

Version 1.1
03/27/2020

Title: Indications, Implantation and Outcomes of Leadless Pacing

Sponsor: Department of Pediatrics, The Children's Hospital of Philadelphia

Amendment 1 Date:
03/27/2020

Amendment 4 Date:

Amendment 2 Date:

Amendment 5 Date:

Amendment 3 Date:

Amendment 6 Date:

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ABBREVIATIONS AND DEFINITIONS OF TERMS

TPS	Trans Catheter Pacing
AVB	Atrioventricular Block
CHD	Congenital Heart Disease
PM	Pacemaker
EPI	Epicardial
ECG	Electrocardiogram
TV	Transvenous
PACES	Pediatric and Congenital Electrophysiology Society
CHOP	The Children's Hospital of Philadelphia

ABSTRACT

Context:

Permanent cardiac pacing is the only effective solution for patients with symptomatic bradycardia and heart block. About 10% of patients undergoing implantation of the conventional transvenous (TV) and epicardial (EPI) pacing system develop complications related to the subcutaneous pocket or the leads and in pediatric patients lead problems may rise in up to 30% of the patients. The leadless pacemaker devices were developed in order to minimize some of those complications. Currently, only one permanent leadless pacemaker device is available for clinical use. This is the Transcatheter Pacing (TCP) leadless Micra™ device. Early results of the Micra Investigational Device Exemption (IDE) study and Micra Post-Approval Registry (PAR) demonstrated excellent safety and efficacy performance in adults; however, results in the pediatric population and in patients with congenital heart disease (CHD) have not been evaluated.

Objectives:

- The study goal is to describe the clinical indications, implantation characteristics, electrical performance and outcome of patients who have undergone implantation of the Transcatheter Pacing (TCP) Leadless Micra™ device

Study Design:

- Basic design: Multi-center retrospective descriptive study

Setting/Participants:

- The study will be performed by querying the Cardiac Electrophysiology divisions of Children's Hospitals to submit clinical data regarding patients with Leadless Pacemakers.

Study Interventions and Measures:

- Review of medical records
 - Main study outcome measures will be to assess pacemaker system- or procedure-related complications. Electrical performance of pacemaker at implantation and follow-up will also be characterized
-

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Permanent cardiac pacing is the only effective solution for patients with symptomatic bradycardia and heart block. About 10% of patients undergoing implantation of the conventional transvenous (TV) and epicardial (EPI) pacing system develop complications related to the subcutaneous pocket or the leads and in pediatric patients lead problems may rise in up to 30% of the patients. A new technology, leadless pacemaker therapy, was recently introduced clinically to address lead- and pocket-related complications in conventional transvenous and epicardial pacemaker therapy. These leadless devices are self-contained right ventricular single-chamber pacemakers implanted by using a femoral percutaneous approach. Currently, only one Leadless Pacemaker device is approved for clinical use. This is the Transcatheter Pacing (TCP) leadless Micra™ device. The Micra TPS is a single-chamber ventricular pacemaker and is 93% smaller than a TV-PPM system with a total volume of 0.8 mL. The device has similar functionality and features to existing single-chamber ventricular pacemakers, including rate adaptive pacing, remote monitoring capabilities, and automated pacing capture threshold management, designed to maximize battery longevity. Micra is inherently magnetic resonance imaging conditionally safe for full-body scans in both 1.5-T and 3-T scanners.⁷ The device is implanted directly in the right ventricle through a femoral vein. The device is fixated in the myocardium via 4 flexible nitinol tines.¹⁻⁴ The FDA approved indications for this device are 1) Symptomatic paroxysmal or permanent high-grade AV block in the presence of atrial fibrillation (AF) 2) Symptomatic paroxysmal or permanent high-grade AV block in the absence of AF, as an alternative to dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy 3) Symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy.

There are only rare case reports of the use of this technology in children and patients with congenital heart disease.⁵ Potential complications of the Micra™ Leadless transcatheter Pacing (TCP) device include but are not limited to femoral vein injury, device embolization, cardiac perforation, thromboembolic phenomenon, hematoma, and device failure.²⁻⁴

1.2 Relevant Literature and Data

Among the pediatric population, the major complications occurring with implantation of conventional pacemakers include lead fracture, vascular injury, and pocket infections.⁶⁻⁷ The Micra™ Leadless transcatheter Pacing (TCP) device was designed to avoid these complications and it approved by the FDA in 2016. Early results of the Micra™ Investigational Device Exemption (IDE) study and Micra Post-Approval Registry (PAR) demonstrated excellent safety and efficacy performance in adults; however, results in the pediatric population and in patients with congenital heart disease (CHD) have not been evaluated. The Micra™ Leadless Pacemaker can be implanted in select young patients, thus sparing the subclavian veins during puberty and allowing normal participation in sports without movement restrictions, and avoiding the above complications and also avoiding a surgical scar associated with conventional pacemakers. These factors may also have better psychological effects over a young patient who requires long term pacing.⁵

1.3 Compliance Statement

This study will be conducted in full accordance with each sites IRB's policies and procedures, and all applicable Federal and state laws and regulations including 45 CFR 46, and the HIPAA Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with their IRB's Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of the study is to determine the clinical indications, procedural characteristics, complication and outcomes of children with Leadless Pacemakers.

