



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1672 – Procedures for the insertion or removal of a leadless permanent pacemaker for the treatment of bradyarrhythmia

Applicant: **Medtronic Australasia Pty Ltd**

Date of MSAC consideration: **28-29 July 2022**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of percutaneous transcatheter insertion or removal of a leadless permanent pacemaker (LPM) for the treatment of bradyarrhythmia that requires single-chamber ventricular pacing was received from the medical device company Medtronic Australasia Pty Ltd by the Department of Health.

Medtronic also indicated its intention to apply for listing of the LPM, the Micra™ Ventricular (VR) Transcatheter Pacing System (TPS) device on the Prostheses List (PL).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for percutaneous transcatheter insertion or removal of a leadless permanent pacemaker (LPM) for the treatment of bradyarrhythmia that requires single-chamber ventricular pacing. MSAC considered there was an unmet clinical need for a subpopulation of those patients for whom a transvenous pacemaker (TVPM) is inappropriate due to inaccessible upper extremity venous system, increased risk of infection or history of venous thrombosis and advised that this subpopulation needed to be defined in the item descriptor. MSAC noted the limitations in the clinical evidence, but accepted that LPM was noninferior for short-term safety, superior for long-term safety and noninferior for effectiveness compared with TVPM. MSAC advised that a reduction in the proposed cost of the device would be required for the cost-effectiveness of LPM to be considered acceptable at an incremental cost-effectiveness ratio (ICER) of approximately \$50,000 per quality-adjusted-life year which is an acceptable ICER for this population and level of uncertainty around the clinical evidence and utilisation.

The MSAC supported item descriptors are provided below. MSAC advised that the Department should consult with the Cardiac Society of Australia and New Zealand (CSANZ) to further define this indication, and the contraindications that would preclude a TVPM. MSAC considered that the criteria for removal should also be defined.

Category 3 – THERAPEUTIC PROCEDURES T8 Surgical Operations Subgroup 6 – Cardiothoracic
<p>MBS item WWWW</p> <p>LEADLESS PERMANENT CARDIAC PACEMAKER, SINGLE-CHAMBER VENTRICULAR, percutaneous insertion of, <i>for the treatment of bradyarrhythmia</i>, including cardiac electrophysiological services <i>where transvenous pacemaker (TVPM) is inappropriate due to inaccessible upper extremity venous system, increased risk of infection or history of venous thrombosis</i></p> <p>Multiple Operation Rule (Anaes.) Fee: \$797.45 H (75% rebate)</p>
<p>MBS item XXXX</p> <p>LEADLESS PERMANENT CARDIAC PACEMAKER, SINGLE-CHAMBER VENTRICULAR, percutaneous retrieval and replacement of, including cardiac electrophysiological services</p> <p>Multiple Operation Rule (Anaes.) Fee: \$797.45 H (75% rebate)</p>
<p>MBS item YYYY</p> <p>LEADLESS PERMANENT CARDIAC PACEMAKER, SINGLE-CHAMBER VENTRICULAR, percutaneous retrieval of</p> <p>Multiple Operation Rule (Anaes.) Fee: \$797.45 H (75% rebate)</p>
<p>MBS item ZZZZ</p> <p>LEADLESS PERMANENT CARDIAC PACEMAKER, SINGLE-CHAMBER VENTRICULAR, surgical explantation of</p> <p>Multiple Operation Rule (Anaes.) (Assist) Fee: \$2,984.25 H (75% rebate)</p>

Consumer summary

This is an application from Medtronic Australasia Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of the insertion or removal of a permanent leadless pacemaker for the treatment of bradyarrhythmia that requires single-chamber ventricular pacing.

The human heart needs to beat a minimum number of beats per minute to pump enough blood around the body. But in people with bradyarrhythmia, the heart beats too slowly and sometimes erratically, so they need a pacemaker that sends electrical signals to the heart to correct the heart rate.

Traditionally, transvenous pacemakers have a wire lead that delivers electrical impulses from the pulse generator to the heart, and a surgical procedure is required to insert the generator and lead.

The leadless pacemaker (LPM) is inserted through the femoral vein in the leg and implanted directly into the heart muscle of the right ventricle, so no leads are needed. Because there are no leads, the procedure to insert it is less complicated than the procedure needed for a pacemaker with leads. There is also a reduced risk of infection and no chest scar when inserting a leadless pacemaker. In addition, the generator, which is usually located in a person's chest and causes the skin to bulge is absent. This is because the generator is contained within the unit of the LPM itself.

MSAC considered that there will be some patients in whom a transvenous pacemaker cannot be inserted and that these would be the patients in whom an LPM could be inserted instead. MSAC advised that the Department should consult with the Cardiac Society of Australia and New Zealand (CSANZ) to further define this group of patients.

