

2.02.32	Leadless Cardiac Pacemakers		
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Policy Statement

- I. The Micra™ VR or Aveir™ (see Policy Guidelines) single-chamber transcatheter pacing system may be considered **medically necessary** in individuals when **both** conditions below are met:
 - A. The individual has high-grade atrioventricular (AV) block (see Policy Guidelines) in the presence of atrial fibrillation or has significant bradycardia and:
 1. Normal sinus rhythm with rare episodes of 2° or 3° AV block or sinus arrest (see Policy Guidelines)
 2. Chronic atrial fibrillation
 3. Severe physical disability (see Policy Guidelines)
 - B. The individual has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as **any** of the following:
 1. History of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection (see Policy Guidelines)
 2. Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins or planned use of such veins for a semi-permanent catheter or current or planned use of an arteriovenous fistula for hemodialysis
 3. Presence of a bioprosthetic tricuspid valve

- II. The Micra™ AV single-chamber transcatheter pacing system may be considered **medically necessary** in individuals when **both** conditions below are met:
 - A. The individual has high-grade AV block (see Policy Guidelines) in the presence of atrial fibrillation or has significant bradycardia and:
 1. Normal sinus rhythm with rare episodes of 2° or 3° AV block or sinus arrest (see Policy Guidelines)
 2. Chronic atrial fibrillation
 3. Severe physical disability (see Policy Guidelines)
 4. There is an indication for VDD pacing and the individual may benefit from maintenance of AV synchronous ventricular pacing (see Policy Guidelines)
 - B. The individual has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as **any** of the following:
 1. History of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection (see Policy Guidelines)
 2. Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins or planned use of such veins for a semi-permanent catheter or current or planned use of an arteriovenous fistula for hemodialysis
 3. Presence of a bioprosthetic tricuspid valve

- III. The Micra™ and Aveir™ single-chamber transcatheter pacing systems are considered **investigational** in all other situations in which the above criteria are not met.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Policy criteria are informed by U.S. Food and Drug Administration (FDA) labeled indications for use and clinical input.

Physical Disability and Infection Risk

Clinical input suggests that severe physical disability encompasses a variety of comorbidities where conventional pacemaker placement would confer undue short- or long-term risk or further compromise a limited ability to meet activities of daily living, including compliance with postoperative care instructions. Examples include individuals with short expected lifespan, individuals with end-stage heart, lung, neurologic, or skeletal conditions, and individuals with mental health or developmental challenges.

The 2019 European Heart Rhythm Association (EHRA) international consensus paper on the prevention, diagnosis, and treatment of cardiac implantable electronic device (CIED) infections has been endorsed by the Heart Rhythm Society (HRS) and lists the following non-modifiable patient-related risk factors for CIED infections:

- End-stage renal disease
- Corticosteroid use
- Renal failure
- History of device infection
- Chronic obstructive pulmonary disease
- Heart failure (New York Heart Association [NYHA] Class \geq II)
- Malignancy
- Diabetes mellitus

Device Contraindications

As per the FDA label, the Aveir™ Leadless Pacemaker Model LSP112V is contraindicated in the following situations:

- Use of any pacemaker is contraindicated in individuals with a co-implanted implantable cardioverter-defibrillator because high-voltage shocks could damage the pacemaker and the pacemaker could reduce shock effectiveness.
- Single-chamber ventricular demand pacing is relatively contraindicated in individuals who have demonstrated pacemaker syndrome, have retrograde ventriculoatrial conduction, or suffer a drop in arterial blood pressure with the onset of ventricular pacing.
- Programming of rate-responsive pacing is contraindicated in individuals with intolerance of high sensor-driven rates.
- Use is contraindicated in individuals with an implanted vena cava filter or mechanical tricuspid valve because of interference between these devices and the delivery system during implantation.
- Persons with known history of allergies to any of the components of this device may suffer an allergic reaction to this device. Prior to use on the patient, the patient should be counseled on the materials contained in the device and a thorough history of allergies must be discussed.

The Aveir™ Leadless Pacemaker is conditionally safe for use in the magnetic resonance imaging (MRI) environment when used according to the instructions in the MRI-Ready Leadless System Manual (which includes equipment settings, scanning procedures, and a listing of conditionally approved components). Scanning under different conditions may result in severe patient injury, death, or device malfunction.

As per the U.S. Food and Drug Administration (FDA) label, the Micra Model MC1VR01 (Micra VR) and Model MC1AVR1 (Micra AV) pacemakers are contraindicated for individuals who have the following types of devices implanted:

- An implanted device that would interfere with the implant of the Micra device in the judgment of the implanting provider
- An implanted inferior vena cava filter
- A mechanical tricuspid valve

- An implanted cardiac device providing active cardiac therapy which may interfere with the sensing performance of the Micra device

As per the FDA label, the Micra Model MC1VR01 and Model MC1AVR1 pacemakers are also contraindicated for individuals who have the following conditions:

- Femoral venous anatomy unable to accommodate a 7.8 mm (23 French) introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity)
- Morbid obesity that prevents the implanted device to obtain telemetry communication within less than 12.5 cm (4.9 in)
- Known intolerance to titanium, titanium nitride, parylene C, primer for parylene C, polyether ether ketone, siloxane, nitinol, platinum, iridium, liquid silicone rubber, silicone medical adhesive, and heparin or sensitivity to contrast medical which cannot be adequately premedicated

As per the FDA label, Micra pacemakers should not be used in individuals for whom a single dose of 1.0 mg dexamethasone acetate cannot be tolerated because the device contains a molded and cured mixture of dexamethasone acetate with the target dosage of 272 µg dexamethasone acetate. It is intended to deliver the steroid to reduce inflammation and fibrosis.

For the MRI contraindications for patients with a Micra MRI device, refer to the Medtronic MRI Technical Manual.

As per the FDA label, some individuals will not benefit from the AV synchronous (VDD) mode supported by the Micra Model MC1AVR1 pacemaker. Individuals with the following conditions should instead be considered for a dual-chamber transvenous pacing system:

- Sinus node dysfunction
- High sinus rates requiring atrial tracking
- Weak atrial contraction
- Symptoms during loss of atrioventricular (AV) synchrony
- Frequent premature atrial or ventricular contractions

High-Grade Atrioventricular Block

Atrioventricular block occurs when there is interference of the electrical signals from the atrium to the ventricle. AV block is categorized based on severity. First degree AV block occurs when signals are transferred more slowly than normal. Second-degree AV block is divided into Type I and Type II. Type I is also called Mobitz Type I or Wenckebach's AV block. There is gradually slower activity which may produce skipped heartbeats. Second-degree Type II is also called Mobitz Type II where more signals fail to reach the ventricles, resulting in a slower and more abnormal heart rhythm. Second-degree AV block can be paroxysmal (not persistent) or permanent. Additionally, high-degree AV block is a form of second-degree AV block in which the conduction ratio is high representing multiple atrial contractions that are not conducting to the ventricle; however, there is still some AV conduction and as such is not a third-degree AV block. Third-degree AV block is a complete block of the electrical signals; while the ventricles contract on their own, the consequences are reduced and irregular heart rate and reduced cardiac output.

Individuals with rare episodes of AV block or sinus arrest generally do not require pacing intervention, although symptomatic individuals might have significant need for pacing. The Micra™ VR and Aveir™ devices are indicated when there is infrequent AV block. The Micra™ AV device is indicated with infrequent or chronic AV block. These definitions come from the intended use definitions of the devices and clinical input. Note that there is no strict definition of the frequency of episodes or the degree of symptoms.

VDD Pacing

VDD pacing is a pacing mode used in pacemakers whereby sensing occurs in both the atrium and ventricle, with pacing only occurring in the ventricle. The first letter (V) indicates that the Ventricle is the pacing chamber, the second letter (D) indicates that both the atrium and ventricle are the sensing chambers, and the third letter (D) indicates that the mode of operation is dual (inhibited and triggered). Uses of VDD pacing include pacemaker syndrome where there is reduced coordination between the atrial and ventricular contractions resulting in lower cardiac output, and when individuals with an implant have complete AV block with preserved sinus functioning. VDD is used in dual chamber transvenous pacemakers and in single-chamber ventricular pacemakers with leads that float in the atrium for sensing. The Micra™ AV leadless pacemaker supports VDD pacing.

Atrioventricular Synchrony

Devices that support maintenance of AV synchrony can sense atrial electrical activity and pace the ventricular chamber accordingly. Pacemakers maintaining AV synchrony may lead to less morbidity and mortality than ventricular stimulation alone and reduce the risk of pacemaker syndrome. The Micra™ AV device provides AV synchronous ventricular pacing similar to a transvenous VDD system. The implanted device depends on the appropriate sensing of atrial mechanical signals to achieve AV synchrony. The level of AV synchrony may vary in individual patients and may not be predictable prior to implant. The manufacturer cautions that loss of AV synchrony can be caused by the interference of mechanical vibrations stemming from patient activities and environments.

Pacemaker Syndrome

In pacemaker syndrome there is reduced coordination between atrial contraction and ventricular contraction, resulting in reduced cardiac output. The syndrome is most commonly seen in the setting of a single-chamber ventricular pacemaker with ventricular sensing and pacing, as with no atrial sensing the ventricles contract at the programmed rate independently from atrial contraction.

Device Retrieval and Replacement

Leadless pacemakers have a limited lifespan. Removal of devices can be complicated by encapsulation due to fibrosis. Devices can instead be deactivated and remain in place, with another device implanted. Use of deactivated and activated devices might result in electromagnetic interference. Based on bench testing, the current recommendation for device end of service care includes adding a replacement device with or without explantation of the deactivated implant. Explantation of the deactivated implant should be performed by a clinician with expertise in the removal of implanted leads. Use of co-implanted deactivated and activated devices has not been clinically tested, and as such Plans will need to consider the medical necessity of repeat implantation. The Aveir™ device features helix-based active fixation designed to facilitate device removal with a dedicated retrieval catheter; however, limited data are available on retrieval success rates.

Mechanical Interference

For axillary transvenous pacemakers, there is a concern that leads or the generator could be impacted by the recoil of using a firearm (e.g., rifles or shotguns). Thus leadless cardiac pacemakers can provide an alternative for patients who suffer lead fracture or malfunction from mechanical stress and may be considered when axillary venous access is present only on a side of the body that would not allow use of equipment producing such mechanical stress (e.g., a firearm).

Description

Pacemakers are intended to be used as a substitute for the heart's intrinsic pacing system to correct cardiac rhythm disorders. Conventional pacemakers consist of 2 components: a pulse generator and electrodes (or leads). Pacemakers are considered life-sustaining, life-supporting class III devices for patients with a variety of bradyarrhythmias. Even though the efficacy and safety profile of conventional pacemakers are excellent, in a small proportion of patients, they may result in lead

complications and the requirement for a surgical pocket. Further, some patients are medically ineligible for conventional pacemakers due to lack of venous access and recurrent infection. Leadless pacemakers are single-unit devices that are implanted in the heart via femoral access, thereby eliminating the potential for complications as a result of leads and surgical pocket. The Micra and Aveir single-chamber transcatheter pacing systems are the only commercially available leadless pacemakers in the U.S. approved by the U.S. Food and Drug Administration.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In April 2016, the Micra™ transcatheter pacing system (Medtronic) was approved by the FDA through the premarket approval process (PMA number: P150033) for use in patients who have experienced one or more of the following conditions:

- symptomatic paroxysmal or permanent high-grade arteriovenous block in the presence of atrial fibrillation
- paroxysmal or permanent high-grade arteriovenous block in the absence of atrial fibrillation, as an alternative to dual-chamber pacing, when atrial lead placement is considered difficult, high-risk, or not deemed necessary for effective therapy
- symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual-chamber pacing, when atrial lead placement is considered difficult, high-risk, or not deemed necessary for effective therapy.

In January 2020, the Micra AV Transcatheter Pacing System Model MCI AVR1 and Application Software Model SW044.were approved as a PMA supplement (S061) to the Micra system described above. The Micra AV includes an enhanced algorithm to provide AV synchronous pacing.

In November 2021, the FDA issued a letter to health care providers regarding the risk of major complications related to cardiac perforation during implantation of leadless pacing systems.²¹ Specifically, the FDA states that "real-world use suggests that cardiac perforations associated with Micra leadless pacemakers are more likely to be associated with serious complications, such as cardiac tamponade or death, than with traditional pacemakers."

In March 2022, the Aveir™ VR Leadless Pacemaker was approved by the FDA through the premarket approval process (PMA number: P150035) for use in patients with bradycardia and:

- normal sinus rhythm with only rare episodes of atrioventricular block or sinus arrest
- chronic atrial fibrillation

- severe physical disability

Rate-Modulated Pacing is indicated for patients with chronotropic incompetence, and for those who would benefit from increased stimulation rates concurrent with physical activity.

Rationale

Background

Conventional Pacemakers

Pacemakers are intended to be used as a substitute for the heart's intrinsic pacing system to correct cardiac rhythm disorders. By providing an appropriate heart rate and heart rate response, cardiac pacemakers can reestablish effective circulation and more normal hemodynamics that are compromised by a slow heart rate. Pacemakers vary in system complexity and can have multiple functions as a result of the ability to sense and/or stimulate both the atria and the ventricles.

Transvenous pacemakers or pacemakers with leads (hereinafter referred to as conventional pacemakers) consist of 2 components: a pulse generator (i.e., battery component) and electrodes (i.e., leads). The pulse generator consists of a power supply and electronics that can provide periodic electrical pulses to stimulate the heart. The generator is commonly implanted in the infraclavicular region of the anterior chest wall and placed in a pre-pectoral position; in some cases, a subpectoral position is advantageous. The unit generates an electrical impulse, which is transmitted to the myocardium via the electrodes affixed to the myocardium to sense and pace the heart as needed.

Conventional pacemakers are also referred to as single-chamber or dual-chamber systems. In single-chamber systems, only 1 lead is placed, typically in the right ventricle. In dual-chamber pacemakers, 2 leads are placed - one in the right atrium and the other in the right ventricle. Single-chamber ventricular pacemakers are more common.

Annually, approximately 200,000 pacemakers are implanted in the U.S. and 1 million worldwide.¹ Implantable pacemakers are considered life-sustaining, life-supporting class III devices for patients with a variety of bradyarrhythmias. Pacemaker systems have matured over the years with well-established, acceptable performance standards. As per the U.S. Food and Drug Administration (FDA), the early performance of conventional pacemaker systems from implantation through 60 to 90 days have usually demonstrated acceptable pacing capture thresholds and sensing. Intermediate performance (90 days through more than 5 years) has usually demonstrated the reliability of the pulse generator and lead technology. Chronic performance (5 to 10 years) includes a predictable decline in battery life and mechanical reliability, but a vast majority of patients receive excellent pacing and sensing free of operative or mechanical reliability failures.

Even though the safety profile of conventional pacemakers is excellent, they are associated with complications particularly related to leads. Most safety data on the use of conventional pacemakers come from registries from Europe, particularly from Denmark where all pacemaker implants are recorded in a national registry. These data are summarized in Table 1. It is important to recognize that valid comparison of complication rates is limited by differences in definitions of complications, which results in a wide variance of outcomes, as well as by the large variance in follow-up times, use of single-chamber or dual-chamber systems, and data reported over more than 2 decades.² As such, the following data are contemporary and limited to single-chamber systems when reported separately.

In many cases when a conventional pectoral approach is not possible, alternative approaches such as epicardial pacemaker implantation and trans-iliac approaches have been used.³ Cohen et al (2001) reported outcomes from a retrospective analysis of 123 patients who underwent 207 epicardial lead implantations.⁴ Congenital heart disease was present in 103 (84%) of the patients. Epicardial

leads were followed for 29 months (range, 1 to 207 months). Lead failure was defined as the need for replacement or abandonment due to pacing or sensing problems, lead fracture, or phrenic/muscle stimulation. The 1-, 2-, and 5-year lead survival was 96%, 90%, and 74%, respectively. Epicardial lead survival in those placed by a subxiphoid approach was 100% at 1 year and at 10 years, by the sternotomy approach (93.9% at 1 year and 75.9% at 10 years) and lateral thoracotomy approach (94.1% at 1 year and 62.4% at 10 years).