2.1 Primary Objective

The primary objective of this study is to determine Leadless pacemaker system- or implantation procedure-related complications

2.2 Secondary Objectives (or Aim)

The secondary objectives are to:

- Determine indications for implanting the Leadless pacemaker
- Determine electrical performance of pacemaker at implantation and at follow up
- Determine Leadless Pacemaker Implantation procedural characteristics
- Determine fluoroscopy time for implantation of Leadless Pacemaker
- Determine clinical outcome after Leadless Pacemaker
- Determine radiographic (chest x-ray) appearance of Leadless Pacemaker
- Determine echocardiographic appearance of Leadless Pacemaker

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This study is a retrospective, descriptive study of patients who have had implantation of a Leadless Pacemaker.

3.2 Study Duration, Enrollment and Number of Sites

3.2.1 Date Range of Study

Cases will be included if the Leadless pacemaker was implanted between 05/01/2016 and 02/28/2020. Follow-up information through 02/28/2020 will be included, as well as history preceding the implantation of the Leadless Pacemaker.

3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at approximately 15 investigative sites in the United States and abroad.

Recruitment will stop when all identified subjects are enrolled. It is expected that approximately 30 subjects will be enrolled (identified for further review) to produce 30 evaluable subjects.

3.3 Study Population

3.3.1 Inclusion Criteria

- 1) All patients with a Leadless Pacemaker implanted
- 2) Implantation between 05/01/2016 and 02/28/2020
- 3) Follow up of ≥ 1 week
- 4) Age ≤ 21 years
- 5) Completed Leadless Pacemaker implantation procedure note

3.3.2 Exclusion Criteria

- 1) Patients without Leadless Pacemaker
- 2) Patients who have follow up < 1 week
- 3) Age > 21 years
- 4) Incomplete documentation of Leadless implantation procedure note and/or follow up clinical note

4 STUDY PROCEDURES

The study procedures are limited to review of existing medical records.

4.1 Data Sources

4.1.1 Case ascertainment

An invitation to enroll in the study will be sent to the electrophysiology sections of all major children's hospitals in the United States and abroad via the Pediatric and Congenital Electrophysiology Society (PACES) to identify cases. Potential cases at each individual center will be identified by querying billing records for surgeries with the Hospital outpatient procedure code: Category III CPT code 0387T (Transcatheter insertion or replacement of permanent leadless pacemaker, ventricular) and Hospital Inpatient procedure code ICD 10 code 02HK3NZ (Insertion of intracardiac pacemaker into right ventricle, percutaneous approach). The aforementioned inclusion criteria will be verified by the chart abstractor before continuing with the abstraction.

4.1.2 Data sources

Data from patients will be collected from cardiology and electrophysiology databases including EPIC, MUSE, and the cardiac rhythm device database PACEART. EPIC will be queried for demographic information, admission dates and discharge diagnoses as well as clinical information, echocardiogram reports and chest xray reports. MUSE will be queried for ECG information. PACEART will be queried for Leadless pacemaker parameter information. Data from outside institutions will be submitted electronically using the REDCap system.

4.2 Data Elements to Abstracted

Please refer to the Data Elements document that is attached in Section 3.01 (3.0) of the eIRB application.

5 STATISTICAL CONSIDERATIONS

5.1 Primary and Secondary Endpoints

The primary endpoint is complications associated with Leadless Pacemaker implantation. The primary endpoint of complications will be measured from date of implantation of leadless pacemaker to date of last follow-up or death or heart transplantation. Secondary

endpoints will be determined from date of implantation of leadless pacemaker to date of last follow-up or death or heart transplantation . Primary and Secondary Endpoints will be documented in a binary present or absent fashion where applicable and recorded in descriptive manner where applicable. Secondary endpoints of clinical indications, procedural details, clinical outcomes will be documented in descriptive manner. Pacemaker parameters and electrical characteristics will be determined in conventional millivolts (mV) for measured amplitude and in milliseconds (msec) for measured pulse width and ohms for measured impedance. Implantation time will be measured in total minutes taken to complete the procedure. Fluoroscopy time will be measured in total minutes utilized during implantation procedure.

5.2 Measures to Avoid Bias

Due to the small number of cases for this rare procedure only descriptive statistics will be performed to limit potential bias. Given the small number of cases it is unlikely that a single case would be reported by multiple institutions.

