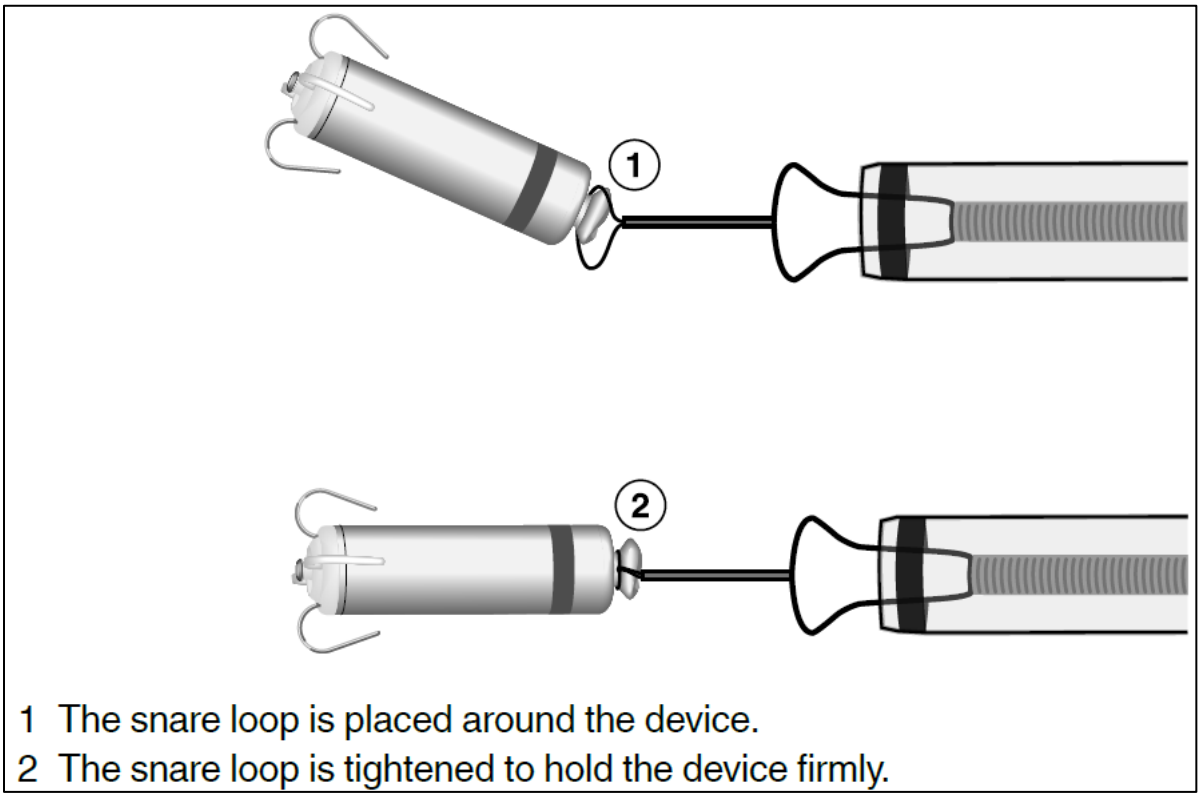
Cardiac devices such as coronary stents and prosthetic valves are designed to remain in the body, and transvenous pacing and defibrillator leads (or portions thereof) are often left in the heart. Concerns of leaving the device *in situ* include inappropriate device-to-device interaction, impairment of valvular or hemodynamic function, and long-term risk of infection. At 0.8 cubic

[28] Hauser RG, Hayes DL, Kallinen LM, et al. Clinical experience with pacemaker pulse generators and transvenous leads: an 8-year prospective multicenter study. Heart Rhythm 2007; 4: 154-60.

[29] Senaratne J, Irwin ME, Senaratne MP. Pacemaker longevity: are we getting what we are promised? Pacing Clin Electrophysiol 2006; 29: 1044-54.

centimeters, a Micra displaces approximately 0.5% of a normal sized right ventricle,[30] similar to the volume occupied in the right ventricle of a 2.8 mm diameter high voltage defibrillator lead (e.g. Medtronic Sprint Quattro), and the 25.9 mm Micra length is less than a third of the distance from the apex to the tricuspid valve.[31] While rate and degree of encapsulation is variable and unknown, complete encapsulation of Micra is expected and likely to provide a protective barrier against device infection. While the most likely approach for managing EOS and deactivation of a chronically implanted Micra will be to program to Device Off and leave in the body, percutaneous retrieval is an alternative. Micra was designed with a retrieval feature at the proximal end to accommodate an off-the-shelf snare which can firmly hold the device for removal (Figure 16).

Figure 16: Micra Device Retrieval Using Percutaneous Loop Snare



6.2 Current experience with Micra System Revisions

In the clinical study, Micra patients experienced 87% fewer system revisions compared to the transvenous pacemaker cohort, driven by the lack of Micra device dislodgements and systemic

[30] Tamborini G1, Marsan NA, Gripari P, Maffessanti F, Brusoni D, Muratori M, Caiani EG, Fiorentini C, Pepi M. Reference values for right ventricular volumes and ejection fraction with real-time three-dimensional echocardiography: evaluation in a large series of normal subjects. J Am Soc Echocardiogr. 2010 Feb;23(2):109-15.

[31] Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography: endorsed by the European Association of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685-713.

infections. Thirteen Micra system revisions have been recorded (ranging from day of implant to 259 days post-implant) from all available data sources (IDE clinical study, U.S. continued access, and commercial patients). The options provided by Micra allowed for the patients' clinical needs to be addressed while maintaining necessary therapy in all 13 cases. See Table 14 for a listing of all Micra system revisions. No adverse events associated with concomitant device placement have been reported.

Table 14: Summary of Micra System Revisions (Clinical Trial + Outside of Trial)

Patient	Data Source	Reason for Revision	Days Post-implant	Micra Removal Attempt	Outcome
1	Commercial	Elevated pacing capture threshold	Same day	Percutaneous	Micra removed. New Micra implanted.
2	Continued access study	Elevated pacing capture threshold	Same day	Percutaneous	Micra removed. Transvenous pacing system implanted 3 days later.
3	Commercial	Recapture of device during procedure (after tether removal)	Same day	Percutaneous	Micra removed. New Micra implanted.
4	IDE study	Elevated pacing capture threshold	17	Percutaneous	Micra removed. New Micra implanted.
5	Commercial	Elevated pacing capture threshold	23	Percutaneous	Micra removed. New Micra implanted.
6	IDE study	Elevated pacing capture threshold	32	None	Micra programmed to Device Off. Transvenous pacing system implanted.
7	IDE study	Pacemaker syndrome	44	None	Micra programmed to VVI 40 bpm. Transvenous BiV pacing system implanted.
8	Commercial	Systemic infection in cancer patient with vegetation noted at Micra electrode area	44	Percutaneous	Micra removed. No further information reported at this time.
9	Commercial	Elevated pacing capture threshold	50	Surgical	Micra removed and repositioned during mitral valve repair.
10	Commercial	Need for BiV therapy	61	Percutaneous	Micra removed. Transvenous BiV system implanted.
11	Continued access study	Need for BiV therapy	102	None	Micra programmed to Device Off. Transvenous BiV system implanted.
12	IDE study	Pacemaker syndrome	229	Percutaneous	Micra unable to be removed, turned to Device Off mode. Transvenous pacing system implanted.
13	IDE study	Need for BiV therapy	259	Percutaneous	Micra device snared but unable to be removed after fluoroscopy malfunction. Abandoned retrieval and turned to Device Off mode. Transvenous BiV system implanted.

Micra was successfully removed percutaneously in 7 of 9 attempts and in all attempts within 6 months post-implant. A new Micra (n = 1) or transvenous pacing system (n = 8) was successfully implanted. The 2 unsuccessful attempts occurred 229 and 259 days post-implant, and 1 was due to fluoroscopy equipment failure. In a pre-clinical study, successful retrieval of Micra at 28 months was achieved in 3 out of 4 ovines using commercially available percutaneous tools and methods. Necropsy analysis of the unsuccessful attempt showed the device was entirely encapsulated.

A final alternative to Micra deactivation is surgical removal. To date, there have been no surgical extraction attempts. However, there is one report of a commercial device that was successfully repositioned surgically during mitral valve repair.