Doll et al (2008) reported results of a randomized controlled trial comparing epicardial implantation versus conventional pacemaker implantation in 80 patients with indications for cardiac resynchronization therapy.⁵ The authors reported that the conventional pacemaker group had a significantly shorter intensive care unit stay, less blood loss, and shorter ventilation times while the epicardial group had less exposure to radiation and less use of contrast medium. The left ventricular pacing threshold was similar in the 2 groups at discharge but longer in the epicardial group during follow-up. Adverse events were also similar in the 2 groups. The following events were experienced by 1 (3%) patient each in the epicardial group: pleural puncture, pneumothorax, wound infection, acute respiratory distress syndrome, and hospital mortality.

As a less invasive alternative to the epicardial approach, the trans-iliac approach has also been utilized. Data using trans-iliac approach is limited. Multiple other studies with smaller sample size report a wide range of lead longevity.

Harake et al (2018) reported a retrospective analysis of 5 patients who underwent a transvenous iliac approach (median age, 26.9 years).⁶ Pacing indications included AV block in 3 patients and sinus node dysfunction in 2 patients. After a median follow-up of 4.1 years (range, 1.0 to 16.7 years), outcomes were reported for 4 patients. One patient underwent device revision for lead position-related groin discomfort; a second patient developed atrial lead failure following a Maze operation and underwent lead replacement by the iliac approach. One patient underwent heart transplantation 6 months after implant with only partial resolution of pacing-induced cardiomyopathy. Tsutsumi et al (2010) reported a case series of 4 patients from Japan in whom conventional pectoral approach was precluded due to recurrent lead infections (n=1), superior vena cava obstruction following cardiac surgery (n=2) and a postoperative dermal scar (n=1). The mean follow-up was 24 months and the authors concluded the iliac vein approach was satisfactory and less invasive alternative to epicardial lead implantation. However, the authors reported that the incidence of atrial lead dislodgement using this approach in the literature ranged from 7% to 21%. Experts who provided clinical input reported that trans-iliac or surgical epicardial approach requires special expertise and long-term performance is suboptimal.⁷

Table 1. Reported Complication Rates with Conventional Pacemakers

Complications	Rates, % ^{8,9,10,a}
Traumatic complications	
RV perforation	0.2 to 0.8
RV perforation with tamponade	0.07 to 0.4
Pneumo(hemo)thorax	0.7 to 2.2
Pocket complications	
Including all hematomas, difficult to control bleeding, infection, discomfort, skin erosion	4.75
Including only those requiring invasive correction or reoperation	0.66 to 1.0
Lead-related complications	
Including lead fracture, dislodgement, insulation problem, infection, stimulation threshold problem, diaphragm or pocket stimulation, other	1.6 to 3.8
All system-related infections requiring reoperation or extraction	0.5 to 0.7

Adapted from U.S. Food and Drug Administration executive summary memorandum (2016).¹¹

^a Rates are for new implants only and ventricular single-chamber devices when data were available. Some rates listed in this column are for single- and dual-chamber devices when data were not separated in the publication. Note that Micra transcatheter pacing system is a single-chamber device.

RV: right ventricle.

Potential Advantages of Leadless Cardiac Pacemakers Over Conventional Pacemakers

The potential advantages of leadless pacemakers fall into 3 categories: avoidance of risks associated with intravascular leads in conventional pacemakers, avoidance of risks associated with pocket creation for placement of conventional pacemakers, and an additional option for patients who require a single-chamber pacer.¹²

Lead complications include lead failure, lead fracture, insulation defect, pneumothorax, infections requiring lead extractions and replacements that can result in a torn subclavian vein or the tricuspid valve. In addition, there are risks of venous thrombosis and occlusion of the subclavian system from the leads. Use of a leadless system eliminates such risks with the added advantage that a patient has vascular access preserved for other medical conditions (e.g., dialysis, chemotherapy).

Pocket complications include infections, erosions, and pain that can be eliminated with leadless pacemakers. Further, a leadless cardiac pacemaker may be more comfortable and appealing because unlike conventional pacemakers, patients are unable to see or feel the device or have an implant scar on the chest wall.

Leadless pacemakers may also be a better option than surgical endocardial pacemakers for patients with no vascular access due to renal failure or congenital heart disease.

Leadless Cardiac Pacemakers in Clinical Development

Leadless pacemakers are self-contained in a hermetically sealed capsule. The capsule houses a battery and electronics to operate the system. Similar to most pacing leads, the tip of the capsule includes a fixation mechanism and a monolithic controlled-release device. The controlled-release device elutes a glucocorticosteroid to reduce acute inflammation at the implantation site. Leadless pacemakers have rate-responsive functionality, and current device longevity estimates are based on bench data. Estimates have suggested that these devices may last over 10 years, depending on the programmed parameters.¹¹

Three systems are currently being evaluated in clinical trials: (1) the Micra Transcatheter Pacing System (Medtronic), (2) the Aveir VR Leadless Pacemaker (Abbott; formerly Nanostim, St. Jude Medical); and (3) the WiCS Wireless Cardiac Stimulation System (EBR Systems). The first 2 devices are free-standing capsule-sized devices that are delivered via femoral venous access using a steerable delivery sheath. However, the fixing mechanism differs between the 2 devices. In the Micra Transcatheter Pacing System, the fixation system consists of 4 self-expanding nitinol tines, which anchor into the myocardium; for the Aveir device, there is a screw-in helix that penetrates into the myocardium. In both devices, the cathode is steroid eluting and delivers pacing current; the anode is located in a titanium case. The third device, WiCS system differs from the other devices; this system requires implanting a pulse generator subcutaneously near the heart, which then wirelessly transmits ultrasound energy to a receiver electrode implanted in the left ventricle. The receiver electrode converts the ultrasound energy and delivers electrical stimulation to the heart sufficient to pace the left ventricle synchronously with the right.¹¹

Of these 3, only the Micra and Aveir single-chamber transcatheter pacing systems are approved by the FDA and commercially available in the U.S. Multiple clinical studies of the Aveir predecessor device, Nanostim, have been published^{1,13,14,15,16,17}, but trials have been halted due to the migration of the docking button in the device and premature battery depletion. These issues have since been addressed with the Aveir device.¹⁸

The Micra is about 26 mm in length and introduced using a 23 French catheter via the femoral vein to the right ventricle. It weighs about 2 grams and has an accelerometer-based rate response.¹⁹

The Aveir is about 42 mm in length and introduced using an 25 French catheter to the right ventricle. It also weighs about 3 grams and uses a temperature-based rate response sensor.²⁰

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Conventional pacemaker systems have been in use for over 50 years and current technology has matured with significant similarities in designs across models. Extensive bench testing data with conventional pacemakers and a good understanding of operative and early postimplant safety and effectiveness are available, which limits the need for clinical data collection to understand their safety and effectiveness with regard to implantation, tip fixation, electrical measures, and rate response. As such, an RCT comparing the leadless pacemakers with conventional pacemakers was not required by the U.S. Food and Drug Administration (FDA).

Ventricular Pacing for Individuals Who are Medically Eligible for a Conventional Pacing System Clinical Context and Therapy Purpose

The purpose of single-chamber transcatheter pacing systems in patients with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker is to provide a treatment option that is an alternative to or an improvement on conventional pacing systems.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker who are medically eligible to receive conventional pacing system.

Interventions

The therapy being considered is a single-chamber transcatheter pacing system. The Micra and Aveir devices are single-chamber, ventricular pacemakers implanted through a femoral vein by advancing a delivery catheter into the right ventricle and affixing the device in the myocardium.

Micra has a programmable mode to deactivate pacing and sensing at the end of the life of the device and may remain in the body indefinitely after deactivation. The device also has a retrieval feature at the proximal end for percutaneous snare retrieval and removal.

Aveir has a unique mapping capability to assess correct positioning prior to placement and is specifically designed to be retrieved when therapy needs evolve or the device needs to be replaced.²²

Comparators

The following therapy is currently being used to make decisions about managing patients requiring a pacemaker: a conventional single-chamber pacemaker.

Outcomes

The general outcomes of interest are treatment-related mortality and morbidity. Specifically, the short-term outcomes include acute complication-free survival rate, the electrical performance of the device, including the pacing capture threshold, and adverse events, including procedural and postprocedural complications. Long-term outcomes include chronic complication-free survival rate, the electrical performance of the device, including pacing impedance and pacing thresholds, and chronic complications, including any system explant, replacement (with and without system explant), and repositions. Further, analysis of summary statistics regarding battery length is important.

To assess short-term safety, the first 30 days postimplant is generally considered appropriate because most device and procedural complications occur within this time frame. To assess long-term efficacy and safety as well as issues related to device end-of-life, a follow-up to 9 to 12 years postimplant with an adequate sample size are required to characterize device durability and complications with sufficient certainty.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies on the currently marketed version of the technology were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Nonrandomized Controlled Trials

Micra Leadless Pacemaker

Pivotal Trial

The pivotal investigational device exemption (IDE) trial was a prospective single cohort study enrolling 744 patients with a class I or II indication for implantation of a single-chamber ventricular pacemaker based on national guidelines. Details on the design²³, and results of the IDE trial have been published.^{24,25,26} Trial characteristics and results at 6 months are summarized in Tables 2 and 3, respectively. System performance from the pivotal trial has been published,²⁷ but results are not discussed further.

Of the 744 patients enrolled, implantation of the Micra transcatheter pacing system was successful in 719 (99.2%) of the 725 patients who underwent the procedure. The demographics of the trial population were typical for a single-chamber pacemaker study performed in the U.S., with 42% being female and an average age of 76 years. Sixty-four percent had a pacing indication associated with

persistent or permanent atrial arrhythmias, 72.6% had any atrial fibrillation at baseline, and 27.4% did not have a history of atrial fibrillation. Among those 27.4% (n=199) without atrial fibrillation, 16.1% (n=32) had a primary indication of sinus bradycardia and 3.5% (n=7) had a primary indication of tachycardia-bradycardia.²⁶

The IDE trial had 2 primary endpoints related to safety and efficacy. The trial would meet its safety endpoint if the lower bound of the 95% confidence interval (CI) for the rate of freedom from major complications related to the Micra transcatheter pacing system or implantation procedure exceeded 83% at 6 months. Major complications were defined as those resulting in any of the following: death, permanent loss of device function due to mechanical or electrical dysfunction of the device (e.g., pacing function disabled, leaving device abandoned electrically), hospitalization, prolonged hospitalization by at least 48 hours, or system revision (reposition, replacement, explant).²⁸ The trial would meet its efficacy endpoint if the lower bound of the 95% CI for the proportion of patients with adequate pacing capture thresholds (PCT) exceeded 80% at 6 months. PCT as an effectiveness objective is a common electrical measure of pacing efficacy and is consistent with recent studies. Pacing capture threshold measured in volts is defined as the minimum amount of energy needed to capture the myocardial tissue electrically. Unnecessary high pacing output adversely shortens the battery life of the pacemaker and is influenced by physiologic and pharmacologic factors.²⁸ As per the FDA, demonstrating that "PCT is less than 2 Volts for the vast majority of subjects will imply that the Micra system will have longevity similar to current pacing systems since Micra's capture management feature will nominally set the safety margin to 0.5 Volts above the PCT with hourly confirmation of the PCT."²⁸

Safety and efficacy results of the IDE trial are summarized in Table 3. At 6 months, the trial met both of its efficacy and safety primary endpoints including freedom from major complications related to the system or procedure in 96.0% of the patients (95% CI, 93.9% to 97.3%), compared with a performance goal of 83%, and an adequate pacing capture threshold in 98.3% of the patients (95% CI, 96.1% to 99.5%), compared with a performance goal of 80%.²⁶

Quality of life results of the IDE trial were published in 2018. At baseline and 12 months, 702 (98%) and 635 (88%) participants completed the 36-Item Short Form questionnaire, respectively.²⁵ The mean 36-Item Short Form Physical Component Scale at baseline was 36.3 (standard deviation [SD], 9.0) and the mean 36-Item Short Form Mental Component Scale was 47.3 (SD, 12.5); the general population mean for both scores is 50. Both the Physical Component Scale and Mental Component Scale improved at 12 months post-implant to a mean Physical Component Scale score of 38.6 (SD, 9.4; p<.001) and a mean Mental Component Scale score of 50.7 (SD, 12.2; p<.001) compared with baseline.

IDE trial results were compared post hoc with a historical cohort of 2667 patients generated from 6 previous pacemaker studies, conducted between 2005 and 2012 by Medtronic, that evaluated the performance requirement at 6 months postimplant of right ventricle pacing leads (single-chamber rates obtained by excluding any adverse events only related to the right atrial lead from the analysis). The Micra device was associated with fewer complications than the historical control (4.0% vs. 7.4%; hazard ratio [HR], 0.49; 95% CI, 0.33 to 0.75; p=.001).²⁶ Because there were differences in baseline patient characteristics between the 2 cohorts (patients in the historical cohort were younger and had a lower prevalence of coexisting conditions vs. the IDE trial), an additional propensity-matched analysis was conducted. It showed similar results (HR, 0.46; 95% CI, 0.28 to 0.74). As per the FDA, the lower rate of major complications with the Micra device was driven by reductions in access site events (primarily implant site hematoma and implant site infections), pacing issues (primarily device capture and device pacing issues), and fixation events (there was no device or lead dislodgements in the Micra IDE trial).¹¹

While the overall rate of complications was low, the rate of major complications related to cardiac injury (i.e., pericardial effusion or perforation) was higher in the Micra IDE trial than in the 6 reference

Medtronic pacemaker studies (1.6% vs. 1.1% ; $p=.288$).¹¹ Thus, there appears to be a trade-off between types of adverse events with the Micra transcatheter pacing system and conventional pacemakers. While adverse events related to leads and pocket are eliminated or minimized with the Micra device, certain adverse events (e.g., groin vascular complications, vascular or cardiac bleeding) occur at a higher frequency or are additive (new events) compared with conventional pacemakers. Of these, procedural complications (e.g., acute cardiac perforations) that were severe enough to result in tamponade and emergency surgery were most concerning.¹¹

In addition to lack of adequate data on long-term safety, effectiveness, reliability, and incidence of late device failures and battery longevity, there is also inadequate clinical experience with issues related to devices that have reached end-of-life, including whether to extract or leave the device in situ and possible device-device interactions.²⁹ There are limited data on device-device interactions (both electrical and mechanical) that may occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. Even though there have been few device retrievals and very limited experience with the time course of encapsulation of these devices in humans, it is highly likely that these devices will be fully encapsulated by the end of its typical battery life, and therefore device retrieval is unlikely.²⁹ Current recommendations for end-of-device-life care for a Micra device may include the addition of a replacement device with or without explantation of the Micra device, which should be turned off.³⁰ Grubman et al (2017) reported on system revisions including patients from the IDE study ($n=720$) and the Micra Transcatheter Pacing System Continued Access Study ($n= 269$; NCT02488681).³¹ The Continued Access study was conducted to allow for continued access of the Micra in the same centers as the IDE study while the device was pending the FDA approval. The mean follow-up duration was 13 months (16 months in the IDE patients and 2 months in the continued access patients). There were 11 system revisions in 10 patients, corresponding to a 1.4% (95% CI, 0.7% to 2.6%) actutimes rate of revisions through 24 months. Micra was disabled and left in situ in 7 of 11 revisions including 5 patients in which there was no retrieval attempt, 1 patient in which retrieval was aborted because of fluoroscopy failure, and 1 patient in which retrieval was unsuccessful because of inability to dislodge the device. There were 3 percutaneous retrievals and 1 retrieval during surgical valve replacement. There were no complications associated with retrievals. The report indicates that when a transvenous system was implanted with a deactivated Micra, there were no reported interactions between the 2 systems, although it is not clear how often this occurred. In the historical controls from the IDE study, there were 123 revisions in 117 patients through 24 months (actutimes rate, 5.3%; 95% CI, 4.4 to 6.4). Using propensity score matching, the reduction in system revisions for Micra compared to historical controls was significant (HR , 0.27; 95% CI, 0.14 to 0.54; $p<.001$).