MSAC considered that the evidence presented showed that the use of a leadless pacemaker is comparatively safe and effective. However, MSAC advised that the price of the LPM device would need to be lowered to make it acceptably cost-effective.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported the MBS listing of the insertion or removal of a permanent leadless pacemaker for the treatment of bradyarrhythmia that requires single-chamber ventricular pacing. MSAC considered there was an unmet need for patients who would not usually be able to have a transvenous pacemaker. MSAC noted some limitations in the evidence but considered the technology to be comparatively safe and effective. However, MSAC advised that the price of the LPM device would need to be lowered to make it acceptable value for money.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this applicant-developed assessment report (ADAR) is from Medtronic Australasia Pty Ltd requesting procedural MBS items for the insertion or removal of a permanent LPM for the treatment of bradyarrhythmia that requires single-chamber ventricular pacing. MSAC noted that the applicant intends to apply for listing of the Micra VR TPS device on the PL [REDACTED].

MSAC noted that the Micra Transcatheter Pacing System (Micra VR TPS) is a single-chamber implantable transcatheter LPM inserted via the femoral vein and implanted directly into the right ventricular myocardium, negating the need for transvenous wires. It is the only LPM currently available in Australia. Due to the absence of leads and absence of necessity of a subcutaneous pocket, the advantages of leadless pacing compared to conventional single-chamber pacing are

based on eliminating lead and pocket complications, therefore presenting advantages from a safety perspective. Other possible advantages include patient satisfaction due the absence of a scar and absence of a subcutaneous device location.

MSAC noted that the proposed population included a subgroup of patients who it was challenging to treat with a TVPM because of difficult venous access or complications (e.g., high risk of infection). MSAC accepted in these patients there was a clinical need for LPM.

MSAC noted the comparator was TVPM which was appropriate for most patients. In those contraindicated or not indicated for TVPM, MSAC considered that the comparator would be a surgically implanted (epicardial) single chamber pacemaker.

MSAC agreed with ESC's suggested changes to the item descriptor. In addition, MSAC considered that those patients for whom a TVPM is inappropriate needed to be defined in the item descriptor. These patients include those with an inaccessible upper extremity venous system, increased risk of infection or history of venous thrombosis. MSAC advised that the Department should consult with the CSANZ to further define the contraindications that would preclude a TVPM. MSAC considered that the criteria for removal should also be defined. MSAC noted an explanatory note could provide further guidance for the included indications, for example "increased risk of infection could include prior cardiac electronic device related infection, requirement for frequent vascular access such as haemodialysis or portacath."

MSAC noted that the pivotal evidence included a large cohort study (the CED study) that included 16,431 patients inserted with a LPM or a transvenous pacemaker (TVPM) based on US claims data with 24 months of follow up available to date. To account for important patient and encounter characteristics, propensity score overlap weights were used to construct a weighted cohort of patients who differed with respect to pacemaker type (LPM vs TVPM) but were similar with respect to other observed characteristics. MSAC agreed with ESC and considered this was appropriate given the study design however may not adjust for all group differences if there are unobserved confounders. MSAC considered that the large sample size of the study and propensity weighting helps overcome some of the potential limitations of observational studies. Thus, the CED data represent the largest and highest-level evidence to inform the comparison of LPM vs. TVPM to date. MSAC noted the other study data included in the ADAR was very poor-quality evidence.

MSAC noted that despite significant baseline differences between treatment groups in the CED study (LPM group were less healthy), that the unadjusted rates of overall complications at 30 days' follow-up (8.4% for the Micra VR TPS and 7.3% for the TVPM) were not substantially different between the treatment groups. LPM was associated with more events at the puncture site because of the percutaneous approach used (inserted via the femoral vein) compared with TVPM. At 2 years after device implantation, there were significantly more complications in the TVPM group compared to the Micra VR TPS group with adjusted rates of 6.5% and 4.6%, respectively (hazard ratio 0.69, 95% CI 0.60 to 0.81, $p < 0.0001$). MSAC noted that when the data was adjusted the difference in the overall complication rates between the Micra VR TPS and the TVPM groups was small.

In terms of comparative effectiveness, MSAC noted that low to very low-quality evidence (GRADE) showed consistent findings of noninferiority with regards to mortality and improvement in quality of life (mental and physical domains), but it was unknown if the quality of life scores (using 36-Item Short Form Survey [SF-36]) were clinically significant as no minimally clinical important difference (MCID) was provided in the ADAR.

MSAC noted the limitations in the clinical evidence, but accepted that LPM was noninferior for short-term safety, superior for long-term safety and noninferior for effectiveness compared with TVPM.

MSAC noted that the economic modelling was a cost-utility analysis with most evidence from the CED study. MSAC agreed with the ESC advice that the simple Markov model using alive and dead states was reasonable. MSAC noted that the cost of the device is the main component of the intervention.