6.3 Information to be Provided to Users on EOS/Deactivation Options (Labeling, Instructions, etc.)

This section addresses what information will be provided to users on EOS/Deactivation options (labeling, instructions, etc.).

The decision to leave the device in place or remove involves multiple factors. Micra was designed to provide options for managing a variety of clinical scenarios including EOS and device deactivation.

Options at End of Service (EOS) are listed below. Note these scenarios could occur at the end of the battery life, or prior to battery depletion if the device is removed from use (e.g. device upgrade, etc.).

- Program Device off
  - implant new Transcatheter Pacemaker
  - implant transvenous system
- Retrieve Device
  - retrieve and implant new Transcatheter Pacemaker
  - retrieve and implant new transvenous system

6.4 Micra Clinical Label and Instructions for Use (IFU):

1. Implanting a new Micra with an existing Micra:
   - Current labeling: Section 5.3 of the IFU provides instruction on how to safely perform the required tasks for implantation of a new Micra device in the presence of an existing Micra device.
2. Retrieving a Micra after tether removal
   - Current labeling: Section 5.4 of the IFU provides instruction on how to safely perform a retrieval of the Micra device using the Micra delivery system and a commercially available snare.
3. Removal of a Micra device
   - Current labeling: Section 2.2 Note: Removal of the Micra device may be difficult because of the development of fibrotic tissue. If removal of the device is required, it is recommended that the removal be performed by a clinician who has expertise in the removal of implanted leads.

- Current labeling: Section 5.4 Warning: Retrieval of the device after it is fully encapsulated may result in injury to the patient's cardiac tissue. If device retrieval is required after it is encapsulated, refer the patient to a medical center that has expertise in the removal of implanted leads or call a Medtronic representative for more information.

4. End of Service Options
   - In addition to the current labeling noted above, Medtronic proposes the following note is added to better describe options for physicians to manage EOS or conditions where the therapy is no longer required.
     - **Proposed Note section 5.4:** Micra is designed to provide options at EOS or for situations where the physician determines the Micra therapy is no longer needed. The Micra design allows for retrieval of the device with commercially available off the shelf tools. However, full encapsulation would likely make it challenging to remove the device and given there is currently no imaging modality that allows for determining level of encapsulation, the Micra design provides the option to program to Device Off mode which permanently disables therapy and allows the device to remain in the body.

7. Draft Panel Question #1 (Clinical Significance of Adverse Events)

7.1 FDA Question: *Please discuss the clinical significance and any concerns you might have for the rate of occurrence of each of the following adverse events observed to occur at implant with leadless pacemaker devices as compared to traditional pacemakers.*
o Perforation
o Pericardial Effusion
o Dislodgement
o Embolization
o Other events. (e.g. stroke, arrhythmia)

7.1.1 Medtronic Response: The overall rate of adverse events with Micra is expected to be the same or lower compared to traditional pacemakers. In the clinical study, Micra patients had significantly fewer major complications than did the historical control of traditional pacemaker patients (hazard ratio, 0.49; 95% CI, 0.33 to 0.75; P = 0.001); see Figure 11: Major Complication Rate (Micra vs Historical Control). A similar result was obtained in the analysis with adjustment for differences in the patient population, in which the propensity-matched control subgroup was used (hazard ratio, 0.46; 95% CI, 0.28 to 0.74).

A comparison of major complications by technology is provided in Table 15 below for the specific events. In summary, the Micra rate is lower for dislodgment, arrhythmias or stroke, and not significantly different for perforation / pericardial effusion. It is important to note the patient population differences. The literature reports risk factors for perforation / effusion with traditional pacemakers includes patients who are: elderly (>75 years), female, small BMI (<25), chronic lung disease, and prior percutaneous coronary artery intervention.[32, 33, 34] Compared to the historical control, Micra subjects were more elderly and had more co-morbidities such as diabetes, COPD, renal dysfunction, etc. (see Table 4). Therefore, the observed effusion / perforation rate with Micra is a function of patient co-morbidity and these patients would be at high risk regardless of device type.

Table 15: Occurrence of Adverse Event Major Complications at 6-months: Micra vs Traditional Pacemakers

	Micra	Traditional	P-Value

[32] Ellenbogen et al. Complications arising after implantation of DDD pacemakers: the MOST experience. Am J Cardiol 2003;92:740-1
[33] Hsu et al. Cardiac Perforation From Implantable Cardioverter-Defibrillator Lead Placement: Insights From the National Cardiovascular Data Registry. Circ Cardiovasc Qual Outcomes. 2013;6:582-590
[34] Mahapatra et al. Incidence and predictors of cardiac perforation after permanent pacemaker placement. Heart Rhythm 2005;2:907-11

		Pacemakers (Historical Control)	
Perforation / Pericardial Effusion	1.6%	1.1%	0.288
Dislodgement	0%	1.5%	0.011
Device Embolization	0%	Not applicable	Not Estimable
Arrhythmias	0%	0.7%	0.156
Stroke (Transient Ischemic Attack)	0%	0.1%	1.000

There were no device dislodgements (i.e. no device emboli) observed during the study. While dislodgement is a risk, this is expected to be greatly reduced from the risk of a lead dislodgement:

- Multiple tines provide redundancy in the holding force: Micra has 4 tines and labeling recommends at least 2 tines be engaged in tissue. A single tine implanted in tissue will hold the device securely in place and protects against dislodgment. Extensive pre-clinical testing was done with sophisticated engineering models. These showed Micra would not dislodge when even subjected to car crash test standards when only 1 tine is engaged.
- Fixation Holding Strength: When 2 of the 4 tines are engaged, there is a 15 times safety margin against dislodgment.
- Encapsulation: The device is further protected as it becomes encapsulated due to the progressively growing fibrotic tissue.

In summary:

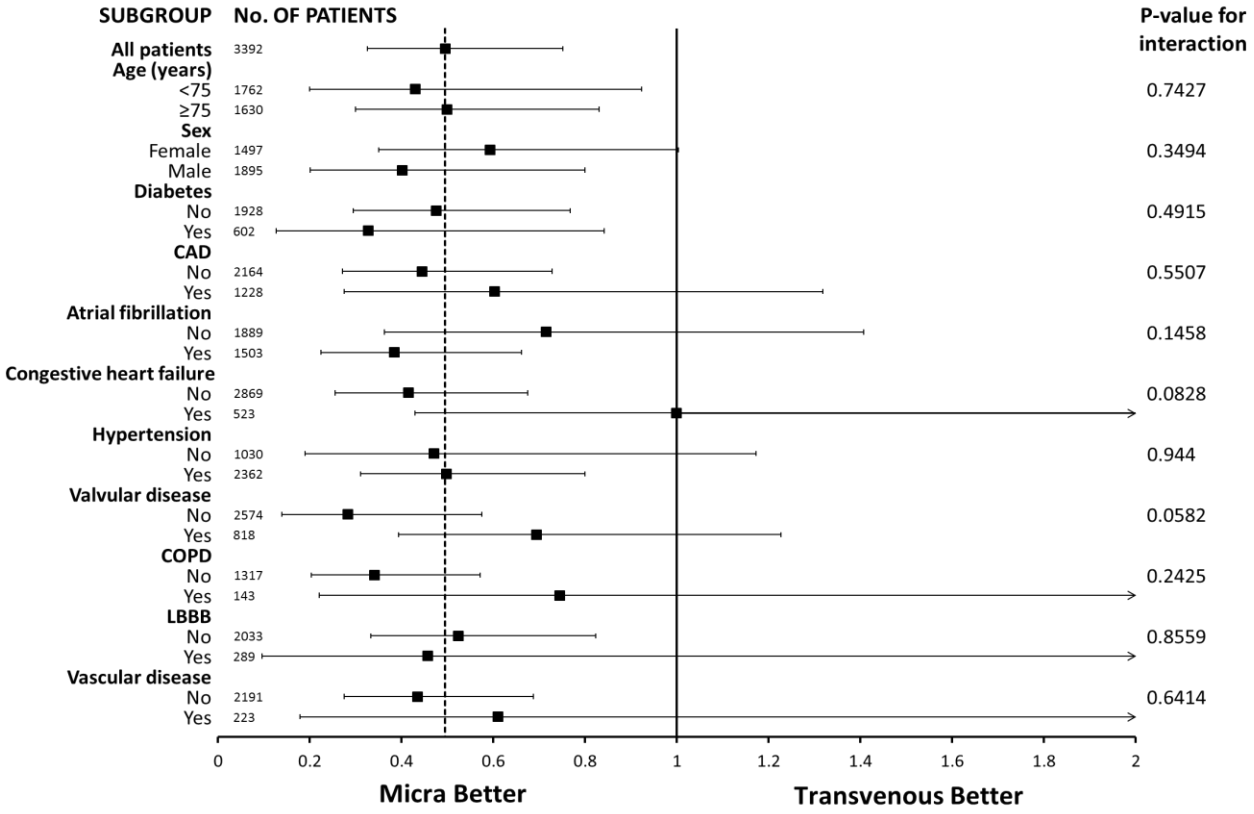
- The overall complication rate for Micra was reduced compared to the historic control: Micra had significantly fewer major complications than did the historical control of traditional pacemakers (hazard ratio, 0.49; 95% CI, 0.33 to 0.75; P = 0.001).
- The 1.6% effusion / perforation rate observed in Micra was not significantly different than the 1.1% rate from the transvenous pacemaker historical control group and was similar to other large pacemaker studies (1.2%, Mayo clinic[35]). Micra patients with effusions had known risk factors associated with device complication (elderly, female, chronic lung disease, etc.). Across subgroups, Micra patients consistently faired favorably over transvenous patients, and no subgroup showed a higher risk of major complication.
- Micra had zero dislodgements (i.e. device emboli).
- Micra patients had no strokes, nor arrhythmias resulting in major complication criteria.