Micra Postapproval Experience

The FDA approval of the Micra transcatheter pacing system was contingent on multiple postapproval studies to provide reasonable assurance of continued safety and effectiveness of the device. Among these, the Micra Transcatheter Pacing System Post-Approval Study, a global, prospective, observational, multicenter study, enrolled 1830 patients to collect data on 1741 patients to estimate the acute complication rate within 30 days of the implant, 500 patients to estimate the 9-year complication-free survival rate, and a minimum of 200 patients with a Micra device revision for characterizing device end of service.²⁸ As per the protocol, if a subsequent device is placed and the Micra is deactivated or explanted, Medtronic would contact the implanting center and request the patient's clinical data concerning the revision. All such data would be summarized, including the type of system revision, how the extraction was attempted, success rate, and any associated complications.²⁹

Study characteristics and results at 1 year (reported in the FDA documents and published) are summarized in Table 2 and 3, respectively. The postapproval study completed enrollment in early March 2018. The definition of a major complication in the postapproval study was the same as the Micra IDE trial. Although some patients who participated in the IDE study consented to also participate in the PAR study, the publication excludes those patients from analysis and therefore

includes an independent population. Results summarized in Table 3 summarize the data at 30 days published by Roberts et al (2017)³² and El-Chami et al (2018)^{33,34}, with a mean follow-up of 6.8 months for 1817 patients, of whom 465 patients had a follow-up for more than 1 year.

At 30 days, the major complication rate was 1.51% (95% CI, 0.78 to 2.62). The major complication rate was lower in the postapproval study than in the IDE trial (odds ratio, 0.58; 95% CI, 0.27 to 1.25) although this did not reach statistical difference. The lower rate of major complications was associated with a decrease in events that led to hospitalization, prolonged hospitalization, or loss of device function in the postapproval study compared with the IDE trial.³² A subsequent subgroup analysis of patients who did not receive perioperative anticoagulation treatment, who received interrupted anticoagulation treatment, or who received continuous anticoagulation treatment did not find a significant difference in rates of acute major complications according to anticoagulation strategy (3.1%, 2.6%, and 1.5%, respectively; $p=0.29$). The most common major complication was pacing problems, including elevated threshold and device capturing issues.³⁵ A subgroup analysis of patients treated with and without atrioventricular node ablation (AVNA) at the time of Micra implantation identified a significantly higher risk of major complications at both 30 days (7.3% vs. 2.0%; $p<0.001$) and 36 months (HR, 3.81; 95% CI, 2.33 to 6.23; $p<0.001$) in the AVNA group versus those without AVNA.³⁶

After a mean follow-up of 6.8 months, the estimated major complication rate at 12 months was 2.7% (95% CI, 2.0% to 3.7%), corresponding to 46 major complications in 41 patients, the majority of which (89%) occurred within 30 days of implantation. The major complications included 14 device pacing issue events, 11 events at the groin puncture site, 8 cardiac effusion/perforation events, 3 infections, 1 cardiac failure event, 1 cardiomyopathy event, and 1 pacemaker syndrome event. Authors compared these results with the same historical cohort of 2667 patients used in the IDE trial and reported a 63% reduction in the risk for major complications through 12 months with the Micra transcatheter pacing system relative to conventional pacemakers (HR, 0.37; 95% CI, 0.27 to 0.52). Additionally, the risk for major complications was lower in the Micra postapproval study than in the IDE trial, but it was a statistically significant difference (HR, 0.71, 95% CI, 0.44 to 1.1).³³ The reduction in major complications compared to historical controls was primarily driven by a significant 74% (95% CI, 54% to 85%; $p=0.0001$) relative risk reduction in system revisions and 71% (95% CI, 51% to 83%; $p=0.0001$) relative risk reduction in hospitalizations. The reduction in risk compared to the IDE trial was driven by significantly lower pericardial effusion rates in the post-approval study.

Piccini et al (2021) published initial data from the ongoing Longitudinal Coverage with Evidence Development Study on Micra Leadless Pacemakers (Micra CED).³⁷ Patients implanted between March 2017 and December 2018 were identified and included from a fee-for-service population with at least 12 continuous months of Medicare enrollment prior to device implantation. A total of 5746 patients with single-chamber leadless Micra pacemakers and 9662 patients with transvenous pacemakers were analyzed. Patients with a Micra pacemaker were more likely to have end-stage kidney disease ($p<0.001$) and a higher mean Charlson Comorbidity Index score (5.1 vs. 4.6; $p<0.001$). The unadjusted acute 30-day complication rate was higher in the Micra subgroup (8.4% vs. 7.3%; $p=0.02$), but no significant difference was found following adjustment for patient characteristics ($p=0.49$). Pericardial effusion and/or perforation within 30 days of implantation was significantly higher in the Micra population in the adjusted model (0.8% vs. 0.4%; $p=0.004$). Patients with Micra pacemakers had a 23% lower risk of complications at 6 months compared to patients receiving a transvenous pacemaker (HR, 0.77; 95% CI, 0.62 to 0.96; $p=0.02$) and a 37% reduction in rates of device revision after adjustment for patient baseline characteristics. The 30-day all-cause mortality rate was not significantly different between groups in both unadjusted ($p=0.14$) and adjusted analyses ($p=0.61$). The study is ongoing with an estimated study completion date of June 2025 (see Table 10). Study characteristics and results are summarized in Tables 2 and 3.

El-Chami et al (2022) subsequently compared reinterventions, chronic complications, and all-cause mortality at 2 years in patients implanted with the Micra leadless pacemaker or a transvenous

pacemaker in the Micra Coverage with Evidence Development study.³⁸ Patients implanted with leadless (n=6219) or transvenous pacemakers (n=10,212) were identified from Medicare claims data and compared contemporaneously. Patients receiving leadless pacemakers had higher rates of end-stage renal disease (12.0% vs. 2.3%) and a higher Charlson comorbidity index (5.1 vs. 4.6). Patients with leadless pacemakers received 37% fewer reinterventions (adjusted HR, 0.62; 95% CI, 0.45 to 0.85; p=.003), defined as system revision lead revision or replacement, system replacement, system removal, or system switch or upgrade to an alternative device. Patients implanted with leadless pacemakers also experienced fewer chronic complications (2.4% vs. 4.8%; adjusted HR, 0.69; 95% CI, 0.60 to 0.81; p<.0001). However, patients receiving leadless pacemakers experienced significantly more other complications, driven by higher rates of pericarditis (adjusted, 1.6% vs. 0.8%; p<.0001). Adjusted all-cause mortality at 2 years was not significantly different between groups (adjusted HR, 0.97; 95% CI, 0.91 to 1.04; p=.37) despite the higher comorbidity index in patients implanted with a Micra device. Study interpretation is limited by reliance on claims data. It is unclear whether all patients receiving leadless devices were considered medically eligible for transvenous devices. Study characteristics and results are summarized in Tables 2 and 3.

Three year outcomes from the Micra Coverage with Evidence Development study were published by Crossley et al in 2023.³⁹ Patients implanted with leadless pacemakers had a 32% lower rate of chronic complications (HR, 0.68; 95% CI, 0.59 to 0.78; p<.001) and a 41% lower rate of any reinterventions compared to patients receiving a transvenous pacemaker (HR, 0.59; 95% CI, 0.44 to 0.78; p=.0002). Use of a leadless system was also associated with a 49% lower rate (p=.01) of upgrades to a dual-chamber system and a 35% lower rate (p=.002) of upgrades to cardiac resynchronization therapy. Heart failure hospitalizations at 3 years were slightly, but significantly lower in adjusted time-to-event models (HR, 0.90; 95% CI, 0.83 to 0.97; p=.005) in patients receiving a leadless system. All-cause mortality rates at 3 years between leadless and transvenous systems were not significantly different after accounting for differences in baseline characteristics (HR, 0.97; 95% CI, 0.92 to 1.03; p=.32). No significant differences in the composite endpoint of time to heart failure hospitalization or death were observed for the original full cohort (p=.28) or in a subgroup of patients without a history of heart failure (p=.98). Study characteristics and results are summarized in Tables 2 and 3.

Hauser et al (2021) analyzed the Food and Drug Administration's Manufacturers and User Facility Device Experience (MAUDE) database to capture major adverse clinical events (MACE) associated with the Micra device compared to the Medtronic CapSureFix transvenous pacing system.⁴⁰ In a search of reports from 2016 through 2020, 363 MACE and 960 MACE were identified for the Micra and CapSureFix devices, respectively. For the Micra device, significantly higher rates of death (26.4% vs. 2.4%; p<.001), cardiac tamponade (79.1% vs. 23.4%; p<.001), and rescue thoracotomy (27.3% vs. 5.2%; p<.001) were reported. Micra patients were more likely to require cardiopulmonary resuscitation (21.8% vs. 1.1%) and to suffer hypotension or shock (22.0% vs. 5.8%) compared to CapSureFix recipients (p<.001). While the overall incidence of myocardial and vascular perforations and tears that may result in cardiac tamponade and death in Micra recipients is estimated to be low (<1%), the authors note that Micra patients were more likely to survive these events if they received surgical repair (p=.014). A subsequent analysis of the MAUDE database focused on rates of Micra perforations from 2016 to 2021. Hauser et al (2022) identified 563 perforations reported within 30 days of implant, resulting in 150 deaths (27%), 499 cardiac tamponades (89%), and 64 pericardial effusions (11%).⁴¹ Emergency surgery was required in 146 patients (26%). Half of all perforations were associated with 139 device problems (25%), 78 operator use problems (14%), and 62 combined device and operator use problems (11%). The most common device problem leading to redeployment were non-capture or inadequate electrical values that required implantable pulse generator recapture and reimplantation or replacement. No device or operator use problems were identified for the remaining 282 perforations (50%), but these were associated with 78 deaths, 245 tamponades, and 57 emergency surgeries. The authors concluded that Micra implantation should be confined to specialized centers capable of managing emergency complications and that a risk score for perforation should be developed and validated. Importantly, these analyses are limited by the

passive nature of the FDA's post-market device surveillance system, which may not capture all voluntary reports from healthcare professionals, consumers, and patients. Such analyses carry a high risk of ascertainment bias which may lead to overestimation of the true prevalence of adverse events.

Atrioventricular Synchrony

Chinitz et al (2022) conducted a prospective, single-arm study (AccelAV) at 20 sites in the United States and Hong Kong to assess the efficacy of the Micra AV leadless pacemaker in promoting atrioventricular synchrony (AVS) in adults with a history of atrioventricular (AV) block (n=157).⁴² This device uses an accelerometer and detection algorithm to mechanically sense atrial contractions to facilitate VDD pacing and AVS in individuals with normal sinus function. Based on a preliminary feasibility study (MARVEL 2),⁴³ a sample size of 150 individuals was expected to provide at least 50 individuals with complete AV block and normal sinus function to permit estimation of AVS. Micra AV implantation and completion of the 1-month study visit was achieved by 139 individuals, of which 54 (mean age, 77 years; 55.6% female) comprised the intended use population with a predominant heart rhythm of complete AV block with normal sinus rhythm. The primary endpoint was the rate of AVS during a 20-minute resting period at 1 month postimplant in these patients. Atrioventricular synchronous pacing was defined as a ventricular marker preceding a P wave within 300 ms, regardless of the underlying cardiac rhythm. Secondary endpoints included stability of AVS during rest between 1 and 3 months, percent AVS during a 24-hr ambulatory period at 1 months, and change in stroke volume. Quality of life was also measured with the EQ-5D-3L health status assessment. At 1 month, AVS percentage at rest was 85.4% (95% CI, 81.1% to 88.9%; median, 90.0%) during VDD pacing, with 85.2% of patients achieving >70% resting AVS. At the 3-month visit, 37/54 remained in the same rhythm. Among these subjects, no significant change in AVS synchrony was detected (p=.43) between the 3-month (mean, 84.1%; 95% CI, 78.3% to 88.6%) and 1-month visits (mean, 84.1%; 95% CI, 81.2% to 89.9%). At the 1 month visit, average 24-hour ambulatory AVS was 74.5% (95% CI, 70.4% to 78.2%). EQ-5D-3L health status scores significantly improved by 0.07 points between baseline and 3 months (p=.031) among patients with complete AV block and normal sinus function. Ambulatory AVS percentage significantly increased from 71.9% to 82.6% (p<.001) in twenty patients who participated in a substudy at a mean follow-up of 9.5 months designed to characterize the impact of optimized device programming. Improvement in AVS was most evident during elevated sinus rates between 80 and 110 bpm. In the safety cohort (n=152), there were 14 major complications, including 4 pericardial effusions and 2 heart failure events. One pericardial effusion resulted in perforation and death in a 92-year-old woman with high baseline risk. A second death was reported in an 83-year-old man at 127 days postimplant but was not considered system- or procedure-related. No device upgrades and 1 device explantation and replacement was reported during follow-up. Study interpretation is limited by lack of a comparator group and short duration of follow-up. The ongoing Micra AV Post-Approval Registry (NCT04253184) has follow-up planned through 3 years. The investigators also noted that the AVS percentage required to maintain a clinical benefit over time is unknown, but likely is not 100%.

Aveir Leadless Pacemaker Pivotal Trial

The pivotal investigational device exemption (IDE) trial of the Aveir leadless pacemaker (LEADLESS II - Phase 2; NCT04559945) was a multicenter, prospective single cohort study enrolling 200 patients with a guidelines-based indication for single-chamber pacing.²⁰ Primary results from the IDE trial have been summarized in a published research correspondence,¹⁸ and FDA documents.²⁰ Trial characteristics and results through 6 and 12 months are summarized in Tables 2 and 3, respectively. Implantation of the Aveir leadless pacing system was successful in 196/200 (98%) trial subjects (mean age, 75.6 years; 37.5% female). The primary indication for pacing was chronic atrial fibrillation with 2nd or 3rd degree atrioventricular block (52.5%). The trial had 2 primary endpoints related to safety and efficacy. The trial would meet its safety endpoint if the lower bound of the 97.5% CI for the complication-free rate exceeded 86% at 6 weeks. A complication was defined as a device- or procedure-related serious adverse event, including those that prevented initial implantation. The trial

would meet its efficacy endpoint if the lower bound of the 97.5% CI for the composite success rate exceeded 85% at 6 weeks. The confirmatory effectiveness endpoint was considered met if the pacing threshold voltage was ≤ 2.0 V at 0.4 ms and the sensed R-wave amplitude was either ≥ 5.0 mV at the 6-week visit or \geq the value at implant.

Safety and efficacy results of the Aveir IDE trial are summarized in Table 3. At 6 weeks, the trial met both of its confirmatory safety and efficacy endpoints, including freedom from device-or-procedure-related complications in 96% of patients (95% CI, 92.2% to 98.2%), compared with a performance goal of 86%, and a composite success rate of 95.9% of patients (95% CI, 92.1% to 98.2%), compared with a performance goal of 85%. The 6-month complication-free rate was 94.9% (95% CI, 90.0% to 97.4%). The most frequent complications included 3 cardiac tamponade events and 3 premature deployment events. The rate of cardiac perforation/tamponade/pericardial effusion was 1.5%. No dislodgement events were reported in the Aveir cohort.

Confirmatory secondary endpoints included assessment of an appropriate and proportional rate-response during a Chronotropic Assessment Exercise Protocol (CAEP) exercise protocol and an estimated 2-year survival rate.²⁸ The CAEP assessment was initiated in 23 subjects, of which 17 were considered analyzable. The rate-response slope was 0.93 (95% CI, 0.78 to 1.08), which fell within the prespecified range of 65% to 135%. The estimated 2-year survival rate based on the Nanostim Phase 1 cohort (N=917) was 85.3% (95% CI, 82.7% to 87.4%), which exceeded the performance goal of 80%.