5.3 Statistical Methods

Analysis will include parametric and non-parametric standard statistical methods for descriptive analysis . All endpoints will be reported with descriptive statistics only.

5.4 Sample Size and Power

The sample size will be a convenience sample of all identified cases. The total number of worldwide pediatric cases of Leadless Pacemakers currently in the literature is approximately 2. With a multi-center study, we estimate a sample size of 30 patients.

6 STUDY ADMINISTRATION

6.1 Data Collection and Management

Only individuals directly involved with the study will have access to data. Information is for research only and will be used for publication purposes. Access to identified patient information will be limited to the investigators listed within this IRB application. Study data will be available to other investigators for future research. If the investigators are requesting access to individually identifiable data, data will only be shared with them after they have obtained IRB approval or an IORB exemption determination. Confidentiality and security will be maintained for the database. The database is stored with the same level of protection as the on-line hospital information system at CHOP. This means that users must logon to a web server that sits between the institutional firewall and the firewall to the database, and only this application server is allowed to query the database. Only users approved through our institutional review board will be allowed access to patient identifiers. Data is initially collected in the medical record for each individual study participant. The information will be extracted from the patient's medical record and then transferred into the attached Case Report Form (CRF). The CRFs will include personal identifiers for participant. However, this data will not be accessible as patient numbers and site numbers are assigned for each participant and these will become the identifying information for each study participant. All data will be transmitted to the coordinating institution (CHOP) via REDCap. A master list with patient demographics will only be accessible to the principle investigator and study coordinator. This data will not be available to others. Personally identifiable information of CHOP patients enrolled will only be available to the principal investigator and study coordinator and kept in a separate password protected spreadsheet. Data will be maintained in REDCap for a minimum of six years.

6.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Safeguards are described under Data Collection and Management. No personally identifiable information will be recorded for the purpose of data analysis. Only the principal investigator and study coordinator will have access to the identities of CHOP enrolled or evaluated patients.

6.3 Regulatory and Ethical Considerations

6.3.1 Risk Assessment

This retrospective review poses no more than minimal risk for the study cases. While there may be risk of breach of privacy and confidentiality with the review, the study procedure attempts to alleviate this by coding the data and assigning each subject a study number for data collection and analysis. Only study team members will have access to the data.

6.3.2 Potential Benefits of Study Participation

There are no direct benefits to subjects who are included. However, inclusion will indirectly facilitate an improved understanding which children will benefit from the Leadless Pacemaker and describe any complications associated with this device.

6.3.3 Risk-Benefit Assessment

The risk to subjects is minimal and the potential for indirect benefit is greater therefore the risk/benefit analysis is favorable. The most significant risk posed will be loss of confidentiality. Data will only be made available to the investigators actively involved in the investigation and analysis as specified earlier and will otherwise be kept confidential. The benefit of this study will be to demonstrate which children will benefit from the Leadless Pacemaker and describe any complications associated with this device.

6.4 Informed Consent/Assent and HIPAA Authorization

This study is a chart review. No further procedures will need to be performed on the study subjects, including those evaluated between 5/1/2016 and 02/28/2020. Therefore, this research involves no more than minimal risk to the subjects. Confidentiality will be maintained, as patient identifiers are required insofar as to identify evaluable subjects and will be eliminated and not abstracted into the database with the necessary variables. Waiver of consent/assent therefore is not expected to adversely affect the health and rights of the subjects. More important, the study time frame covers an extensive period; this makes consent/assent impractical, as updated contact information is not assured. Furthermore, for the patients whose contact information are readily available, such as those who received their pacemakers recently, it may not be appropriate to approach the families, as this research involves subjects who are/were gravely ill, have/had experienced significant morbidities, or died. Contacting these patients or their families for consent may precipitate an emotional burden. In addition, those parents whose children did have a favorable outcome may be more willing to participate than those whose children did not. Thus, only a portion of patients may be contacted and only a portion is likely to agree to the study. This would limit any conclusion that may be drawn from the study because of the introduction of bias. The validity of this study depends on the inclusion of all subjects.

6.4.1 Waiver of Consent

Waiver of consent is requested based on the minimal risk to subjects and use of existing data.

6.4.2 Waiver of Assent

Waiver of assent is requested based on minimal risk to subjects and the use of existing data.

6.4.3 Waiver of HIPAA Authorization

Waiver of HIPAA authorization is requested based on the minimal risk to subject involved in collection and analysis of this data.

6.5 Payment to Subjects/Families

Not applicable-This is a retrospective descriptive study and there will be no payment to subjects /families.

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

Unanticipated problems involving risks to subjects and others will be monitored throughout the study.

7.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be reported to the appropriate site's IRB in accordance with that IRB's policies and procedures. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8 PUBLICATION

Data will be presented in a publication submitted to a peer reviewed journal of cardiology.

9 REFERENCES

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