[35] Mahapatra S, Bybee KA, Bunch TJ, Espinosa RE, Sinak LJ, McGoon MD, et al. Incidence and predictors of cardiac perforation after permanent pacemaker placement. Heart Rhythm 2005;2:907–11.

7.2. *FDA Question:* *Please identify any subgroups of patients (e.g., based on anatomical characteristics, demographics, etc.) as having an increased risk based on the adverse event rates associated with these devices.*

7.2.1 Medtronic Response: There are no subgroups where Micra shows a higher risk than traditional pacemakers (Figure 17). Relative risk estimates for all subgroups were less than one, suggesting Micra provided a consistently lower risk of major complication through 6-months compared to traditional transvenous systems. Of note, the Micra study did not exclude co-morbid conditions as long as life expectancy was ≥12 months. Therefore, the study participants reflected a very broad exposure of patients with a significant burden of concomitant illness. The Micra study did not exclude patients with lung disease or subjects with recent cardiovascular or peripheral vascular surgery (this is a difference from the Nanostim IDE trial where these were exclusions).

Figure 17: Major Complications Across Subgroups: Micra vs Traditional Pacemakers



7.3 *FDA Question:* *Please discuss what measures you would recommend to ensure that implanting physicians are adequately trained/informed regarding the potential occurrence of adverse events and appropriate device and patient selection.*

7.3.1 Medtronic Response: The Instructions for Use include potential adverse events. In addition, as described in Section 4, the training program has a didactic session which covers the

clinical study experience, including potential occurrence of adverse events and understanding patient risk factors in patient selection. Please refer to Table 11 for more details on how the training program has been updated to include lessons learned.

8. Draft Panel Question #2 (Post Approval Study)

Medtronic plans to leverage multiple sources to ensure inclusive data reporting and expedite time to evidence (facilitating more rapid EOS characterization than what would be possible via the post-approval study alone):

- Prospective enrollment of 1895 patients in a post-approval study (PAS)
- Medtronic's Device and Registrant Tracking (DART) system to identify Micra system revisions

A detailed review of Medtronic's proposed Post-Approval Study (PAS) is provided in Appendix B. In summary, Medtronic proposes to conduct a global, prospective, observational, multi-center, post-approval study. The study will include:

- An Acute Objective (n=700 at 30 days)
- A Long Term safety objective (n=1000 at 5 years)
- A Secondary Objective to characterize n=250 Micra devices at End of Service (EOS), including end of device battery life or other scenarios where the device is removed from use prior to battery depletion (e.g. upgrades, etc.).

Accounting for attrition, an estimated enrollment of 1895 patients is required to satisfy sample size requirements for all study objectives. All patients enrolled and successfully implanted with a Micra pacing system will be followed for a minimum of 5 years, with a total estimated study duration of 7.5 years. In addition to the Micra post-approval study data, the Medtronic Device and Registrant Tracking system will be monitored to identify end of device service/deactivation (EOS) occurrences of the Micra system for additional EOS data collection.

8.1 FDA Question A

A. *Please comment on how to best collect data for acute performance/ implant experience in the post- approval setting.*

i. Acute performance can be defined as 30 days from implant. The adverse events most likely to occur within these 30 days are dislodgements, threshold increases, etc. Implant experience can be defined as pre-discharge/24 hours from implant. The events most likely to occur within these 24 hours include groin complications, hematoma, vascular issues, and perforations. Please indicate which issues you believe should be addressed through collection of post approval data.

ii. FDA would expect sample sizes large enough to provide estimates of adverse events to a specific resolution with confidence intervals (keep in mind the high occurrence of acute adverse events). Please indicate which sample size is appropriate based on the table below.

ODE assumed complication rate	*Target CI Width*	*Minimum Sample Size Needed*	*Upper limit of the 95% CI*

1%	*+/- 0.5%*	*1741*	*1.6%*
1%	*+/- 1.0%*	*497*	*2.3%*
1%	*+/- 1.5%*	*251*	*3.2%*

FDA Question:
Acute performance can be defined as 30 days from implant. The adverse events most likely to occur within these 30 days are dislodgements, threshold increases, etc. Implant experience can be defined as pre-discharge/24 hours from implant. The events most likely to occur within these 24 hours include groin complications, hematoma, vascular issues, and perforations. Please indicate which issues you believe should be addressed through collection of post approval data.

8.1.1 Medtronic Response (A-i): The purpose of the Micra System Post-approval Study (PAS) is to further confirm the safety and effectiveness of the Micra System when used as intended in "real-world" clinical practice. The PAS requires the systematic collection, analysis, and interpretation of performance data, as well as its dissemination and application on clinical practice in a timely manner.

Post approval data should provide evidence the Micra system is performing as expected with sufficient data to further characterize performance, confirming adequacy of product labeling and facilitate the interpretation of observed safety trends (e.g. sub-group analysis). Data collection and frequency will align with the endpoints of interest and include all Micra related adverse events and all events directly related to the implantation/modification of the Micra system, inclusive of events most likely to occur within the first 24 hours such as groin complications, hematoma, vascular issues, and perforations. Both successful and unsuccessful implant experience will be collected. All patients intended to be implanted with a Micra System are eligible to enroll and patients are consented prior to the Micra implant procedure to minimize potential bias.

All reported system and/or procedure related adverse events will be reviewed by an independent Clinical Events Committee (CEC). The CEC will adjudicate the event as a complication or an observation and confirms relatedness to the system and/or procedure.

A successful implant occurs when the Micra system is chronically placed in the body. If a Micra system is not successfully implanted, patients may be exited unless a Micra system and/or procedure related Adverse Event (AE) is identified. If a Micra system and/or procedure related AE is identified, the patient is followed until the event is resolved or no further actions need to be taken.

FDA Question: FDA would expect sample sizes large enough to provide estimates of adverse events to a specific resolution with confidence intervals (keep in mind the high occurrence of acute adverse events). Please indicate which sample size is appropriate based on the table below.

ODE assumed complication rate	*Target CI Width*	*Minimum Sample Size Needed*	*Upper limit of the 95% CI*
1%	*+/- 0.5%*	*1741*	*1.6%*
1%	*+/- 1.0%*	*497*	*2.3%*
1%	*+/- 1.5%*	*251*	*3.2%*

8.1.2 Medtronic Response (Question A-ii): The sample size required for the acute safety objective is based on the desire to obtain a high level of precision for any individual event type that occurs at an underlying rate of 1%. Based on the individual complication rates observed in the Micra IDE study it is reasonable to assume an individual complication rate of 1.0% for the PAS study sample size calculation.