Reddy et al (2023) reported 1-year outcomes from the LEADLESS II IDE trial.⁴⁴ Confirmatory safety and efficacy endpoints at 1 year were both met for European regulatory approval, including freedom from device-or-procedure-related complications in 93.2% of patients (95% CI, 88.7% to 95.9%), compared with a performance goal of 83%, and a composite success rate of 95.1% (95% CI, 91.2% to 97.6%), compared with a performance goal of 80%. Most complications (11 of 15) were reported within the first 3 days post-implantation, including 4 cardiac tamponade events, 3 premature deployments with or without device migration, 2 access site bleeding events, 1 pulmonary embolism, and 1 case of deep vein thrombosis. Four long-term complications were reported between 3.8 and 9.5 months post-implantation, including 2 cases of heart failure and 2 cases of pacemaker-induced cardiomyopathy. Based on the device-use conditions in this analysis cohort, the investigators estimate that mean device battery longevity is 17.6 ± 6.6 years (95% CI, 16.6 to 18.6).

The current evidence on the use of the Aveir device is limited by a lack of adequate data on quality of life, long-term safety, effectiveness, reliability, and incidence of late device failures and direct evidence on battery longevity. While the device is designed to be retrieved when therapy needs evolve or the device needs to be replaced, there is currently inadequate clinical experience with issues related to devices that have reached end-of-life. Survival data for the currently marketed version of the Aveir device has not been reported.

Table 2. Summary of Key Nonrandomized Trial Characteristics

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Micra						
Reynolds et al (2016)²⁶; NCT02004873	Prospective single cohort	19 countries in North America, Europe, Asia, Australia, and Africa	2013-2015	Patients who met a class I or II guidelines-based indication for pacing and suitable candidates for single-chamber ventricular demand pacing	Micra pacemaker (n=744)	6
Roberts et al (2017)³²;	Prospective single cohort (Micra Post-	23 countries in North America, Europe, Asia,	2016-2018	Any patient to be implanted with a Micra device	Micra pacemaker (n=795 ^a and 1830 ^b)	1.8 ^a
El-Chami et al (2018)^{33,34};	Approval Study)	Australia, and Africa				6.8 ^b
NCT02536118						

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Piccinni et al (2021) ³⁷	Prospective Medicare registry	United States	2017-2018	All Medicare patients implanted with a leadless single-chamber pacemaker or transvenous single-chamber pacemaker with at least 12 months of continuous Medicare enrollment prior to implantation	Micra pacemaker (n=5746); Transvenous pacemaker (n=9662)	6
El-Chami et al (2022) ³⁸	Prospective Medicare registry	United States	2017-2018	All Medicare patients implanted with a leadless single-chamber pacemaker or transvenous single-chamber pacemaker with at least 12 months of continuous Medicare enrollment prior to implantation	Micra pacemaker (n=6219); Transvenous pacemaker (n=10,212)	24
Crossley et al (2023) ³⁹	Prospective Medicare registry	United States	2017-2018	All Medicare patients implanted with a leadless single-chamber pacemaker or transvenous single-chamber pacemaker with at least 12 months of continuous Medicare enrollment prior to implantation	Micra pacemaker (n=6219); Transvenous pacemaker (n=10,212)	36
Chinitz et al (2022) ⁴²	Prospective single-cohort	United States and Hong Kong	2020-2021	Adults with a history of AV block or complete AV block and normal sinus rhythm implanted with the Micra AV leadless pacemaker	Micra AV pacemaker (N=157) Micra AV pacemaker in adult with complete AV block and normal sinus rhythm (n=54)	3
Aveir						
FDA SSED (2022); PMA P150035 ²⁰ ; Reddy et al (2021) ¹⁸	Prospective single cohort	43 sites in the United States, Canada, and Europe	2020-2021	Patients with a guidelines-based indication for single-chamber pacing	Aveir pacemaker (n=200)	6
Reddy et al (2023) ⁴⁴	Prospective single cohort	43 sites in the United States, Canada, and Europe	2020-2021	Patients with a guidelines-based indication for single-chamber pacing	Aveir pacemaker (n=210)	12

AV: atrioventricular; FDA: U.S. Food and Drug Administration; NCT: national clinical trial; PMA: premarket approval; SSED: Summary of Safety and Effectiveness Data.

^a 30-day results reported by Roberts et al (2017).³²

^b Results after a mean follow-up of 6.8 months reported by El-Chami et al (2018)^{33,34}.

Table 3. Summary of Key Nonrandomized Trial Results

Study	Freedom From System- or Procedure-Related Major Complications	Percentage of Patients With Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
Micra IDE Trial	6 Months	6 Months	6 Months	6 Months
Reynolds et al (2016) ²⁶				

Study	Freedom From System- or Procedure-Related Major Complications	Percentage of Patients With Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
N	719 ^a ; 300 ^b	719	725	725
Micra	96.0%	98.3% (≤ 2.0 V)	<ul style="list-style-type: none"> • Death: 1 (0.1) • Loss of device function: 1 (0.1) • Hospitalization: 13 (2.3) • Prolonged hospitalization (≥ 48 h): 16 (2.6) • System revision^c: 3 (0.4) 	TMCs: 28 in 25 patients (3.5%) <ul style="list-style-type: none"> • DVT: 1 (0.1) • Pulmonary TE: 1 (0.1) • Events at groin puncture site: 5 (0.7) • Cardiac perforation: 11 (1.6) • Pacing issues: 2 (0.3) • Others: 8 (1.7)
95% CI	93.9% to 97.3%	95.4% to 99.6%	NA	NA
	12 Months	12 Months	12 Months	12 Months
Duray et al (2017)⁴⁵				
N	726	NA	726	726
Micra	96.0%	NR (93%)	<ul style="list-style-type: none"> • Death: NR (0.1) • Loss of device function: NR (0.1) • Hospitalization: NR (2.3) • Prolonged hospitalization (≥ 48 h): NR (2.2) • System revision^c: NR (0.7) • Loss of device function: NR (0.3) 	TMCs: 32 in 29 patients (4.0) <ul style="list-style-type: none"> • DVT: 1 (0.1) • Pulmonary TE: 1 (0.1) • Events at groin puncture site: 5 (0.7) • Cardiac perforation: 11 (1.6) • Pacing issues: 2 (0.3) • Others: 11 (1.7)
95% CI	94.2% to 97.2%	NA		
Micra Post-Approval Study				
	30 Days	30 Days	30 Days	30 Days
Roberts et al (2017)³²				
N	795	NA	795	795
Micra	97.3% ^d	87.2% (≤ 1.0 V) 97.0% (≤ 2.0 V)	<ul style="list-style-type: none"> • Death: 1 (0.13%) • Hospitalization: 4 (0.50) • Prolonged hospitalization (≥ 48 h): 9 (1.01) 	TMCs: 13 in 12 patients (1.51% [95% CI, 0.78 to 2.62]) <ul style="list-style-type: none"> • DVT: 1 (0.13) • Events at groin puncture site: 6 (0.75) • Cardiac effusion/perforation: 1 (0.13)

Study	Freedom From System- or Procedure- Related Major Complications	Percentage of Patients With Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
			<ul style="list-style-type: none"> System revision: 2 (0.25) 	<ul style="list-style-type: none"> Device dislodgement: 1 (0.13) Pacing issues: 1 (0.13) Others: 3 (0.38)
OR (95% CI)	0.58 (0.27 to 1.25) ^e	NA	NA	NA
	1 Year	1 Year	1 Year	1 Year
El-Chami et al (2018)³⁴				
N	1817	NA	NA	1817
Micra	97.3% ^d	NA	NA	TMCs: 46 in 41 patients (2.7% [95% CI, 2.0% to 3.6%]) <ul style="list-style-type: none"> Pericardial effusions: 8 (0.44) Dislodgement: 1 (0.06) Procedure-related infections: 3 (0.17) Procedure-related deaths: 5 (0.28) As per FDA: Complications: 61 in 53 (deaths: 4 procedure-related; 3 unknown relatedness; 3 pending adjudication)
HR (95% CI)	0.71 (0.44 to 1.1) ^e 0.37 (0.27 to 0.52) ^g	NA	NA	NA
Micra CED Study				
	30 days and 6 months	NA	NA	30 days and 6 months
Piccini et al (2021)³⁷				
N	5746	NA	NA	5746
Micra	30-d, unadjusted: NR	NA	NA	Acute (30 days), n (%):
complicatio	30-d, adjusted: 0.3 (-			<ul style="list-style-type: none"> Overall: 484 in 5746 patients (8.4) Embolism and thrombosis, 202 (3.5) Events at puncture site, 78 (1.4) Cardiac effusion and/or perforation, 47 (0.8) Device-related complication, 81 (1.4) Other complications, 136 (2.4)
n rate, RR or	0.6 to 1.3)			
HR (95% CI)	6-mo, unadjusted: 0.84 (0.68 to 1.03)			6-Month CIF Estimates, % (95% CI)
	6-mo, adjusted: 0.77 (0.62 to 0.96)			

Study	Freedom From System- or Procedure- Related Major Complications	Percentage of Patients With Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
				<ul style="list-style-type: none"> Overall: 3.2 (2.9 to 3.6) Embolism and thrombosis: <10 events Device-related complications: 1.7 (1.5 to 1.9) Other complications: 1.6 (1.3 to 1.8)
	24 months ^h	NA	NA	24 months ⁱ
El-Chami et al (2022)³⁸				
N	6219 (Micra) 10,212 (transvenous)	NA	NA	6219 (Micra) 10,212 (transvenous)
Micra	adjusted, 3.1%	NA	NA	Chronic complications CIF Estimates, % (95% CI) <ul style="list-style-type: none"> Overall: 4.6 (4.2 to 4.9) Embolism and thrombosis: <10 events Device-related complications: 2.4 (2.2 to 2.5) Other complications: 2.1 (2.0 to 2.3) <ul style="list-style-type: none"> Pericarditis: 1.6 (1.4 to 1.9)
Transvenous	adjusted, 4.9%	NA	NA	Chronic complications CIF Estimates, % (95% CI) <ul style="list-style-type: none"> Overall: 6.5 (6.1 to 6.9) Embolism and thrombosis: 0.2 (0.2 to 0.2) Device-related complications: 4.8 (4.7 to 5.0) Other complications: 1.4 (1.3 to 1.6) <ul style="list-style-type: none"> Pericarditis: 0.8 (0.7 to 0.9)
RR or HR (95% CI)	adjusted, 0.62 (0.45 to 0.85)	NA	NA	Relative risk reduction (95% CI) <ul style="list-style-type: none"> Overall: 31 (19 to 40) Embolism and thrombosis: 46 (-17 to 75)

Study	Freedom From System- or Procedure-Related Major Complications	Percentage of Patients With Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
				<ul style="list-style-type: none"> • Device-related complications: 52 (42 to 60) • Other complications: -48 (-91 to -15) <ul style="list-style-type: none"> ○ Pericarditis: -105 (-180 to -50)
	36 months ^h	NA	NA	36 months ⁱ
Crossley et al (2023)³⁹,				
N	6219 (Micra) 10,212 (transvenous)	NA	NA	6219 (Micra) 10,212 (transvenous)
Micra	adjusted, 3.6%	NA	NA	Chronic complications CIF Estimates, % (95% CI) <ul style="list-style-type: none"> • Overall: 4.9 (4.6 to 5.2) • Embolism and thrombosis: <11 events • Device-related complications: 2.6 (2.5 to 2.7) • Other complications: 2.1 (2.0 to 2.2) <ul style="list-style-type: none"> ○ Pericarditis: 1.7 (1.4 to 1.9) ○ Hemothorax: 0.7 (0.6 to 0.8)
Transvenous	adjusted, 6.0%	NA	NA	Chronic complications CIF Estimates, % (95% CI) <ul style="list-style-type: none"> • Overall: 7.1 (6.7 to 7.6) • Embolism and thrombosis: 0.3 (0.3 to 0.3) • Device-related complications: 5.2 (5.1 to 5.3) • Other complications: 1.5 (1.4 to 1.6) <ul style="list-style-type: none"> ○ Pericarditis: 0.9 (0.8 to 1.0) ○ Hemothorax: 0.9 (0.7 to 1.0)
RR or HR (95% CI)	adjusted, 0.41 (0.22 to 0.56)	NA	NA	Relative risk reduction (95% CI) <ul style="list-style-type: none"> • Overall: 32 (22 to 41)

Study	Freedom From System- or Procedure- Related Major Complications	Percentage of Patients With Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
				<ul style="list-style-type: none"> Embolism and thrombosis: 56 (6 to 79) Device-related complications: 51 (41 to 59) Other complications: -39 (-76 to -9) <ul style="list-style-type: none"> Pericarditis: -93 (-161 to -42) Hemothorax: 22 (-18 to 48)
Micra AV AccelAV Study				
	3 months	NA	NA	3 months
Chinitz et al (2022)⁴²				
N	54; 152 ^j	NA	NA	54; 152 ^j
Micra AV	Overall (n=152): 90.8%	NA	NA	Events, n (%) - Overall
	Intended Use (n=54): 90.7%			<ul style="list-style-type: none"> Total events: 14/152 (9.2) Cardiac effusion/perforation: 4 (2.6) Elevated threshold: 1 (0.7) Cardiac rhythm disorder: 4 (2.6) Other: 5 (3.3)
				Events, n (%) - Intended Use
				<ul style="list-style-type: none"> Total events: 5/54 (9.3) Cardiac effusion/perforation: 0 (0) Elevated threshold: 1 (1.9) Cardiac rhythm disorder: 1 (1.9) Other: 3 (5.6)
Aveir LEADLESS II IDE Trial				
	6 Weeks 6 Months	6 Weeks 6 Months	NR	6 Weeks
FDA SSED (2022); PMA P150035²⁰; Reddy et al (2021)¹⁸				
N	200	200	NR	200
Aveir	0.960 (0.922 to 0.982); 0.933 (0.898 to 0.956)	0.959 (0.921 to 0.982); 0.934 (0.899 to 0.960)	NR	SADEs: 9 in 8 patients (4.0% [95% CI, NR])
				<ul style="list-style-type: none"> Cardiac perforation/tamponade: 3 (1.5)

Study	Freedom From System- or Procedure- Related Major Complications	Percentage of Patients With Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
				<ul style="list-style-type: none"> • Premature deployment with migration: 2 (1.0) • Premature deployment without migration: 1 (0.5) • Vascular access site complication - bleeding: 1 (0.5) • Embolism: 1 (0.5) • Thrombosis (0.5)
	• 1 year	1 year	NR	1 year
Reddy et al (2023)⁴⁴				
N	210	210	NR	210
Aveir	0.932 (0.887 to 0.959)	0.915 (0.912 to 0.976)	NR	SADEs: 15 in 14 patients (6.7% [95% CI, NR]) <ul style="list-style-type: none"> • Cardiac perforation/tamponade/pericardial effusion: 4 (1.9) • Premature deployment with or without migration: 3 (1.5) • Vascular access site bleeding event: 2 (1.0) • Heart failure: 2 (1.0) • Pacemaker-induced cardiomyopathy: 2 (1.0) • Pulmonary embolism: 1 (0.5) • DVT: 1 (0.5)

CED: coverage with evidence development; CI: confidence interval; CIF: cumulative incidence function; DVT: deep vein thrombosis; FDA: U.S. Food and Drug Administration; HR: hazard ratio; IDE: investigational device exemption; OR: odds ratio; NA: not available; NR: not reported; PMA: premarket approval; RR: relative risk; SADE: serious adverse device effects; SSED: Summary of Safety and Effectiveness Data; TE: thromboembolism; TMC: Total major complication.

^a Total number of patients who received the implant successfully.

^b Number of patients for whom data were available for 6-month evaluation.

^c Device explant, reposition, or replacement.

^d Calculations performed by BCBSA based on the major complication rate (2.7%; 95% CI 2.0% to 3.6%) reported by El-Chami et al (2018).

^e Major complication vs. IDE trial.

^f Unclear if the complications met the definition of a major complication as events leading to death, hospitalization, prolonged hospitalization by 48 hours, system revision, or loss of device therapy.

^g Major complication vs. historical controls.

^h Device reintervention rate.

ⁱ Chronic complications.

^j Overall safety and intended use (n=54) subpopulation.

Aveir Postapproval Experience

Continued FDA approval of the Aveir transcatheter pacing system is contingent on the results of the Aveir VR Real-World Evidence Study.⁴⁶ This post-approval study is designed to evaluate the long-term safety of the Aveir device in a real-world sample of 2100 participants. Both acute and long-term safety will be evaluated as post implant complication-free rates at 30-days and 10-years. Six-month data were submitted to the FDA in September 2022 but have not yet been published as of March 2023. Ten-year reports are due in March 2032.

Tables 4 and 5 display notable limitations identified for key studies.

Table 4. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Micra					
Reynolds et al (2016) ²⁶ ; Duray et al (2017) ⁴⁵ .			2. This was a single cohort study; there was no comparator		1-2. Insufficient duration for benefit and harms
Roberts et al (2017) ³² ; El-Chami et al (2018) ³⁴ .			2. This was a single cohort study; there was no comparator		1-2. Insufficient duration for benefit and harms
Piccini et al (2021) ³⁷ .	1. It is unclear whether all patients were considered medically eligible for a transvenous device.				1-2. Insufficient duration for benefit and harms
El-Chami et al (2022) ³⁸ .	1. It is unclear whether all patients were considered medically eligible for a transvenous device.				1-2. Insufficient duration for benefit and harms
Crossley et al (2023) ³⁹ .	1. It is unclear whether all patients were considered medically eligible for a transvenous device.				1-2. Insufficient duration for benefit and harms
Chinitz et al (2022) ⁴² .	1. Approximately 25% of patients were not considered medically eligible for a		2. This was a single cohort study; there was no comparator	1. Outcomes not stratified by medical eligibility; 5. Clinically significant difference for atrioventricular	1-2. Insufficient duration for benefit and harms

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
	transvenous device			synchrony not known	
Aveir FDA SSED (2022); PMA P150035²⁰; Reddy et al (2021)¹⁸.			2. This was a single cohort study; there was no comparator	1. Survival data not based on currently marketed device; quality of life outcomes are not available	1-2. Insufficient duration for benefit and harms
Reddy et al (2023)⁴⁴.			2. This was a single cohort study; there was no comparator	1. Survival data and quality of life outcomes not reported	1-2. Insufficient duration for benefit and harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical Reporting ^f
Micra Reynolds et al (2016)²⁶; Duray et al (2017)⁴⁵.	1. Participants not randomly allocated; design was prospective single cohort study	1. Not blinded to treatment assignment; 2. Not blinded outcome assessment. However, adverse events analyzed by an independent clinical event committee. Trial oversight provided by an independent data and safety monitoring committee.				
Roberts et al (2017)³²; El-Chami et al (2018)³⁴.	1. Participants not randomly allocated; design was prospective registry	1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome				

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
		assessed by treating physician				
Piccini et al (2021) ³⁷ ,	1. Participants not randomly allocated; design was prospective registry	1. Not blinded to treatment assignment; 2. Outcome assessment not described.				
El-Chami et al (2022) ³⁸ ,	1. Participants not randomly allocated; design was prospective registry	1. Not blinded to treatment assignment; 2. Outcome assessment not described.				
Crossley et al (2023) ³⁹ ,	1. Participants not randomly allocated; design was prospective registry	1. Not blinded to treatment assignment; 2. Outcome assessment not described.				
Chinitz et al (2022) ⁴² ,	1. Participants not randomly allocated; design was prospective single cohort study	1. Not blinded to treatment assignment; 2. Blinding of outcome assessment unclear.				
Aveir FDA SSED (2022); PMA P150035²⁰; Reddy et al (2021)¹⁸,	1. Participants not randomly allocated; design was prospective single cohort	1. Not blinded to treatment assignment; 2-3. Blinding of outcome assessment not described				
Reddy et al (2023)⁴⁴,	1. Participants not randomly allocated; design was prospective single cohort	1. Not blinded to treatment assignment; 2-3. Blinding of outcome assessment not described				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Ventricular Pacing for Individuals Who Are Medically Eligible for a Conventional Pacing System

The evidence for use of the Micra transcatheter pacing system consists of a pivotal prospective cohort study, a postapproval prospective cohort study, a Medicare registry, and a retrospective FDA database analysis. Results at 6 months and 1 year for the pivotal study reported high procedural success (>99%) and device effectiveness (pacing capture threshold met in 98% of patients). Most of the system- or procedural-related complications occur within 30 days. At 1 year, the incidence of major complications did not increase substantially from 6 months (3.5% at 6 months vs. 4% at 1 year). Results of the postapproval study were consistent with a pivotal study and showed a lower incidence of major complications up to 30 days postimplantation and 1 year (1.5% and 2.7%, respectively). In both studies, the point estimates of major complications were lower than the pooled estimates from 6 studies of conventional pacemakers used as a historical comparator. While the Micra transcatheter pacing system eliminates adverse events associated with lead and pocket issues, its use results in additional complications related to the femoral access site (groin hematomas, access site bleeding) and implantation and release of the device (traumatic cardiac injury). Initial data from a Medicare registry found a significantly higher rate of pericardial effusion and/or perforation within 30 days in patients with the leadless Micra pacemaker compared to patients who received a transvenous device; overall 6-month complication rates were significantly lower in the Micra group in the adjusted analysis ($p=.02$). In a real-world study of Medicare patients, the Micra device was associated with a 41% lower rate of reinterventions and a 32% lower rate of chronic complications compared with transvenous pacing, with no significant difference in adjusted all-cause mortality at 3 years despite the higher comorbidity index for patients implanted with a Micra device. However, patients receiving the Micra device experienced significantly more other complications, driven by higher rates of pericarditis. No significant differences were noted in the composite endpoint of time to heart failure hospitalization or death for the full cohort ($p=.28$) or the subgroup without a history of heart failure ($p=.98$). It is also unclear whether all patients were considered medically eligible for a conventional pacing system. A 2021 analysis of the FDA Manufacturer's and User Facility Device Experience (MAUDE) database revealed significantly higher rates of death, cardiac tamponade, and rescue thoracotomy in Micra recipients compared to patients implanted with a transvenous pacemaker ($p<.001$), although this study is limited by potential risk of ascertainment bias. A single-arm study of the Micra AV device reported that 85.2% of individuals with complete AV block and normal sinus rhythm successfully achieved a >70% resting AV synchrony (AVS) rate at 1 month postimplant and that AVS rates could be further enhanced with additional device programming. However, clinically meaningful rates of AVS are unknown. Longer-term device characterization is planned in the Micra AV Post-Approval Registry through 3 years. The evidence for the use of the Aveir transcatheter pacing system consists of a pivotal prospective cohort study. Primary safety and efficacy outcomes at 6 weeks exceeded performance goals for complication-free rate and composite success rate (96.0% and 95.9%, respectively). Results at 6 months were similar and at 1 year were 93.2% and 91.5%, respectively. Incidence of major complications at 1 year was 6.7% compared to 4.0% at 6 months. The 2-year survival estimate of 85.3% is based on Phase 1 performance with the predecessor Nanostim device.

Considerable uncertainties and unknowns remain in terms of the durability of the devices and end-of-life device issues. Early and limited experience with the Micra device has suggested that retrieval is unlikely because in due course of time, the device will be encapsulated. There are limited data on device-device interactions (both electrical and mechanical), which might occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. While the Aveir device is specifically designed to be retrieved when therapy needs evolve or the device needs to be replaced, clinical experience with device retrieval has not yet been reported.

Ventricular Pacing for Individuals who are Medically Ineligible for a Conventional Pacing System Clinical Context and Therapy Purpose

The purpose of single-chamber transcatheter pacing systems in patients with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker is to provide a treatment option that is an alternative to or an improvement on conventional pacing systems.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with a class I or II guidelines-based indication for implantation of a single-chamber ventricular pacemaker who are medically ineligible for a conventional pacing system.

Interventions

The therapy being considered is a single-chamber transcatheter pacing system (e.g., Micra, Aveir).

Comparators

The following therapy and practice are currently being used to make decisions about managing patients ineligible for a conventional pacemaker: medical management and/or conventional single-chamber pacemakers placed via trans-iliac venous lead placement or surgical epicardial pacemaker.

Outcomes

The general outcomes of interest are treatment-related mortality and morbidity. Specifically, the short-term outcomes include acute complication-free survival rate, the electrical performance of the device, including the pacing capture threshold, and adverse events, including procedural and postprocedural complications. Long-term outcomes include chronic complication-free survival rate, the electrical performance of the device, including pacing impedance, and pacing thresholds and chronic complications, including any system explant, replacement (with and without system explant), and repositions. Further, analysis of summary statistics regarding battery length is important.

To assess short-term safety, the first 30 days postimplant is generally considered appropriate because most device and procedural complications occur within this time frame. To assess long-term efficacy and safety as well as issues related to device end-of-life, a follow-up to 9 to 12 years postimplant with an adequate sample size are required to characterize device durability and complications with sufficient certainty.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies on the currently marketed version of the technology were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Nonrandomized Controlled Trials

No studies that exclusively enrolled patients who were medically ineligible to receive a conventional pacing system were identified.

Micra Leadless Pacemaker

In the IDE trial, 6.2% or 45 patients received the Micra Transcatheter Pacing System because they were medically ineligible for a conventional pacing system due to compromised venous access, the need to preserve veins for hemodialysis, thrombosis, a history of infection, or the need for an indwelling venous catheter. A stratified analysis of these 45 patients was not presented in the originally published paper²⁶, or the FDA documents.^{11,19,28,29}

In the postapproval registry, the authors reported stratified results for 105 of 1820 patients who had previous cardiac implantable electronic device (CIED) infection.⁴⁷ Of these 105, 83 patients (79%) were classified as medically ineligible to receive a conventional pacemaker in the opinion of the physician. A stratified analysis of these 83 patients was not presented in the publication. Trial characteristics and results are summarized in Tables 6 and 7, respectively. In this cohort of patients with CIED infection, the Micra device was implanted successfully in 104 patients and the previous CIED was explanted the same day as the Micra device was implanted in 37% of patients. Major complications were reported in 3.8% of patients with an average follow-up of 8.5 months. Ten deaths were reported (14% at 12 months) but none were related to the Micra transcatheter pacing system or the implantation procedure.

Garg et al (2020) conducted a post-hoc analysis on safety and all-cause mortality outcomes for 546 patients enrolled in the Micra IDE study, the Micra Continued Access (CA) study, and the Micra Post-Approval Registry who were deemed ineligible for conventional pacing system implantation.⁴⁸ Most common reasons for conventional pacing system ineligibility included impaired venous access (42.5%) and history of device infection or bacteremia (38.8%). Implant success rates were >99% for both medically ineligible and nonprecluded subgroups implanted with Micra devices. Both acute mortality (2.75% vs. 1.32%; $p=.022$) and total mortality at 36 months (38.1% vs. 20.6%; $p<.001$) were significantly higher in the medically ineligible group compared to the nonprecluded Micra group. Mortality was also significantly higher in the medically ineligible group compared to a historical cohort implanted with a conventional transvenous pacing system (38.1% vs. 23.2%). The rate of acute major complications (2.93% vs. 2.47%; $p=.55$) and total major complications through 36 months (4.30% vs. 3.81%; $p=.40$) was not significantly different between the medically ineligible and nonprecluded Micra groups, respectively. The authors emphasized that the elevated rate of all-cause mortality may be related to a higher incidence of chronic comorbidities in the medically ineligible population, such as diabetes, renal dysfunction, and current dialysis treatment, which may have increased overall mortality risk during follow-up. The majority of medically ineligible patients were enrolled in the CA and Post-Approval Registry studies, which unlike the IDE study, did not exclude patients with a life expectancy <12 months.

Table 6. Summary of Key Nonrandomized Trial Characteristics in Patients Ineligible for a Conventional Pacing System and/or Previous Cardiac Implantable Electronic Device Infection

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
El-Chami et al (2018) ⁴⁷ ; NCT02536118	Prospective single cohort (Micra Post-Approval Registry)	23 countries in North America, Europe, Asia, Australia, and Africa	2016-2018	Any patient to be implanted with a Micra with a CIED infection	Micra pacemaker (N=105)	8.5 (range, 0 to 28.5)
Garg et al (2020) ⁴⁸ .	Post hoc analysis of prospectively collected data from Micra studies	Multinational	NR	Any patient in a Micra study considered ineligible for a conventional pacing system	Micra pacemaker (N=546)	23.5 ± 14.7

CIED: cardiac implantable electronic device; NCT: national clinical trial.

Table 7. Summary of Key Nonrandomized Trial Results in Patients Ineligible for a Conventional Pacing System and/or Previous Cardiac Implantable Electronic Device Infection

Study	No. of Patients With System- or Procedure-Related Major Complications at 1 Year, % (n/N)	Average Pacing Threshold at 1 Year	Major Complications at 1 Year
El-Chami et al (2018)⁴⁷			
N	105	82	105
Micra	4 (4/105)	0.6 V	Total major complications: 6 in 4 patients; (patient 1: effusion requiring pericardiocentesis; patient 2: elevated thresholds, complication of device removal [IVC filter entanglement], and subsequent abdominal wall infection, patients 3 and 4: pacemaker syndrome)
Garg et al (2020)⁴⁸			
N	546	NR	546
Micra	4 (22/546) ^a	NR	Total major complications: 24 in 22 patients; (4 cases cardiac effusion/perforation, 4 events at groin puncture site, 1 case of thrombosis, 4 cases of pacing issues, 1 case of cardiac rhythm disorder, 3 cases of infection, and 7 other)

IVC: inferior vena cava filter; NR: not reported.

^a Outcome reported at 36 months.

Tables 8 and 9 display notable limitations identified in selected studies.

Table 8. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
El-Chami et al (2018) ⁴⁷			2. This was a single cohort study; there was no comparator		1. Insufficient duration for benefit; 2. Insufficient duration for harms
Garg et al (2020) ⁴⁸					1. Insufficient duration for benefit; 2. Insufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 9. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
El-Chami et al (2018)⁴⁷	1. Participants not randomly allocated; design was prospective registry	1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician				
Garg et al (2020)⁴⁸	1. Participants not randomly allocated; post-hoc analysis	1-3. Blinding and outcome assessment not described.				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Ventricular Pacing for Individuals Who Are Medically Ineligible for a Conventional Pacing System

No studies that exclusively enrolled patients who were medically ineligible for a conventional pacing system were identified. However, a subgroup of patients in whom the use of conventional pacemakers was precluded was enrolled in the pivotal and the postapproval trials of the Micra device. Information on the outcomes in these subgroups of patients from the post approval study showed that Micra was successfully implanted in 98% to 99% of cases and safety outcomes were similar to the original cohort. Even though the evidence is limited and long-term effectiveness and safety are unknown, the short-term benefits may outweigh the risks because the complex trade-off of adverse events for these devices needs to be assessed in the context of the life-saving potential of pacing systems in patients ineligible for conventional pacing systems.