There are multiple methods (refer to section 8.1.2.1, 8.1.2.2, and 8.1.2.3) to determine an appropriate sample size to detect individual failures and obtain estimates with high resolution. Based on the following methods, a sample size of 700 patients is appropriate to reliably evaluate the acute safety performance of the Micra System. Assuming an individual event rate of 1%, a sample size of 700 for the acute (30 days) safety objective is large enough to:

- Provide greater than 99% probability to detect such an event (Section 8.1.2.1)
- Provide reliable estimates of event rates (Section 8.1.2.2)
- Facilitate event trending by providing statistical inference on events with higher incidence (Section 8.1.2.3)

8.1.2.1 Probability of Detecting a Complication

As the sample size increases, the probability of observing any adverse event will increase, providing assurance that no one adverse event of any type is undetected.

Table 16: Probability of Detecting a Complication

Sample Size	Complication Rate Assumption	Probability of Observing (at least 1 incidence)
100	1%	63.4%
250	1%	91.9%
500	1%	99.3%
700	1%	99.9%
800	1%	100.0%
1000	1%	100.0%
1250	1%	100.0%
1500	1%	100.0%
1750	1%	100.0%

A sample size of 500 provides a probability of event detection of greater than 99%, if the true complication rate is 1%. When the sample size is equal to or greater than 700, the probability of observing an event approaches 100%.

8.1.2.2 Event Rate Estimation Precision

The sample size requirement for a given objective is also determined in a manner to ensure sufficient precision to characterize performance with meaningfully narrow confidence intervals for the parameter(s) of interest. At the same time, there is a diminishing return in terms of the estimation of the precision as sample sizes increase above 700 patients.

Table 17 illustrates that above 700 patients, increasing the sample size by 100 reduces the confidence interval width by 0.1% or less.

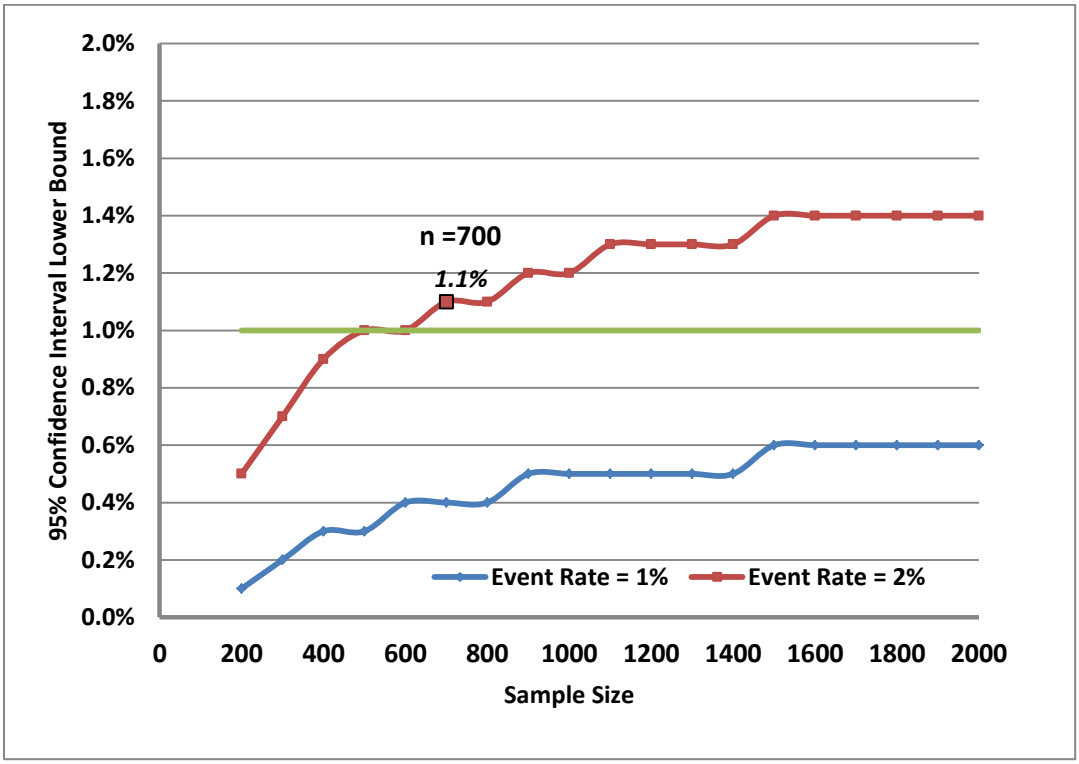
Table 17: Confidence Interval Width

Sample Size	Complication Rate	2-sided 95% CI Width
500	1%	0.020
600	1%	0.018
700	1%	0.016
800	1%	0.015
900	1%	0.014
1000	1%	0.014

8.1.2.3 High Incidence Event Detection

The Y-axis in the figure below displays the 95% confidence limit lower bounds when the observed event rate is 1% or higher. As an example, if the observed event rate is 2% for a given event type, with a sample size of 700, the confidence interval lower bound will be above 1%, implying the event rate may be significantly higher than the assumed 1%.

Figure 18: High Incidence Event Detection



8.2 *FDA Question B:*

FDA acknowledges that the long-term performance of leadless pacemakers is not well understood at this time. The estimated battery life for these devices is predicted to be anywhere from 6 to 12 years.

i. Please comment on the types of late life failures you would expect to be important to capture, given the design of leadless pacemakers.

ii. Based on the current paradigm for post-approval studies for leads, a complication-free rate is used as the endpoint for long-term performance. Please comment on the appropriateness of this endpoint for leadless pacemakers or suggest an alternative endpoint for long term performance of these devices.

iii. Please provide recommendations for ways to insure the completion of a long-term post approval study considering the following:

a. the difficulty in implementing such a study;

b. patients lost to follow-up over the course of a long study;

c. the ability to characterize end of life device failures; and

d. the ability to accurately collect device disposition when a new device is placed.

iv. *Please comment on the ideal duration of follow-up time to assess long term performance of leadless pacemakers.*

FDA Question: Please comment on the types of late life failures you would expect to be important to capture, given the design of leadless pacemakers.

8.2.1 Medtronic Response (Question B-i): There is no prior long term performance data on any leadless pacing system; however, based on current pacemaker generator performance, potential late life failures for the Micra system would include:

- Tine Fixation Complication
- Capture/Sense Failure
- Battery Malfunction
- Early Battery Depletion
- Electrical Component Malfunction
- Mechanical Integrity
- Software Malfunction
- Device Explant/Modification

Refer to Section 5 of this document for additional details regarding expected device failures over time.

The post-approval study will collect all Micra related events as categorized above and all system modifications throughout the PAS follow-up period. Additionally, following completion of the PAS analysis, patients will continue to be followed prospectively as part of Medtronic's product surveillance program.

FDA Question: Based on the current paradigm for post-approval studies for leads, a complication-free rate is used as the endpoint for long-term performance. Please comment on the appropriateness of this endpoint for leadless pacemakers or suggest an alternative endpoint for long term performance of these devices.

8.2.2 Medtronic Response (Question B-ii): Medtronic believes the current practice of utilizing a system and/or procedure related complication-free rate is an appropriate endpoint applicable for leadless pacemakers.

Evaluating long-term performance as a function of time using the survival analysis method is widely used in medical research and more specifically in the device industry, thereby facilitating comparisons across products. The Micra system has no lead components; therefore, the system survival probability will be based on device related complications/malfunctions. The combination of acute and long term performance endpoints provides a comprehensive evaluation of the safety profile of the Micra system when used as intended in post market clinical environments.

FDA Question: Please provide recommendations for ways to insure the completion of a long-term post approval study considering the following:
a. the difficulty in implementing such a study;
b. patients lost to follow-up over the course of a long study;
c. the ability to characterize end of life device failures; and

d. the ability to accurately collect device disposition when a new device is placed.