Summary of Evidence

For individuals with a guidelines-based indication for a ventricular pacing system who are medically eligible for a conventional pacing system who receive a single-chamber transcatheter pacing system, the evidence includes pivotal prospective cohort studies, a postapproval prospective cohort study, a Medicare registry, and a retrospective FDA database analysis. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Results at 6 months and 1 year for the Micra pivotal study reported high procedural success (>99%) and device effectiveness (pacing capture threshold met in 98% of patients). Most of the system- or procedure-related complications occurred within 30 days. At 1 year, the incidence of major complications did not increase substantially from 6 months (3.5% at 6 months vs. 4% at 1 year). Results of the Micra postapproval study were consistent with the pivotal study and showed a lower incidence of major complications up to 30 days postimplantation as well as 1 year (1.5% and 2.7%, respectively). In both studies, the point estimates of major complications were lower than the pooled estimates from 6 studies of conventional pacemakers used as a historical comparator. While Micra device eliminates lead- and surgical pocket-related complications, its use can result in potentially more serious

complications related to implantation and release of the device (traumatic cardiac injury) and less serious complications related to the femoral access site (groin hematomas, access site bleeding). Initial data from a Medicare registry found a significantly higher rate of pericardial effusion and/or perforation within 30 days in patients with the leadless Micra pacemaker compared to patients who received a transvenous device; however, overall 6-month complication rates were significantly lower in the Micra group in the adjusted analysis ($p=.02$). In a real-world study of Medicare patients, the Micra device was associated with a 41% lower rate of reinterventions and a 32% lower rate of chronic complications compared with transvenous pacing, with no significant difference in adjusted all-cause mortality at 3 years despite the higher comorbidity index for patients implanted with a Micra device. However, patients receiving the Micra device experienced significantly more other complications, driven by higher rates of pericarditis. No significant differences were noted in the composite endpoint of time to heart failure hospitalization or death for the full cohort ($p=.28$) or the subgroup without a history of heart failure ($p=.98$). It is also unclear whether all patients were considered medically eligible for a conventional pacing system. A single-arm study of the Micra AV device reported that 85.2% of individuals with complete AV block and normal sinus rhythm successfully achieved a >70% resting AV synchrony (AVS) rate at 1 month postimplant and that AVS rates could be further enhanced with additional device programming. However, clinically meaningful rates of AVS are unknown. Longer-term device characterization is planned in the Micra AV Post-Approval Registry through 3 years. The Aveir pivotal prospective cohort study primary safety and efficacy outcomes at 6 weeks exceeded performance goals for complication-free rate and composite success rate (96.0% and 95.9%, respectively). Results at 6 months were similar and at 1 year were 93.2% and 91.5%, respectively. Incidence of major complications at 1 year was 6.7% compared to 4.0% in the Micra pivotal trial. The 2-year survival estimate of 85.3% is based on Phase 1 performance with the predecessor Nanostim device. Considerable uncertainties and unknowns remain in terms of the durability of the devices and device end-of-life issues. Early and limited experience with the Micra device has suggested that retrieval of these devices is unlikely because in due course, the device will be encapsulated. There are limited data on device-device interactions (both electrical and mechanical), which may occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. Although the Aveir device is specifically designed to be retrieved when therapy needs evolve or the device needs to be replaced, limited data are available on retrieval outcomes. While the current evidence is encouraging, overall benefit with the broad use of FDA-approved single-chamber transcatheter pacing systems compared with conventional pacemakers has not been shown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system who receive a single-chamber transcatheter pacing system, the evidence includes subgroup analysis of a pivotal prospective cohort study and a postapproval prospective cohort study for the Micra device. It is unclear whether the Aveir pivotal study enrolled patients medically ineligible for a conventional pacing system. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Information on the outcomes in the subgroup of patients from the postapproval study showed that the Micra device was successfully implanted in 98% to 99% of cases, and safety outcomes were similar to the original cohort. Even though the evidence is limited and long-term effectiveness and safety are unknown, the short-term benefits may outweigh the risks because the complex trade-off of adverse events for these devices needs to be assessed in the context of the life-saving potential of pacing systems for patients ineligible for conventional pacing systems. There are little data available regarding outcomes associated with other alternatives to conventional pacemaker systems such as epicardial leads or transiliac placement. Epicardial leads are most relevant for the patient who is already going to have a thoracotomy for treatment of their underlying condition (e.g., congenital heart disease). Epicardial leads are associated with a longer intensive care unit stay, more blood loss, and longer ventilation times compared to conventional pacemaker systems. The evidence for transiliac placement is limited to small case series and the incidence of atrial lead dislodgement

using this approach in the literature ranged from 7% to 21%. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2023 Input

Clinical input was sought to help determine whether the use of an Aveir or Micra AV transcatheter pacing system for an individual with a guidelines-based indication for a ventricular pacing system would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice depending on individual medical eligibility for a conventional pacing system. In response to requests, clinical input was received from 2 respondents, including 1 specialty society-level response including physicians with academic medical center affiliation and 1 physician-level response with academic affiliation identified through a specialty society.

For individuals with a guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system who receive a Micra AV or Aveir transcatheter pacing system, clinical input supports this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients when both conditions below are met:

- The patient has significant bradycardia and:
 - Normal sinus rhythm with rare episodes of 2° or 3° atrioventricular (AV) block or sinus arrest and severe physical disability or short expected lifespan; OR
 - Chronic atrial fibrillation.
- The patient has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following:
 - History of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection;
 - Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins, or planned use of such veins for a semi-permanent catheter or current or planned use of an arteriovenous fistula for hemodialysis;
 - Presence of a bioprosthetic tricuspid valve.

For individuals with a guidelines-based indication for a ventricular pacing system who are medically eligible for a conventional pacing system who receive a Micra AV or Aveir transcatheter pacing system, clinical input indicates this use is consistent with generally accepted medical practice but reports mixed support that this use provides a clinically meaningful improvement in net health outcomes.

Further details from clinical input are included in the Appendix.

2019 Input

Clinical input was sought to help determine whether the use of leadless cardiac pacemakers for individuals with a guidelines-based indication for a ventricular pacing system would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2

respondents, including 1 specialty society-level response and 1 physician-level response identified through specialty societies including physicians with academic medical center affiliations.

For individuals with a guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system who receive a Micra transcatheter pacing system, clinical input supports this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice in a subgroup of appropriately selected patients when both conditions below are met:

- The patient has symptomatic paroxysmal or permanent high-grade arteriovenous block or symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses).
- The patient has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following:
 - History of an endovascular or CIED infection or who are very high-risk for infection
 - Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins or planned use of such veins for a semi-permanent catheter or current or planned use of an arteriovenous fistula for hemodialysis
 - Presence of a bioprosthetic tricuspid valve

Further details from clinical input are included in the Appendix.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Institute for Health and Care Excellence

In 2018, the NICE issued evidence-based recommendations on leadless cardiac pacemaker implantation for adults with bradyarrhythmias.⁴⁹ The guidance states that the evidence "on the safety of leadless cardiac pacemaker implantation for bradyarrhythmias shows that there are serious but well-recognised complications. The evidence on efficacy is inadequate in quantity and quality:

- For people who can have conventional cardiac pacemaker implantation, leadless pacemakers should only be used in the context of research;
- For people in whom a conventional cardiac pacemaker implantation is contraindicated following a careful risk assessment by a multidisciplinary team, leadless cardiac pacemakers should only be used with special arrangements for clinical governance, consent and audit or research."

The guidance is awaiting development as of April 2023 with expected publication in June 2024.

Heart Rhythm Society

In 2020, the Heart Rhythm Society (HRS), along with the International Society for Cardiovascular Infectious Diseases (ISCVID) and several other Asian, European and Latin American societies, endorsed the European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections.⁵⁰ The consensus states that for patients at high risk of device-related infections, avoiding a transvenous system, and implanting an epicardial system, may be preferential. It makes the following statements regarding leadless pacemakers:

- 'There is hope that 'leadless' pacemakers will be less prone to infection and can be used in a similar manner [as epicardial systems] in high-risk patients.'

- 'In selected high-risk patients, the risk of infection with leadless pacemakers appears low. The device also seems safe and feasible in patients with pre-existing [cardiovascular implantable electronic device] infection and after extraction of infected leads.'

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid (CMS) cover leadless pacemakers under coverage with evidence development criteria when procedures are performed in prospective longitudinal studies approved by the U.S. Food and Drug Administration (FDA) using "leadless pacemakers...in accordance with the FDA approved label for devices that have either:

- An associated ongoing FDA approved post-approval study; or
- Completed an FDA post-approval study.

Each study must be approved by CMS and as a fully-described, written part of its protocol, must address the following research questions:

- What are the peri-procedural and post-procedural complications of leadless pacemakers?
- What are the long term outcomes of leadless pacemakers?
- What are the effects of patient characteristics (age, gender, comorbidities) on the use and health effects of leadless pacemakers?"⁵¹

The following 6 studies are currently approved by CMS:⁵²

1. Aveir VR Coverage With Evidence Development Post-Approval Study (NCT05336877); CMS approval date: 6/2/22;
2. Effectiveness of the EMPOWER™ Modular Pacing System and EMBLEM™ Subcutaneous ICD to Communicate Antitachycardia Pacing (NCT04798768); CMS approval date: 1/20/22;
3. The LEADLESS II IDE Study (Phase II): A Safety and Effectiveness Trial for a Leadless Pacemaker System (NCT04559945); CMS approval date: 3/16/21;
4. Longitudinal Coverage with Evidence Development Study on Micra AV Leadless Pacemakers (Micra AV CED) (NCT04235491); CMS approval date: 2/5/2020;
5. The Micra CED Study (NCT03039712); CMS approval date: 03/09/17; and
6. Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118); CMS approval date: 02/09/17.

See Table 10 for additional details.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT04559945 ^{a,b}	The LEADLESS II IDE Study (Phase II): A Safety and Effectiveness Trial for a Leadless Pacemaker System	326	Aug 2023 (ongoing)
NCT05528029	International Leadless Pacemaker Registry (i-LEAPER)	2000	Dec 2024 (recruiting)
NCT04253184 ^a	Micra AV Transcatheter Pacing System Post-Approval Registry (Micra AV PAS)	802	Apr 2025 (ongoing)
NCT05498376	The Leadless AV Versus DDD Pacing Study: A Randomized Controlled Single-center Trial on Leadless Versus Conventional Cardiac Dual-chamber Pacing (LEAVE DDD)	100	Feb 2026 (recruiting)
NCT04235491 ^{a,b}	Longitudinal Coverage With Evidence Development Study on Micra AV Leadless Pacemakers (Micra AV CED)	37000	Jun 2027 (ongoing)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04051814	A Retrospective Trial to Evaluate the Micra Pacemaker	500	May 2025 (recruiting)
NCT03039712 ^{a,b}	Longitudinal Coverage With Evidence Development Study on Micra Leadless Pacemakers (Micra CED)	37000	Jun 2027 (ongoing)
NCT04926792	Taiwan Registry for Leadless Pacemaker	300	Jun 2025 (not yet recruiting)
NCT05252702 ^a	Aveir Dual-Chamber Leadless i2i IDE Study	550	Nov 2025 (recruiting)
NCT02536118 ^{a,b}	Micra Transcatheter Pacing System Post-Approval Registry	3100	Aug 2026 (ongoing)
NCT05336877 ^{a,b}	Aveir Single-Chamber Leadless Pacemaker Coverage With Evidence Development (ACED) Post-Approval Study	8744	Jan 2028 (recruiting)
NCT04798768 ^{a,b}	Effectiveness of the EMPOWER™ Modular Pacing System and EMBLEM™ Subcutaneous ICD to Communicate Antitachycardia Pacing (MODULAR ATP)	300	Dec 2030 (recruiting)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

^b Denotes CMS-approved study.

Appendix 1

2023 Clinical Input

Objective

Clinical input was sought to help determine whether the use of the Aveir or Micra AV transcatheter pacing systems for an individual with a guidelines-based indication for a ventricular pacing system would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice depending on individual medical eligibility for a conventional pacing system.

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- Heart Rhythm Society (HRS)
- Ijeoma A. Ekeruo, MD, Cardiac Electrophysiology, University of Texas Health Sciences Center at Houston, identified by the American College of Cardiology (ACC)

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication; and
- Supporting evidence from the authoritative scientific literature (please include PMID).
 - Use of an Aveir transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who is medically **eligible** for a conventional pacing system

Rationale

- 1 The Heart Rhythm Society (HRS) endorses that Aveir and other leadless pacemaker (LP) systems provide incremental health benefit in select patients who are otherwise eligible for conventional pacing (CP) systems.

LP systems can mitigate or eliminate complications and sequela that are specific to CP systems. CP implant complications that are eliminated with LPs include pneumothorax, surgical pocket hematoma and upper extremity deep venous thrombosis. These complications then require additional interventions such as reoperations, chest tube placement, thrombolysis, or anticoagulation that have their own risks of complications. Intermediate or long-term sequela of chronically implanted CP include pectoral pocket or lead infection, chronic CP pocket pain due to device migration or pre-erosion or erosion of the CP generator through the skin. Device infection is an important source of morbidity and mortality from both the infection or lead extraction. Since 80% of device infections involve the pacemaker generator pocket, LPs would eliminate CP pectoral pocket infections.

Patients with comorbidities are at higher risk when CP complications occur. Patients at risk for poor wound healing from radiation, chronic cachexia, burns or autoimmune disease such as scleroderma or would benefit from LP as an alternative to the CP implant procedure. Patients with severe lung disease or chronic ventilation are at increased risk when pneumothorax occurs. Patients undergoing chronic hemodialysis have ongoing challenges with vascular access, bleeding risk and infection when CPs are placed ipsilateral to upper extremity AV fistulas. Some patients have illnesses where preserving upper extremity vascular access sites is critical for future therapies such as infusions. Patients who require continuous anticoagulation due to mechanical heart valves or left ventricular assist devices (LVADs) are at risk if anticoagulation is suspended to manage pocket hematomas. Patients who have upper body central venous stenosis are at risk for complete occlusion with chronically indwelling CP leads, so LPs would eliminate this risk. These patients may need vascular interventions that would compromise the CP lead or require its removal. A CP ventricular lead implanted interacts with the tricuspid valve with every heartbeat 100,000 times per day. There is increasing awareness that years of this can contribute to tricuspid valve dysfunction that require tricuspid valve repair or replacement. For patients that have had these interventions, clinicians have reasonable concern that placement of CP leads could adversely affect the function of the repaired or replaced tricuspid valve.

References

Armaganijan, L. V., et al. (2012). "Are elderly patients at increased risk of complications following pacemaker implantation? A meta-analysis of randomized trials." *Pacing and clinical electrophysiology* 35(2): 131-134

Beyene, R. T., et al. (2020). "The effect of comorbidities on wound healing." *Surgical Clinics* 100(4): 695-705

Cho, M. S., et al. (2019). "Incidence and predictors of moderate to severe tricuspid regurgitation after dual-chamber pacemaker implantation." *Pacing and clinical electrophysiology* 42(1): 85-92.

Link, M. S., et al. (1998). "Complications of dual chamber pacemaker implantation in the elderly." *Journal of interventional cardiac electrophysiology* 2(2): 175.

- 2 There are cases in which a leadless pacemaker would be placed in a patient that can otherwise receive a transvenous pacemaker. The major limitation to the leadless pacemaker not being standard of care in these patients seems to be limited data on long term effects of pacer placement, and lack of clarity on what to do with battery depletion. Though this is theoretically addressed in the Aveir transcatheter system, there is still no long-term data to prove efficacy.