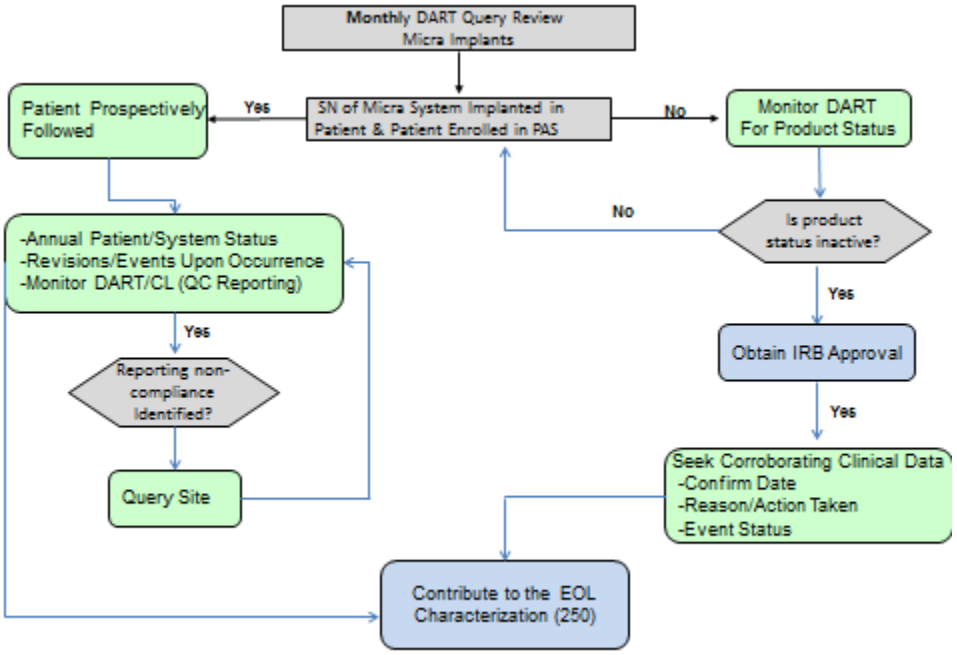
8.2.3 Medtronic Response (Question B-iii): Successful completion of a long-term post-approval study requires active oversight and execution vigilance. Patient retention is challenging with any clinical study but that challenge is exacerbated with long-term post-market studies. Medtronic has been conducting post market registries since 1983, and throughout this time period, has continually worked to adapt systems and processes to increase the utility and value of the data, to more effectively monitor product performance following market release.

Based on Medtronic surveillance data, some key factors in study attrition are unavoidable, e.g. patient death. It is estimated for a 5-year study such as the Micra PAS the patient mortality could be as high as 35% (annual pacemaker patient mortality rate is approximately 5-8%). Other unavoidable attrition factors include device change-out or upgrades to an Implanted Cardiac Defibrillator (ICD) or Cardiac Resynchronization Therapy (CRT). The impact of these factors on the overall study attrition is compounded for studies with a long follow-up duration when combined with the nature of cardiac disease progression and patient comorbidities.

Managing avoidable attrition, e.g. Lost to Follow-up (LTFU), also poses challenges for long-term studies. Significant effort is required to minimize attrition associated with LTFU including but not limited to: frequent touch points with sites, regular review of remote monitoring data, automatic edit checks, discrepancy management and regular reconciliation with Device Registration and Returned Products. This reconciliation process is used to assure study site reporting compliance and to identify potential revisions for non-PAS participants.

However, finding new ways to stay connected to patient/device status offers potential opportunities to further minimize the impact of attrition on assessing long-term performance. In accordance with industry standards, Medtronic has a Device and Registrant Tracking (DART) system for all U.S. Medtronic implanted cardiac rhythm devices that includes implant details and captures any system revisions. Medtronic plans to leverage the DART system to identify Micra system revisions representative of the full U.S. Micra experience to facilitate more rapid and complete End of Service/Deactivation (EOS) characterization than what would be possible via the post-approval study alone. This and other novel ways to ascertain relevant clinical data helps to mitigate the impact of attrition inherent with any long-term study and reduces the time necessary for useful clinical evidence dissemination. A flow chart of how the data will be collected from the post-approval study in combination with the DART is summarized in the figure below.

Figure 19: Data Collection / Integration to Capture EOL Characterization



FDA Question: Please comment on the ideal duration of follow-up time to assess long term performance of leadless pacemakers.

8.2.4 Medtronic Response (Question B-iv):
Medtronic believes a five (5) year follow-up time (combined with DART for EOS characterization) provides the necessary duration to adequately characterize long-term performance, obtain 250 Micra system EOS occurrences and provide optimal time to evidence.

Background: Current post-approval studies for leads are based on a five (5) year follow-up duration.

Rationale: Given the pacemaker population is typically elderly with multiple co-morbidities, a follow-up duration of no more than 5-years is ideal. The IDE study results demonstrate the occurrence of system related complications post 30-days of implant is very low. It is expected that the device survival probability will remain stable after the acute phase until battery depletion. Therefore, the Micra system survival probability estimate is expected to be very similar at 5-years and 7-years post implant.

Table 18 provides a comparison of different follow-up durations and the impact on the objectives of interest. The confidence intervals are the same at 5-years and 7-years; however, a 7-year follow-up duration delays the dissemination of clinical evidence, minimizing the utility of the information to optimally benefit patient care/treatment guidance.

Medtronic believes 250 devices at end of service is an acceptable sample size as it provides >90% chance of capturing EOS related events which occur at a 1% rate. The PAS + DART combined approach provides the sample size of 250 at 5 years. Note these 250 devices could be obtained from devices at the end of their battery life or from devices which are taken out of use (e.g. upgrade, deactivation, etc.).

Table 18: Impact of Study Duration on Clinical Evidence Generation

	PAS + DART	**PAS Only**
Endpoint	5 year	7 year
Effective Sample Size at Endpoint	1,000	1,000
2-side 95% CI Width[1]	3.8%	3.8%
Estimated Incidence of EOS/Deactivation	250	50
Probability of EOS related Event Detection (rate 1%)	92%	39%
Total Study Duration (years)[2]	7.5	10
Expected date year of evidence (study completion)	2023	2026

[1]Micra system/procedure related complication-free survival probability = 90%
[2]Enrollment period + follow-up

8.3 FDA Question C

C. FDA is interested in collecting data on what clinicians decide to do with devices after they reach end of life (EOL).

FDA foresees four (4) likely scenarios for device EOL:

- *Explant Leadless Pacemaker and implant*
  - *another LP*
  - *a traditional pacemaker system*
- *Turning OFF the existing LP and implanting an adjacent LP next to it*
- *Turning OFF the existing LP and implanting an adjacent transvenous pacemaker next to it.*

FDA expects that physicians may prefer one or two approaches over the others. It should be noted that the LP is expected to be fully encapsulated, which differs from traditional pacemaker/lead systems. FDA expects this aspect of the PAS to be observational. Please comment on the following questions:

i. Given the observational nature of the Post Approval Study, what criteria should be used to determine the sample size i.e. acceptable rates of occurrence and precision of rates?

ii. Regarding the scenarios outlined above, what is an appropriate follow-up time to observe for new device interactions with the previously implanted device?

iii. Please recommend an approach to evaluate device removal/extraction i.e. how often it is attempted, success rates, and complications associated with removal/extraction?

FDA Question: Given the observational nature of the Post Approval Study, what criteria should be used to determine the sample size i.e. acceptable rates of occurrence and precision of rates?

8.3.1 Medtronic Response (Question C-i):

Medtronic believes 250 devices at end of service is an acceptable sample size as it provides >90% chance of capturing EOS related events which occur at a 1% rate. Note this includes devices at the end of their battery life and scenarios where the device is taken out of use prior to the end of battery life (e.g. upgrade).

The PAS includes a secondary objective to characterize treatments and/or procedures related to the Micra system at end of service (EOS). Given there is no prior data on the distribution of proportion of treatment methods for the Micra system, there is no significance in terms of the scientific meaningfulness for calculating a precision estimate at this time.

Based on results observed with other Medtronic pacemaker surveillance data[36], patient mortality is a major competing risk, affecting the effective endpoint sample size for long-term studies. Therefore, relying solely on the PAS enrollments to achieve a meaningful number of Micra EOS occurrences, within a time frame that benefits patients and clinicians is not feasible. EOS data is collected for patients enrolled in the PAS throughout their 5-year follow-up period via event and system modification reporting. Following IRB approval, similar information is collected concurrently for EOS revisions identified through Medtronic's DART system to capture the complete U.S. commercial release experience. This combined PAS + DART approach provides the implant volume and information to collect meaningful and significant EOS characterization data representative of the full product lifecycle rapidly and reliably. It is projected that 250 EOS Micra revisions will be obtained within 5-years of US market release.

FDA Question: Regarding the scenarios outlined above, what is an appropriate follow-up time to observe for new device interactions with the previously implanted device?

8.3.2 Medtronic Response (Question C-ii): The Instructions for Use recommend to avoid mechanical interaction with any existing devices, similar to leads. If mechanical interaction were to occur, it would be expected to be identified during implant electrical testing.

Device removal/extraction is captured via adverse event and or via system modification reporting throughout the 5-year follow-up period. System modification information is collected when a re-operation is completed regardless of the reason. Additionally, patients enrolled in the PAS are followed over their full cardiac care continuum, meaning if they are implanted with a new

[36] A Medtronic post market study cohort of 2,297 pacemaker patients with a median follow-up of 2.4 years had an annual death rate of 5-6% within the first 5-years following the date of implant with a low cumulative EOS rate (3.5%).

Medtronic cardiac rhythm device, the patient continues to be followed as part of Medtronic's cardiac post market surveillance program.

> *FDA Question: Please recommend an approach to evaluate device removal/extraction i.e. how often it is attempted, success rates, and complications associated with removal/extraction?*

8.3.3 Medtronic Response (Question C-iii): The evaluation of EOS scenarios, inclusive of extraction attempts and other EOS scenarios, will be completed for a minimum of 250 Micra patients. Both the EOS occurrence and the outcome are reported. This data provides an opportunity to assess the prevalence of Micra removal/extraction procedures and complications associated with these procedures. Ancillary objectives of the PAS include:

- Characterize Micra system and/or procedure related complications stratified by implant type:
    - De Novo
    - Existing previous pacing system e.g. transcatheter, traditional IPG, etc.
- Characterize post-implant Micra System revisions, including system explant, replacement (with and without system explant) and reposition, etc.:
    - Reason for modification
    - Time from Micra implant to modification

Finally, the PAS includes descriptive statistics, including frequency tables characterizing the success probability of device removal/extraction as well as the proportions of patients with procedure related complications.

9. Draft Panel Question #3 (End-of-life Options and Labeling)

9.1 FDA Question: *In the absence of data on long term performance and end-of-life options for leadless pacemakers, please comment on content and points to address for appropriate labeling regarding extractions, replacements, and best practices at this time.*

9.1.1 Medtronic Response:

Given its small size (0.8 cc, representing 0.5% volume of right ventricle), Micra was designed to remain in the body. Micra has a unique programmable Device Off mode which has the capability to permanently deactivate pacing and sensing (OOO) even in the event of an electrical reset ("power on reset") or upon reaching battery replacement status. The device can also be removed percutaneously, if needed. The decision to leave the device in place or remove involves multiple factors. Micra was designed to provide options for managing a variety of clinical scenarios including EOS and device deactivation. While rate and degree of encapsulation is variable and unknown, complete encapsulation of Micra is expected and likely to provide a protective barrier against device infection. Thus, while the most likely approach for managing EOS and deactivation of a chronically implanted Micra will be to program to Device Off and leave in the body, percutaneous retrieval is an alternative.

In summary, it is expected:

- The majority of Micra patients will require only one device in their lifetime
- For those patients who need more than one device or need a device upgrade, most implanters will choose to leave Micra *in situ* (program Micra OFF) and implant a second Micra or implant a transvenous system
- When necessary, percutaneous or surgical retrieval is an option

The current clinical labeling in the sections below describes potential risks for removal requiring surgical disruption of cardiac tissue:

- **Section 2.2 Note:** Removal of the Micra device may be difficult because of the development of fibrotic tissue. If removal of the device is required, it is recommended that the removal be performed by a clinician who has expertise in the removal of implanted leads.
- **Current labeling: Section 5.4 Warning:** Retrieval of the device after it is fully encapsulated may result in injury to the patient's cardiac tissue. If device retrieval is required after it is encapsulated, refer the patient to a medical center that has expertise in the removal of implanted leads or call a Medtronic representative for more information.

In addition to the current clinical labeling noted above, Medtronic proposes to add the following note to better describe options for physicians to manage EOS or conditions where the therapy is no longer required.

- **Proposed Note section 5.4**: Micra is designed to provide options at EOS or for situations where the physician determines the Micra therapy is no longer needed. The Micra design allows for retrieval of the device with commercially available off the shelf tools.

However, full encapsulation would likely make it challenging to remove the device and given that there is currently no imaging modality that allows for determining level of encapsulation. The Micra design provides the option to program to Device Off mode which permanently disables therapy and allows the device to remain in the body.

END OF DOCUMENT

Appendix A: NEJM Article Citation

Reynolds D, Duray GZ, Omar R, et al. **A Leadless Intracardiac Transcatheter Pacing System**. *New Engl. J. Med.*;0(0). (ePub ahead of print)

Appendix B: Proposed Post Approval Study Overview

During the PMA process Medtronic will collaborate with FDA to ensure agreement on the Post Approval Study (PAS) requirements for the Micra™ Transcatheter Pacing System (TPS). To facilitate preliminary discussion and alignment on the Micra PAS, an overview of the proposed PAS is provided within this document.

Background and Purpose

The Micra™ Transcatheter Pacing System has been demonstrated to be safe and effective when used according to the labeling requirements (IDE G130245). Medtronic is sponsoring the Micra Transcatheter Pacing System PAS to further confirm safety and effectiveness of the system when used as intended, in "real-world" clinical practice. The Micra PAS is conducted within Medtronic's the Product Surveillance Registry (PSR), Medtronic's active surveillance platform.

Methodology

The Micra PAS is a global, prospective, observational, multi-center, study. The PAS includes two primary objectives. These objectives will be analyzed at different time points when the appropriate sample size is achieved for each.

All patients enrolled in the Micra PAS will be prospectively followed through 5 years post implant or until study closure. Data collection occurs pre-procedure/baseline, procedure, pre-hospital discharge, 30-days post implant and at regularly scheduled follow-up visits at least annually, or as prompted by reportable adverse events. This follow-up frequency aligns with the expected routine care practice for the pacemaker patient population however if more frequent scheduled visits occur as per a providers standard care practice, those visits are to be reported. Total estimated PAS duration is 7.5 years.

Enrollment and Duration

Patients intended to be implanted with a Micra Transcatheter Pacing System are eligible for enrollment into the Micra Registry, all patients must be consented prior to the Micra System implant.

Accounting for attrition, an estimated enrollment of 1895 patients is required to satisfy sample requirements for all PAS objectives. All patients enrolled and successfully implanted with a Micra pacing system will be followed for a minimum of 5 years, unless a patient is exited from the PAS due to an unavoidable reason such as death, physician discretion, or patient withdrawal of consent. If a Micra system is not successfully implanted, patients will be exited from the study unless a Micra System and/or implant procedure related Adverse Events (AE) is identified. If a Micra and/or implant procedure related AE is identified, the patient will be followed until the event is resolved or no further actions need to be taken.

It is estimated that it will take approximately 30-months to enroll the required 1895 patients with an estimated 200 centers participating globally. There is no minimum enrollment requirement per center but the goal is to have enrollments from all participating centers with no one site contributing more than 10% of the total enrollment. The actual enrollment rate will be determined by sales and will be regularly assessed throughout the conduct of the PAS. The last follow-up is expected 5-years following the date of the last enrolled patient.

Objectives

PAS Primary & Secondary Objectives	
Primary Objective #1 (Acute, ≤30 Days)	To estimate acute complication rate related to the Micra system and/or procedure • 700 Micra system implant procedure ensure complication detection and produces a 2-sided 95% CI width of 1.6% when the event rate is 1%
Primary Objective #2 (Chronic, 5 Years)	To estimate the 5-year Micra related complication free survival probability • 1,000 patients at 5-years produces a 2-sided CI width of 3.8% with a CI lower limit of 88.0%
Secondary Objective (EOS / Deactivation Experience)	To characterize devices at EOS / deactivation A minimum of 250 devices at EOS (including any one of the following possible revision scenarios): • Explant of Micra System with new leadless pacemaker system • Explant of Micra System with new transvenous pacemaker system • Implant of new leadless pacemaker without explant of Micra System (set to OOO) • Implant of new transvenous pacemaker system without explant of Micra System (set to OOO)

Note: The primary objectives will be analyzed at different time points when the appropriate sample size is achieved.