Literature available (PMID: 32763431, 34319383) report a decrease in major complications post implant, though an increase in pericardial effusion following implant, with reduction occurring mainly with lack of

#	Rationale
	<p>pneumothorax, pocket hematoma and pocket infection in the acute period. Interestingly, there is also no significant difference in mortality with patients who received an intravenous device when followed for up to 36 months post implant.</p> <p>With this in mind, it is reasonable to conclude that placement of a leadless device in a patient who is otherwise a candidate for a transvenous single lead device would be acceptable, with consideration of the patient's age and need for generator change as a result of battery depletion.</p>
	<ul style="list-style-type: none"> o Use of an Aveir transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who is medically ineligible for a conventional pacing system

#	Rationale
1	<p>HRS strongly supports the use of Aveir and other LP systems that meet ventricular pacing indications who are medically ineligible for CP systems. These would include, but not be limited to, obstructed vascular access, inability to place the CP generator in an appropriate surgical plane, recurring infections, or clinical scenarios where therapies or surgery would disrupt, damage, entrap, or subject the CP system components. Before LP availability, the only alternative for these patients would be a thoracotomy-based epicardial pacing system or off-label CP implant techniques such as transiliac or transhepatic approaches. LPs offer a less invasive alternative with established long-term benefits. Patients could also be deemed ineligible if they are unable to comply with CP postoperative instructions due to mental health or developmental challenges.</p>
2	<p>The development of the leadless pacing system was borne out of necessity, in cases where patients did not have upper extremity venous access to the right heart (either as a result of venous occlusion, or congenital malformation), or in patients with recurrent infections.</p> <p>There are no trials comparing patients ineligible for a conventional pacing system who receive leadless pacemakers to those with transiliac or epicardial devices for a completely pacing indication. When compared to the alternative, placement of a leadless pacing system in this group of patients should be deemed necessary, as the alternative would confer a higher degree of mortality and morbidity in this population.</p>

Question 2:

Also please comment on whether or not the patient selection criteria (as adapted from device instructions for use) below are reasonable to define the population for use of an Aveir transcatheter pacing system among individuals who are medically **ineligible** for a conventional pacing system.

- The patient has significant bradycardia and:
 - o Normal sinus rhythm with only rare episodes of 2° or 3° atrioventricular (AV) block or sinus arrest and severe physical disability or short expected lifespan; OR
 - o Chronic atrial fibrillation.
- The patient has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following:
 - o History of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection;
 - o Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins, or planned use of such veins for a semi-permanent catheter or current or planned use of an arteriovenous fistula for hemodialysis;
 - o Presence of a bioprosthetic tricuspid valve.

#	YES/NO	Rationale
1	YES	<p>The Society believes that the Aveir system is a suitable alternative in clinical situations where the clinician believes that CP placement or its long-term sequela places the patient at undue risk. Many of these conditions (infection, vascular access, dialysis, bioprosthetic tricuspid valve) were reviewed in the previous section.</p> <p>Some patients have infrequent episodes of atrioventricular block with severe symptoms and</p>

YES/NO Rationale

rarely need intervention from a pacemaker. LPs can provide this therapy without the long-term risk of chronically implanted CP systems. Aveir is designed to be removed and the LP can be replaced with a CP or other device if needed later in life. Patients who are frail or elderly are at increased risk from CP complications, so LP could be used as an alternative to mitigate risks that are specific to CPs.

The Society also believes it is reasonable to use Aveir and other LPs for intermediate (>48 hours) or longer-term temporary pacing when a patient's clinical status precludes them from receiving a CP or other device, such as with infection or after cardiac procedures. External temporary pacing systems are currently used for this, and the patient is unable to leave their bed or the ICU until it is removed. These external systems are vulnerable to dislodgement and can lose their ability to pace after several days. Aveir's ability to be implanted then later removed offers would allow to ambulate and be housed in less acute settings or even discharged, allowing limited healthcare resources available for other patients.

References

Sohail, M. R., et al. (2007). "Risk factor analysis of permanent pacemaker infection." *Clinical Infectious Diseases* 45(2): 166-173

Beccarino, N. J., et al. (2023). "Concomitant leadless pacing in pacemaker-dependent patients undergoing transvenous lead extraction for active infection: Mid-term follow-up." *Heart Rhythm*

Gonzales, H., et al. (2019). "Comparison of leadless pacing and temporary externalized pacing following cardiac implanted device extraction." *The Journal of Innovations in Cardiac Rhythm Management* 10(12): 3930

2 YES NR

NR: no response.

Question 3:

Please describe how severe physical disability is measured and defined for the Aveir intended use population. Please describe whether this definition is applicable across device types (i.e., Micra VR, Micra AV). If not, please clarify important differences.

Rationale

1 Severe physical disability encompasses a variety of conditions where CP placement would confer undue acute or long-term risk. This could be inability to comply with postoperative wound care instructions due to physical, mental health, or developmental challenges. Severe disability due to end stage heart, lung, neurologic or skeletal diseases could raise the risk of CP implants. Patients with severe disabilities would benefit from an LP implant procedure that does not involve surgery and its associated postoperative discomfort that could further compromise their limited ability to meet their activities of daily living.

2 It is hard for this physician to think of significant physical disability that would preclude placement of a transvenous device. Maybe severe scoliosis or upper extremity spasm limiting access to the subclavian or axillary vein, and would also increase the possibility of lead dislodgement or fracture. In this case, this definition would be applicable across all device types.

Question 4:

Please comment on how the clinical use of the Aveir system differs from the Micra VR and AV systems. Are these devices used in the same subset of patients? What clinical considerations drive the choice of transcatheter pacing system?

Rationale

1 All LPs such as Aveir can be appropriately used in patients that meet guideline-based ventricular pacing indications. Aveir and Micra VR provide rate responsive ventricular pacing (VVIR). In addition to VVIR pacing the Micra AV can sense atrial electrical signals that trigger and synchronize ventricular pacing (VDDR). This atrioventricular (AV) synchrony allows the Micra AV to be used in patients with chronic AV block that do not need atrial pacing. Aveir and Micra VR are only indicated where AV block occurs rarely. The distinguishing feature of Aveir is the FDA approved tools and technique for device removal.

Aveir devices have been removed as long as 9 years after implant. This would be an attractive option if

#	Rationale
	removal of the device is needed or desired. The manufacturer (Abbott) claims that the Aveir has better longevity across a wider range of pacing outputs. This would be advantageous since pacing thresholds tend to increase over time. Reference Neužil, P., et al. (2023). "Retrieval and replacement of a helix-fixation leadless pacemaker at 9 years post-implant." HeartRhythm Case Reports
2	The clinical use of the Aveir system and the Micra VR system would be similar. The Micra AV system differs in that it has an added benefit of allowing for AV synchrony, and so can be used in cases where pacemaker syndrome would be a consideration, or where synchrony would be preferred.

Question 5:

We are seeking your opinion on whether using a Micra AV transcatheter pacing system for each of the indications below provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication; and
- Supporting evidence from the authoritative scientific literature (please include PMID).
 - Use of Micra AV transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who is medically **eligible** for a conventional pacing system

#	Rationale
1	Heart Rhythm Society (HRS) endorses that Micra AV and other leadless pacemaker (LP) systems provide clinically meaningful improvement in net health outcome several scenarios in which patients are medically eligible for conventional pacing (CP) system (i.e. high grade AV block in the presence or absence of atrial fibrillation; symptomatic bradycardia or sinus node dysfunction as an alternative to atrial or dual chamber pacing; patients with adequate sinus rates but AV block who may benefit from AV synchronous ventricular pacing). 1. Alternative to dual chamber pacing when transvenous pacing system insertion is considered difficult (e.g. venous obstruction prohibiting access) or high risk (e.g. current infection or recently extracted infected system). 2. Prevent pocket erosion in patients with inadequate subcutaneous tissue. 3. Mitigate risk of chronic vascular occlusion in young patients with rare severe vasovagal mediated syncope. 4. Reduce risk of transvenous lead failure associated with mechanical stress related to activity (e.g. hunting, golf). 5. Avoid cosmetic scars associated with traditional prepectoral pocket formation. 6. There is some evidence that the Micra could be used safely concomitantly with a subcutaneous implantable cardioverter defibrillators. References: (1) JACC: Clinical Electrophysiology, 3 (2017) 1487-1498. doi:10.1016/j.jacep.2017.04.002; (2) Journal of the American College of Cardiology, 67 (2016) 1865-1866. doi:10.1016/j.jacc.2016.02.039
2	The development of the Micra AV transcatheter pacing system has increased indications for leadless pacemaker placement in patients in need of AV synchrony, particularly patients with second or third degree AV block. The system suffers from the same limitations as its sister device, with longevity limited to <10 years and long term outcomes not available for that reason. Though this device provides AV synchrony, it is not as robust as that provided with a transvenous system, with no ability to provide such at HR >105 bpm, and limited in patients with significant diastolic dysfunction. In patients with need for AV synchrony at higher heart rates, they would be better served with a conventional system.

Rationale

The patients that would benefit from this device remain older patients, with limited activity, in whom device infection or lead dislodgement remains a significant concern. Otherwise, patients in whom placement of a conventional system would be impossible remain the greatest beneficiaries of this technology.

See PMID 33179814, 31709982

- Use of Micra AV transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who is medically **ineligible** for a conventional pacing system

Rationale

1 HRS supports the use of Micra AV and other LP systems as an alternative solution in circumstances when CP systems are not favorable or even feasible. Traditional transvenous pacemakers require the formation of a subcutaneous pocket to house the pulse generator and the insertion of transvenous lead(s). These steps could be limited or not possible in many scenarios including the following:

1. Skin and subcuticular conditions (skin burns, prior radiation)
2. Venous system occlusion (subclavian, SVC syndrome, etc.)
3. Persistent left sided SVC or other congenital venous anomalies
4. Presence of central venous catheters
5. Presence of Arterio-Venous fistula for dialysis on the same upper extremity
6. Bioprosthetic tricuspid valve and the desire to avoid any transvalvular lead

These anatomical challenges are more pronounced after extraction of an infected device as the options are limited to the opposite prepectoral side for new system implantation. The inability to perform implantation of a transvenous pacemaker system has traditionally led to trans-iliac or surgical epicardial pacemaker approaches. These approaches require special expertise or necessitate a surgical invasive procedure. Additionally, the long term performance of transiliac leads or epicardial leads is suboptimal.

References

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2 Like the VR systems available, placement of a Micra AV in a patient that is ineligible for transvenous system placement would be an improvement on present alternatives (epicardial pacing, transiliac pacing [with generator in the abdomen]). There is significant concern for increase in lead threshold in the forer, and lower extremity pain in the latter to confer a clear advantage for the leadless system.

See PMID 518184, 22192754

Question 6:

Also please comment on whether or not the patient selection criteria (as adapted from device instructions for use) below are reasonable to define the population for use of an Micra AV transcatheter pacing system among individuals who are medically **ineligible** for a conventional pacing system.

- The patient has significant bradycardia and:
 - Normal sinus rhythm with only rare episodes of 2° or 3° AV block or sinus arrest and severe physical disability or short expected lifespan; OR

- Chronic atrial fibrillation.
- The patient has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following:
 - History of an endovascular or CIED infection or who are at high risk for infection;
 - Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins, or planned use of such veins for a semi-permanent catheter or current or planned use of an arteriovenous fistula for hemodialysis;
 - Presence of a bioprosthetic tricuspid valve.

#	YES/NO	Rationale
1	YES	<p>HRS agrees the patient selection criteria are reasonable. Criterion 1: Patients with rare episodes of AV block or sinus arrest will rarely require pacing intervention. LPs can provide this therapy with less risk in patients with severe physical disability or short expected lifespan including potential transvenous lead infection or failure. If a patient has high degree AV block frequently, Micra AV will result in the preservation of AV synchrony.</p> <p>Criterion 2: Patients with significant contraindication precluding CP system including endovascular or CIED infection, limited access for transvenous pacing, and presence of bioprosthetic tricuspid valve. LP systems have low risk of infection (1). Alternative external temporary pacing systems are vulnerable to dislodgment and loss of capture. LP systems can be inserted alternatively to occluded axillary venous systems.</p> <p>Reference</p> <p>1. El-Chami MF, Bonner M, Holbrook R, Stromberg K, Mayotte J, Molan A, Sohail MR, Epstein LM. Leadless pacemakers reduce risk of device-related infection: Review of the potential mechanisms. <i>Heart Rhythm</i>. 2020 Aug;17(8):1393-1397. doi: 10.1016/j.hrthm.2020.03.019. Epub 2020 Apr 2. PMID: 32247833.</p>
2	YES	NR

NR: no response.

Question 7:

Please comment on how the clinical use of the Micra VR system (Model MCIVR01) differs from the Micra AV system (Model MCIAVR1). Can these devices be used in the same subset of patients? What clinical considerations drive the choice of transcatheter pacing system?

#	Rationale
1	<p>Micra VR and Micra AV systems can be used in the same subset of patients who require ventricular pacing as described above. Micra AV differs from Micra VR in that it provides AV synchrony in patients with AV block without persistent atrial arrhythmia. AV synchrony results in improved cardiac output, reducing risk of atrial fibrillation, and minimizing incidence of pacemaker syndrome (1).</p> <p>Micra AV has several additional atrial sensing algorithms that detect cardiac movement. Micra AV is able to adjust pacing in the ventricle to coordinate with the atrium enabling AV synchronous pacing to people with atrioventricular block. Optimized programmed AV synchrony has been shown to significantly improve quality of life (2).</p> <p>References</p> <p>1. Steinwender C, Khelae SK, Garweg C, Chan JYS, Ritter P, Johansen JB, Sagi V, Epstein LM, Piccini JP, Pascual M, Mont L, Sheldon T, Splett V, Stromberg K, Wood N, Chinitz L. Atrioventricular Synchronous Pacing Using a Leadless Ventricular Pacemaker: Results From the MARVEL 2 Study. <i>JACC Clin Electrophysiol</i>. 2020 Jan;6(1):94-106. doi: 10.1016/j.jacep.2019.10.017. Epub 2019 Nov 11. PMID: 31709982.</p> <p>2. Chinitz LA, El-Chami MF, Sagi V, Garcia H, Hackett FK, Leal M, Whalen P, Henrikson CA, Greenspon AJ, Sheldon T, Stromberg K, Wood N, Fagan DH, Sun Chan JY. Ambulatory atrioventricular synchronous pacing over time using a leadless ventricular pacemaker: Primary results from the AccelAV study. <i>Heart Rhythm</i>. 2023 Jan;20(1):46-54. doi: 10.1016/j.hrthm.2022.08.033. Epub 2022 Sep 6. PMID: 36075532</p>
2	<p>The Micra AV system can be used in all populations indicated for a leadless pacemaker. The Micra VR system is limited to patient population in whom AV synchrony would not be an advantage. So mostly patients with permanent atrial fibrillation or patients with very limited (but significant) pacing needs.</p>

Question 8:

Please provide in the box below any additional narrative rationale or comments regarding clinical pathway and/or any relevant scientific citations (including the PMID) supporting your clinical input on this topic.

#	Rationale
1	See above comments
2	The use of a leadless system for pacing might also be considered in elderly patients who have transient pacing needs that are significant in the short term. For example, there are no firm indications for placement of pacemakers post TAVR, anecdotal evidence suggests transient AV block that might resolve in 30 days post procedure, too long for an inpatient stay, but maybe too short for the permanent reminder of a device with a pocket and increased risk of infection. A leadless pacing system would be a fine alternative in this specific subset of patients.

Question 9:

Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

#	YES/NO	Rationale
1	NO	NR
2	NO	NR

NR: no response.

2019 Clinical Input**Objective**

In 2019, clinical input was sought to help determine whether the use of leadless cardiac pacemakers for 2 populations including individuals with a guidelines-based indication for a ventricular pacing system who are either medically eligible or medically ineligible for a conventional pacing system would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. Clinical input was also sought to help determine reasonable patient selection criteria.