Primary Objective #1:

To estimate acute complication rate related to the Micra system and/or implant procedure

Analysis Method:

The acute complication rate will be calculated by dividing number of patients with a Micra system and/or implant procedure related complication by total number of patients who undergo a Micra implant attempt. The 2-sided 95% confidence interval will be calculated using the Exact binomial method.

All reported adverse events will be reviewed by Clinical Events Committee (CEC) and classified as complication vs. observation, and for relatedness to the system and/or implant procedures. An acute complication for this objective is defined as a MICRA system and/or implant procedure related complication which occurred within 30 days (inclusive) of the Micra System implant.

Endpoint justification

The Micra IDE study (G130245) currently reported an overall system or implant procedure complication rate of 6.62% (Micra Transcatheter Pacing Study, PMA Clinical Report, Oct 06,

2015). Complications observed within the clinical study are presented in Table 19 and ranged from 0.14-1.24% for any individual adverse event type. An individual complication rate of 1% for any individual adverse event was assumed for the PAS study sample size calculation.

Table 19: Micra IDE Study Observed Procedure or System Related Complications

	No. Events, (No. Subjects, %)	
Adverse Event Keyterm	**All Complications**	**Major Complications**
TOTAL EVENTS	**54 (48, 6.62%)**	**28 (25, 3.45%)**
CARDIAC ARRHYTHMIAS	**7 (7, 0.97%)**	**0 (0, 0%)**
ATRIOVENTRICULAR BLOCK COMPLETE	5 (5, 0.69%)	0 (0, 0%)
VENTRICULAR FIBRILLATION	1 (1, 0.14%)	0 (0, 0%)
VENTRICULAR TACHYCARDIA	1 (1, 0.14%)	0 (0, 0%)
EMBOLISM AND THROMBOSIS	**3 (3, 0.41%)**	**2 (2, 0.28%)**
DEEP VEIN THROMBOSIS	2 (2, 0.28%)	1 (1, 0.14%)
PULMONARY EMBOLISM	1 (1, 0.14%)	1 (1, 0.14%)
EVENTS AT GROIN PUNCTURE SITE	**11 (11, 1.52%)**	**5 (5, 0.69%)**
ARTERIAL INJURY	1 (1, 0.14%)	0 (0, 0%)
ARTERIOVENOUS FISTULA	4 (4, 0.55%)	4 (4, 0.55%)
INCISION SITE HAEMATOMA	1 (1, 0.14%)	0 (0, 0%)
INCISION SITE HAEMORRHAGE	2 (2, 0.28%)	0 (0, 0%)
INCISIONAL DRAINAGE	2 (2, 0.28%)	0 (0, 0%)
VASCULAR PSEUDOANEURYSM	1 (1, 0.14%)	1 (1, 0.14%)
TRAUMATIC CARDIAC INJURY	**12 (12, 1.66%)**	**11 (11, 1.52%)**
CARDIAC PERFORATION	3 (3, 0.41%)	3 (3, 0.41%)
PERICARDIAL EFFUSION	9 (9, 1.24%)	8 (8, 1.10%)
PACING ISSUES	**2 (2, 0.28%)**	**2 (2, 0.28%)**
DEVICE DISLOCATION	1 (1, 0.14%)	1 (1, 0.14%)
DEVICE PACING ISSUE	1 (1, 0.14%)	1 (1, 0.14%)
OTHER	**19 (19, 2.62%)**	**8 (8, 1.10%)**
ACUTE MYOCARDIAL INFARCTION	1 (1, 0.14%)	1 (1, 0.14%)
CARDIAC FAILURE	3 (3, 0.41%)	3 (3, 0.41%)
HYPOTENSION	3 (3, 0.41%)	0 (0, 0%)
MEDICATION ERROR	2 (2, 0.28%)	0 (0, 0%)
METABOLIC ACIDOSIS	1 (1, 0.14%)	1 (1, 0.14%)
NON-CARDIAC CHEST PAIN	1 (1, 0.14%)	0 (0, 0%)
OSTEOARTHRITIS	1 (1, 0.14%)	0 (0, 0%)
PACEMAKER SYNDROME	1 (1, 0.14%)	1 (1, 0.14%)
PERICARDITIS	1 (1, 0.14%)	0 (0, 0%)
PRESYNCOPE	3 (3, 0.41%)	1 (1, 0.14%)
SYNCOPE	1 (1, 0.14%)	1 (1, 0.14%)
URINARY RETENTION	1 (1, 0.14%)	0 (0, 0%)

Sample Size Requirement

Assuming an event rate of 1%, a sample size of 700 undergoing a Micra system implant procedure produces a two-sided 95% confidence interval width of 1.6% (Table 20) and provides greater than 99.9% probability to detect a complication of any type (

Table 21).

Table 20: Estimation Precision

Sample Size	Complication Rate	2-sided 95% CI Width
500	1%	0.020
600	1%	0.018
700	1%	0.016
800	1%	0.015
900	1%	0.014
1000	1%	0.014

Table 21: Probability of Detecting a Complication

Sample Size	Complication Rate Assumption	Probability of Observing (at least 1 incidence)
100	1%	63.4%
250	1%	91.9%
500	1%	99.3%
700	1%	99.9%
800	1%	100.0%
1000	1%	100.0%
1250	1%	100.0%
1500	1%	100.0%
1750	1%	100.0%

Primary Objective #2

To estimate the 5-year complication free survival rate of the Micra Pacing System.

Analysis Method

The analysis cohort will include all enrolled patients who undergo an implant procedure with a Micra system in the registry. All adverse events adjudicated by the CEC as being a complication related to the Micra System and/or procedure will be included in the analysis regardless of when the event occurred.

A survival analysis, using the Kaplan-Meier method, will be conducted to estimate the Micra system/procedure related complication free probability as a function of time. The 2-sided 95% confidence interval will be calculated. Time 0 is the time of system implant; failure time is the onset date when a Micra system related complication occurs. Patients will be censored at their last visit, or death/exit due to any non-Micra system related reasons.

Endpoint Justification

The Micra IDE study observed a system related complication rate of 4% when patients were followed for 6 months (a Kaplan-Meier estimate). A traditional pacemaker often presents

complications such as lead dislodgment, lead perforation, pneumothorax, connector issue, lead malfunction or failures and Twiddler syndrome, etc., requiring re-operation. The overall system related complication rate for a traditional single chamber pacemaker can be 5-10% or higher, we conservatively assumed a long term complication rate of 10% for the sample size calculation.[37],[38],[39] Accounting for a 12% annual attrition, an enrollment of 1,895 patients is required to achieve 1,000 patients at 5-years post-implant, providing a confidence interval width 3.8% with a lower CI bound of 88% for Micra related complication free survival probability estimate.

Table 22: Sample Size Calculation for Objective #2

Enrollment Size	Effective Sample Size @ 5 years post implant	Complication Rate	2-sided 95% CI Width
1516	800	10%	0.043
1895	1000	10%	0.038
2274	1200	10%	0.035
2653	1400	10%	0.032
3032	1600	10%	0.030
3411	1800	10%	0.028

Summary of Data Collection

Data collection is consistent with standard care practices for the pacemaker patients and is summarized in the following table. Additional details of the proposed data collection are attached.

[37] Poole, J. E., Gleva, M. J., Mela, T., Chung, M. K., Uslan, D. Z., Borge, R., ... & Seide, H. (2010). Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures results from the REPLACE registry. *Circulation*, *122*(16), 1553-1561.

[38] Bond, R., Augustine, D., & Dayer, M. (2012). Pacemaker complications in a district general hospital. *British Journal of Cardiology*, *19*(2), 90.

[39] Kiviniemi, M. S., Pirnes, M. A., ERÄNEN, H. J. K., KETTUNEN, R. V., & HARTIKAINEN, J. E. (1999). Complications related to permanent pacemaker therapy. *Pacing and clinical electrophysiology*, *22*(5), 711-720.

Table 23: PAS Data Collection Summary

	Enrollment/ Baseline	Procedure/Pre-hospital Discharge	30-days Post Procedure	Follow-up	System Mod.	Exit
Consent	X					
Medical History	X					
Device/System Information		X	X	X	X	X
Electrical Measurements & Device Interrogations		X		X	X	
Procedure Details		X			X	
Device Disposition					X	X
Events assessment		X	X	X	X	X
Events	Upon Occurrence					
Device Deficiency	Upon Occurrence					
Deaths	Upon Occurrence					

Overall Primary Objective Sample Size Considerations
The sample size determination must satisfy the sample size requirements for both primary objectives. Primary objective #1 requires a minimum of 700 patients with a Micra system implant attempt, primary objective #2 requires a sample size of 1,000 at 5-years. Therefore, a minimum enrollment requirement for the study is 1,895 patients.

Secondary Objective:

- To characterize treatment and/or procedure related to Micra system End of Service or Deactivation (EOS)

A minimum of 250 patients with a Micra system revision will be required to characterize Micra EOS/Deactivation experience. Any one of the following revision scenarios contributes equally to the required 250. Possible revision scenarios include:

- Explant of Micra System with new leadless pacemaker system
- Explant of Micra System with new transvenous pacemaker system
- Implant of new leadless pacemaker without explant of Micra System (set to OOO)
- Implant of new transvenous pacemaker system without explant of Micra System (set to OOO)

The Medtronic pacemaker PAS data was analyzed to understand the proportion of patients who may provide pacemaker EOS experience data. The analysis was conducted using the survival analysis method; results are displayed in Table 24. A total of 2927 patents who were implanted with a least one Medtronic pacemaker were included in this analysis.
Median follow-up time was 2.4 years, range 0 - 6.5 years. Annual patient death rate was 5-6% in the first 5 years post implant. The EOS rate was low throughout with a cumulative EOS rate of 3.4% at 5 years.

Table 24: Pacemaker End of Service Estimates

Year post implant	Patient Death Rate	Device EOS Rate
0-1	5.1%	1.2%
1-2	5.6%	0.4%
2-3	5.5%	0.4%
3-4	5.2%	0.9%
4-5	6.2%	0.6%
5 -6	5.7%	NA
6-7*	8.3%	NA

**Effective same size was less than 30. The estimates may not be reliable.*

It is observed that patient mortality will be a major competing risk limiting the effective sample size for analysis at 5+ years post implant. Based on these study data, it is expected that with a registry enrollment size of 1895 patients, approximately 40 patients may experience a revision within 5-years of their implant, or 7.5 years after the first study enrollment (Table 25).

EOS characterization data will be collected for patients enrolled in the PAS throughout their follow-up period (5-years); however, given the expected mortality and low revision rate (0.4%-0.9%) Medtronic's Device and Registrant Tracking (DART) system will be monitored concurrently with the PAS patient follow-up to identify Micra revisions associated with patients not enrolled in the PAS. DART provides the necessary implant volume (all US Micra implants) and information to augment the PAS patient cohort to reliably characterize EOS for the Micra system. The combined approach facilitates the collection of meaningful and significant data representative of the entire device life for rapid EOS characterization.

Table 25: EOS Characterization Duration Estimation Assumptions

Year	Revision Rate Assumption*	PAS Patient Population (= 1895)	PAS Cohort Revision (Min – Max)	Assumption US Unit Sales (PAS Included)	Estimated Cumulative DART + PAS*
Year 1	0.4% - 1.2%	700	3 - 8	1922	9
Year 2	0.4% - 0.9%	1330	6 - 12	6184	41
Year 3	0.4% - 0.9%	1692	7 - 15	9118	107
Year 4	0.4% - 0.9%	1523	7 - 14	9862	204
Year 5	0.4% - 0.9%	1371	6 -12		297
Year 6	0.4% - 0.9%	1233	5 - 11		
Year 7	0.4% - 0.9%	1110	5 - 10		
Year 8	0.4% - 0.9%	999	4 - 9		
Cumulative			43 - 91		297

*assuming 12% annual attrition

PAS Enrolled Patients: Micra revision details are reported upon occurrence throughout the 5-year follow-up period via event and system modification forms. Reconciliation with DART is used as a tool to facilitate site reporting compliance for all PAS enrolled patients.

Non-PAS enrolled Micra patients: Patients implanted with a Micra system who are not enrolled in the PAS, revisions will be identified DART review. DART provides the necessary information

for identifying patients with revisions and includes all patients implanted with a Micra system in the United States (US) are tracked in the Medtronic DART system. Relevant EOS data collected in DART includes:

- Device Model
- Device SN
- Implanter
- Date of Implant
- Device Status (Active or Inactive)
    - Action taken when a device moves from active to inactive
- Status Date

When a device moves from Active to Inactive a revision is indicated. Following IRB approval corroborating clinical data will be collected to characterize EOS for DART identified revisions. Medtronic's ability to collect this information is dependent on:

- IRB approval to gather clinic data
- Willingness and ability of clinic to provide revision information, including but not limited to:
    - Date of revisions
    - Reasons for Revision
    - Type of Revision
    - Revision Outcome (e.g. successful revision, etc.)

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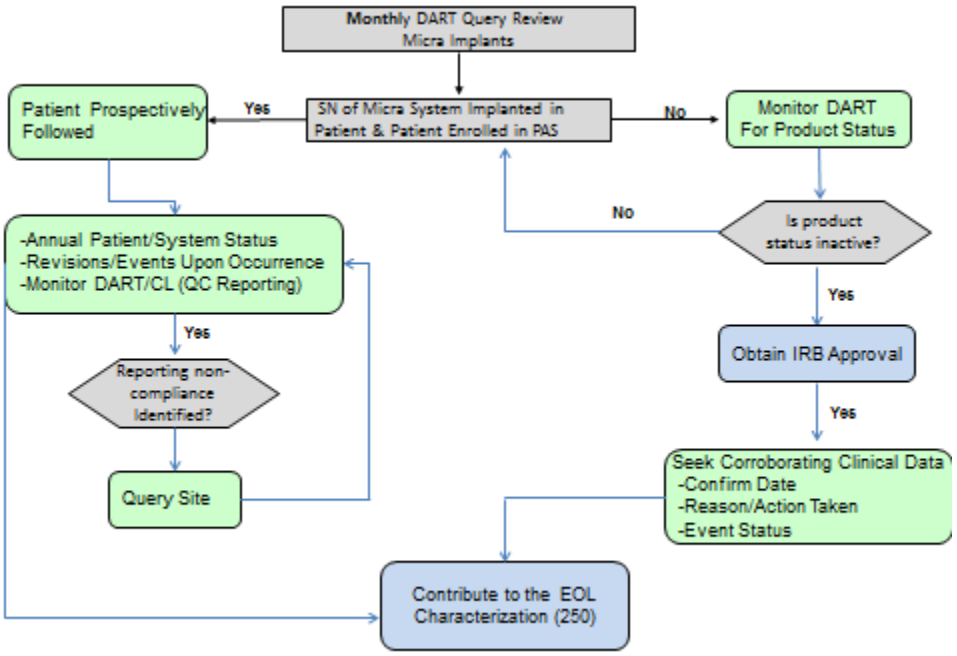
A flow chart of how the data will be collected/integrated is summarized in Figure 20.

Figure 20: Data Collection / Integration to Capture EOL Characterization



Ancillary Objectives

The secondary objectives are descriptive in nature and are intended to gain additional information about the performance of the Micra System:

- Characterize electrical performance overtime
- Characterize the implant procedure
    - Total implant time
    - Implant success rate
- Characterize Micra system and/or procedure related complications stratified by implant type:
    - De Novo, existing previous pacing system e.g. transcatheter, traditional IPG, etc.
- Characterize post-implant Micra System revisions, including system explant, replacement (with and without system explant) and reposition, etc.
    - Reason for modification
    - Time from Micra implant to modification
- Characterize System Longevity

Report and Analysis Schedule

Regular PAS Progress Reports will be provided to FDA in alignment with the guidelines provided in Guidance for Industry and FDA Staff: Procedure for Handling Post-Approval Studies Imposed by FDA Order, 15 June 2009. PAS Progress Reports will be submitted every six month for the first two years following approval, and annually thereafter.

Following completion of the PAS, device end of life characterization data will be provided in the annual PMA update report.