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- Heart Rhythm Society (HRS)
- Kousik Krishnan, MD, Clinical Cardiac Electrophysiology, Rush University Identified by American College of Cardiology (ACC)**

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide a review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

- We are seeking your opinion on whether using Micra transcatheter pacing system for each of the indications below in Questions 1a and 1b provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:
 - Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
 - Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
 - Supporting evidence from the authoritative scientific literature (please include PMID).
 - Use of a Micra transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who are medically **eligible** for a conventional pacing system

Rationale

- 1 We assert that the use of the Micra can provide clinically meaningful improvement in net health outcome for patients who are eligible for a conventional pacing system in multiple contexts and for multiple reasons. See references in Tables 4 and 5 of the BC/BS ES Draft. Along with the FDA and CMS, we assert that the existing studies establish appropriate safety and efficacy for use in the general population.
 1. While the use of the Micra requires ongoing evaluation, it is no longer considered “investigational” given that it has been approved for use by both the FDA and CMS (albeit with specific requirements for follow-up and ongoing evaluation) and thus should be covered by medical insurance across-the-board when considered medically necessary for standard pacing indications.
 2. Future technology will likely include dual-chamber leadless devices and as such it is important for operators to become facile with this technology. For this same reason, we assert that operators who chose to learn this technique should perform this procedure regularly to improve technique and decrease complications that inevitably are more common in rarely performed procedures.
 3. There is some preliminary evidence that the Micra could be used safely concomitantly with a subcutaneous ICD. (Refs: (1) JACC: Clinical Electrophysiology, 3 (2017) 1487-1498. doi:10.1016/j.jacep.2017.04.002; (2) Journal of the American College of Cardiology, 67 (2016) 1865-1866. doi:10.1016/j.jacc.2016.02.039)
 4. There is a spectrum between “eligible” and “ineligible” and as such this distinction is not black and white (see answer to 1a). For example, patients who have had a replaced tricuspid valve but require a ventricular pacing system may not be absolutely “ineligible” for a transvenous system (e.g., could have a small diameter lead placed across the valve) but would likely benefit from having a Mica placed to avoid long-term interaction with the replaced tricuspid valve – and there will likely never be a study large enough to test this clinical judgement).
 5. Young patients with malignant vasovagal syncope who will require rare ventricular pacing but a life-time of devices may benefit from a single-chamber leadless pacemaker as an initial strategy for pacing to minimize risk for device infection and vascular occlusion.
- 2 Micra is a viable option in these patients but does not have superiority data. The data would support that, in a situation with shared decision making, some patients and physicians may prefer a Micra to conventional pacing. (examples: Patients that are younger and would have longer to develop lead related issues, patients at higher infection risk, patients without sufficient subcutaneous tissue to prevent device erosion, patients where vascular access is or will be challenging). This is not an exhaustive list.

- Use of a Micra transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who are medically **ineligible** for a conventional pacing system

Rationale

- 1
 - MICRA leadless pacemaker, which is now FDA approved, has provided electrophysiologists with alternative solution to offer patients in circumstances when traditional transvenous pacemakers are not favorable or not even feasible. Traditional transvenous pacemakers require the formation of a subcutaneous pocket to house the pulse generator and the insertion of transvenous lead(s) into the venous system, system, across the tricuspid valve into the cardiac chambers. These steps could be limited or not possible in many scenarios including the following:
 1. Skin and subcuticular conditions (skin burns, prior radiation)

Rationale

2. Venous system occlusion (subclavian, SVC syndrome, etc...)
3. Persistent left sided SVC or other congenital venous anomalies
4. Presence of central venous catheters
5. Presence of Arterio-Venous fistula for dialysis on the same upper extremity
6. Bioprosthetic tricuspid valve and the desire to avoid any transvalvular lead

These anatomical challenges are more pronounced after extraction of an infected device as the options are limited to the opposite prepectoral side for new system implantation. The inability of performing an implantation of a transvenous pacemaker system has usually led to trans-iliac or surgical epicardial pacemaker approaches. These approaches require special expertise or necessitate a surgical invasive procedure. Additionally, the long term performance of transiliac leads or epicardial leads is suboptimal.

- Infection is a major complication after CIED implantation and 60% of these infections present with pocket infection. Leadless pacemaker by virtue of the technology does not require pocket and therefore could minimize at least the incidence of pocket infection. This is of particular importance among patients at high risk for infection including those who required prior CIED extraction for infection and patients on hemodialysis. Whether the risk of endovascular infection is lower in leadless pacemaker is yet to be determined.
- Majority of transvenous pacemaker complications are related to lead complications and these often result from mechanical stress on the lead itself. Certain activities like hunting, golfing and some professions represent particular stress on transvenous leads. Leadless pacemaker can provide an alternative for patients who suffer lead fracture or malfunction from mechanical stress or could even be first line option pre-emptively when these stresses are expected.
- When single chamber ventricular pacing is indicated, leadless pacemaker can provide an alternative for cosmetic reasons among certain patients in order to avoid prepectoral pocket formation and its associated scar.

These scenarios are not uncommon and frequently encountered in any electrophysiology practice. Complication rates with leadless pacemakers are less than those with traditional pacemaker system (both historical control and more current large patient cohorts from both Europe and US). More importantly, the complication rates with leadless pacemakers have gone down significantly as operators gained more experience. Therefore, building the experience among certain electrophysiologists in implantation technique for leadless pacemakers is critical. While the technology is limited to single chamber ventricular pacing systems, the field is advancing towards multi chamber leadless pacing systems.

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2. 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 May;35(18):1186-94. doi: 10.1093/eurheartj/ehu511. Epub 2013 Dec 17. PubMed PMID: 24347317; PubMed Central PMCID: PMC4012708.
3. Udo EO, Zuithoff NP, van Hemel NM, de Cock CC, Hendriks T, Doevendans PA, Moons KG. Incidence and predictors of short - and long-term complications in pacemaker therapy: the FOLLOWPACE study. *Heart Rhythm*. 2012 May;9(5):728-35. doi: 10.1016/j.hrthm.2011.12.014. Epub 2011 Dec 17. PubMed PMID: 22182495

2 This would be an ideal situation for Micra. All other options are higher in morbidity and mortality (example- surgical pacemaker)

NR: not reported

- Also please comment on whether or not the patient selection criteria below (requiring all 4 criteria below to be met) are reasonable to define the population for Question 1b.
 - The patient has symptomatic paroxysmal or permanent high-grade arteriovenous block or symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses).
 - The patient has any of the following, which precludes implantation of a single-chamber ventricular pacemaker:
 - Need for persistent anticoagulation therapy
 - Persistent severe bleeding tendencies

- Severe lung disease and positive end-expiratory pressure ventilation that precludes internal jugular and subclavian access
- Congenitally acquired venous anomalies that preclude transvenous access to the heart
- OR
- Presence of any of the following and delay in implantation of a single-chamber ventricular pacemaker could be life-threatening:
 - Persistent or recurrent local infection at implantation site
 - Persistent or recurrent active systemic infection with bacteremia.
- The patient does not have any of the following:
 - An implanted device that would interfere with the implant of the Micra device in the judgment of the implanting surgeon
 - An implanted inferior vena cava filter
 - A mechanical tricuspid valve
 - An implanted cardiac device providing active cardiac therapy that may interfere with the sensing performance of the Micra device.
- The patient does not have any of the following:
 - A femoral venous anatomy unable to accommodate a 7.8 mm (23 French) introducer sheath
 - Conditions or anatomy that cannot accommodate an implant on the right side of the heart (e.g., due to obstructions or severe tortuosity)
 - Morbid obesity that prevents the implanted device from obtaining telemetry communication within ≤ 12.5 cm (4.9 in)
 - Known intolerance to titanium, titanium nitride, parylene C, primer for parylene C, polyether ether ketone, siloxane, nitinol, platinum, iridium, liquid silicone rubber, silicone medical adhesive, and heparin
 - Known sensitivity to contrast media that prevents adequate premedication.
 - Cannot tolerate a single dose of dexamethasone acetate 1.0 mg.

#	YES / NO	Additional comments related to selection criteria for patients who may be medically ineligible for a conventional pacing system
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1	Yes	<p>Yes, the patient selection criteria are reasonable with the following caveats and suggested revisions.</p> <p>Criterion 2: The patient has any of the following, which precludes implantation of a single-chamber ventricular pacemaker: Need for persistent anticoagulation therapy</p> <ul style="list-style-type: none"> • Persistent severe bleeding tendencies • Severe lung disease and positive end-expiratory pressure ventilation that precludes internal jugular and subclavian access • Congenitally acquired venous anomalies that preclude transvenous access to the heart <p>--Comment: We do not think that the first 3 bullets are relevant. In the fourth bullet, we would delete "congenitally acquired" since a leadless pacemaker would be indicated for a venous anomaly of any etiology either congenital or acquired.</p> <p>Criterion 2: Presence of any of the following and delay in implantation of a single-chamber ventricular pacemaker could be life-threatening:</p> <ul style="list-style-type: none"> • Persistent or recurrent local infection at implantation site • Persistent or recurrent active systemic infection with bacteremia. <p>--Comment: Usually a clinician would try not to implant any permanent device when bacteremia is present. Suggested revision for Criterion 2:</p> <ul style="list-style-type: none"> • Have a history of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are very high risk for infection • Have limited access for transvenous pacing given venous occlusion of axillary veins or planned use of such veins for a semi-permanent catheter or current or planned use of an AV fistula for hemodialysis • Have axillary venous access only on a side of the body that would not allow use of a firearm • Presence of a bioprosthetic tricuspid valve
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YES / NO Additional comments related to selection criteria for patients who may be medically ineligible for a conventional pacing system

2 No Criterion 1: The patient has symptomatic paroxysmal or permanent high-grade arteriovenous block or symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses).
 -- Comment: These patients could be considered if the pacing needs are rare. If a patient has high degree AV block frequently, Micra will result in the loss of AV synchrony.

Criterion 2: The patient has any of the following, which precludes implantation of a single-chamber ventricular pacemaker:

- Need for persistent anticoagulation therapy
 --Comment: This is not a contraindication for a single chamber ppm
 - Persistent severe bleeding tendencies
 --Comment: This would be ok for both technologies.
 - Severe lung disease and positive end-expiratory pressure ventilation that precludes internal jugular and subclavian access
 -- Comment: This is one situation that may favor Micra.
 - Congenitally acquired venous anomalies that preclude transvenous access to the heart
- OR

Presence of any of the following and delay in implantation of a single-chamber ventricular pacemaker could be life-threatening:

- Persistent or recurrent local infection at implantation site
 - Persistent or recurrent active systemic infection with bacteremia.
- Comment: These are all potential Micra options. The patient does not have any of the following:
- An implanted device that would interfere with the implant of the Micra device in the judgment of the implanting surgeon
 - An implanted inferior vena cava filter
 - A mechanical tricuspid valve
 - An implanted cardiac device providing active cardiac therapy that may interfere with the sensing performance of the Micra device.

The patient does not have any of the following:

- A femoral venous anatomy unable to accommodate a 7.8 mm (23 French) introducer sheath
- Conditions or anatomy that cannot accommodate an implant on the right side of the heart (e.g., due to obstructions or severe tortuosity)
- Morbid obesity that prevents the implanted device from obtaining telemetry communication within ≤ 12.5 cm (4.9 in)
- Known intolerance to titanium, titanium nitride, parylene C, primer for parylene C, polyether ether ketone, siloxane, nitinol, platinum, iridium, liquid silicone rubber, silicone medical adhesive, and heparin
- Known sensitivity to contrast media that prevents adequate premedication.
- Cannot tolerate a single dose of dexamethasone acetate 1.0 mg.

-- Comment: These are all reasonable contraindications for Micra

- Based on the evidence and your clinical experience for each of the clinical indications described below:
 - Respond YES or NO for each clinical indication whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND
 - Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	Indications	YES / NO	Low Confidence	Intermediate Confidence	High Confidence
		1	2	3	4
					5
1	Use of a Micra transcatheter pacing system for an individual with guidelines-based indication	Yes			X

#	Indications	YES / NO	Low Confidence	Intermediate Confidence	High Confidence
	for a ventricular pacing system who are medically eligible for a conventional pacing system				
	Use of a Micra transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system	Yes			X
2	Use of a Micra transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who are medically eligible for a conventional pacing system	Yes		X	
	Use of a Micra transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system	Yes			X

NR: not reported

- Based on the evidence and your clinical experience for each of the clinical indications described below:
 - Respond YES or NO for each clinical indication whether this intervention is consistent with generally accepted medical practice; AND
 - Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	Indications	YES / NO	Low Confidence		Intermediate Confidence		High Confidence	
			1	2	3	4	5	
1	Use of a Micra transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who are medically eligible for a conventional pacing system	Yes						X
	Use of a Micra transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system	Yes						X
2	Use of a Micra transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who are medically eligible for a conventional pacing system	Yes			X			
	Use of a Micra transcatheter pacing system for an individual with guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system	Yes						X

NR: not reported

- Additional narrative rationale or comments regarding clinical pathway and/or any relevant scientific citations (including the PMID) supporting your clinical input on this topic.

#	Additional Comments
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1	See above comments.
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2	NR
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NR: not reported

- Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

#	YES / NO	Citations of Missing Evidence
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1	Yes	See references in 1a and 1b.
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2	No	
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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
 - Clinical findings (i.e., pertinent symptoms and duration)
 - Type of dysrhythmia to be treated
 - Reason for device including but not limited to any contraindications for a standard device (with leads)
 - Type of device requested
 - Pertinent past procedural and surgical history
 - Past and present diagnostic testing and results
 - Prior conservative treatments, duration, and response
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Operative/Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	33274	Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (e.g., fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (e.g., interrogation or programming), when performed
	33275	Transcatheter removal of permanent leadless pacemaker, right ventricular, including imaging guidance (e.g., fluoroscopy, venous ultrasound, ventriculography, femoral venography), when performed
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/01/2019	BCBSA Medical Policy adoption
07/01/2023	Policy reactivated. Previously archived from 08/01/2020 to 06/30/2023.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	AFTER <u>Blue font: Verbiage Changes/Additions</u>
<p>Reactivated Policy</p> <p>Policy Statement: N/A</p>	<p>Leadless Cardiac Pacemakers 2.02.32</p> <p>Policy Statement:</p> <ol style="list-style-type: none"> I. The Micra™ VR or Aveir™ (see Policy Guidelines) single-chamber transcatheter pacing system may be considered medically necessary in individuals when both conditions below are met: <ol style="list-style-type: none"> A. The individual has high-grade atrioventricular (AV) block (see Policy Guidelines) in the presence of atrial fibrillation or has significant bradycardia and: <ol style="list-style-type: none"> 1. Normal sinus rhythm with rare episodes of 2° or 3° AV block or sinus arrest (see Policy Guidelines) 2. Chronic atrial fibrillation 3. Severe physical disability (see Policy Guidelines) B. The individual has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following: <ol style="list-style-type: none"> 1. History of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection (see Policy Guidelines) 2. Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins or planned use of such veins for a semi-permanent catheter or current or planned use of an arteriovenous fistula for hemodialysis 3. Presence of a bioprosthetic tricuspid valve II. The Micra™ AV single-chamber transcatheter pacing system may be considered medically necessary in individuals when both conditions below are met: <ol style="list-style-type: none"> A. The individual has high-grade AV block (see Policy Guidelines) in the presence of atrial fibrillation or has significant bradycardia and: <ol style="list-style-type: none"> 1. Normal sinus rhythm with rare episodes of 2° or 3° AV block or sinus arrest (see Policy Guidelines) 2. Chronic atrial fibrillation

POLICY STATEMENT	
BEFORE	AFTER
	<p style="text-align: center;">Blue font: Verbiage Changes/Additions</p> <ul style="list-style-type: none"> 3. Severe physical disability (see Policy Guidelines) 4. There is an indication for VDD pacing and the individual may benefit from maintenance of AV synchronous ventricular pacing (see Policy Guidelines) B. The individual has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads such as any of the following: <ul style="list-style-type: none"> 1. History of an endovascular or cardiovascular implantable electronic device (CIED) infection or who are at high risk for infection (see Policy Guidelines) 2. Limited access for transvenous pacing given venous anomaly, occlusion of axillary veins or planned use of such veins for a semi-permanent catheter or current or planned use of an arteriovenous fistula for hemodialysis 3. Presence of a bioprosthetic tricuspid valve III. The Micra™ and Aveir™ single-chamber transcatheter pacing systems are considered investigational in all other situations in which the above criteria are not met.