MSAC noted that the time horizon (assumed based on 12-year battery life) is a major driver of the model. MSAC noted ESC's concern that the model should have considered a lifetime analysis but accepted the pre-MSAC response that both arms of the model may require a second device at a similar rate (and then may not have a substantial impact on the incremental cost-effectiveness ratio (ICER). MSAC also noted ESC's concern that the absence of a lead and chest pocket for LPMs was included as a utility improvement over TVPMs, which was not based on any specific evidence and a key driver of the model; MSAC noted that the pre-MSAC response reasoned that this was only a modest assumption that the quality of life of patients living with LPMs vs TVPMs is better on average by a utility score of only 0.005 each year.

MSAC noted that given the high and uncertain ICER, ESC had queried whether there may be a subpopulation with greater need that may benefit more with an LPM, and potentially with more favourable cost-effectiveness. MSAC noted that in those people contraindicated or unsuitable for TVPM, the comparator would be a surgically implanted pacemaker. MSAC considered that because inserting a pacemaker surgically would be associated with a higher post-operative disutility, that LPM would likely have more favourable cost-effectiveness in this subpopulation.

Overall, MSAC supported MBS listing of the insertion or removal of a permanent leadless pacemaker for the treatment of bradyarrhythmia that requires single-chamber ventricular pacing subject to the applicant agreeing to a reduction in the proposed price of the device to be approximately \$ [REDACTED] (a reduction from \$ [REDACTED]). This would be required for the cost-effectiveness of LPM to be considered acceptable at an ICER of approximately \$50,000 per quality-adjusted-life year which is an acceptable ICER for this population and level of uncertainty around the clinical evidence and utilisation. MSAC noted that this Public Summary Document (PSD) forms its advice in relation to comparative safety, effectiveness, and cost-effectiveness for any application to list the LPM on the PL.

MSAC noted that the major financial and budgetary impact will be the prostheses costs to private health insurers. Using the MSAC cost-effective price of LPM of \$ [REDACTED], the aggregate national prostheses costs to health insurers are forecast to increase by \$ [REDACTED] in Year 1, rising to \$ [REDACTED] in Year 6.

MSAC noted that younger people may find the LPM's cosmetic appearance and suitability for an active lifestyle advantageous. However, it was noted that because the average life of the device battery is 12 years, there is a higher risk that younger people will need additional devices to be implanted over time.

MSAC queried whether there should be a maximum number of LPM devices implanted per lifetime, particularly relevant for younger patients who could potentially end up with several deactivated devices in their ventricle, as per the recommendation for deactivated devices to be left in situ following its useful life. MSAC noted that in its pre-MSAC response, the applicant agreed it may be appropriate that a maximum number of LPM devices be implanted per lifetime, and that could be informed by a CSANZ consensus document.

MSAC noted that retrieval of the LPM is straightforward in the first few months post-implantation as it has a dedicated mechanism for retrieval and the device will have not become encapsulated.

However, extraction once encapsulated, requires an invasive approach and is difficult, so few clinicians would want to perform the procedure and instead would opt to leave the pacemaker in situ. MSAC noted that the Department will seek the advice of CSANZ to provide clarity on the approaches to device retrieval and surgical explantation.

MSAC noted the Department will progress implementation of its advice following usual process for the procedural items for the insertion or removal of the LPM on the MBS which require the listing of the device on the PL.

4. Background

MSAC has not previously considered the insertion, removal or explantation of a permanent LPM for the treatment of bradycardia.

On the July 2021 Prostheses List, various single-chamber pacemaker generators (Grouping 08.04.03) and right ventricular pacemaker leads were available (Groupings 08.08.08 and 08.08.09), but no LPM was listed.

5. Prerequisites to implementation of any funding advice

The Micra VR TPS has been included in the Australian Register of Therapeutic Goods (ARTG) since December 2016, together with an ‘introducer’ for inserting the device. Table 1 provides details of the Therapeutic Goods Administration (TGA) status from the ARTG for the Micra VR TPS and its consumables under number 283235.

Table 2 Micra VR TPS and consumables included in the ARTG

Product name & Sponsor	ARTG summary	Functional description	Intended purpose
Micra single-chamber transcatheter pacing system - Intracardiac pacemaker Medtronic Australasia Pty Ltd	ARTG ID: 283235 Start date: 06/12/2016 Category: AIMD GMDN: 60789 Intracardiac pacemaker	MR conditional single-chamber implantable transcatheter pacing system with SureScan technology is a programmable cardiac device that monitors and regulates the patient's heart rate by providing rate-responsive bradycardia pacing to the right ventricle. The device senses the electrical activity of the patient's heart using the sensing and pacing electrodes enclosed in the titanium capsule of the device.	Indicated for use in patients who have experienced one or more of the following conditions: <ul style="list-style-type: none"> • symptomatic paroxysmal or permanent high-grade AV block in the presence of AF • symptomatic paroxysmal or permanent high-grade AV block in the absence of AF, as an alternative to dual-chamber pacing when atrial lead placement is considered difficult, high risk or not deemed necessary for effective therapy • symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual-chamber pacing when atrial lead placement is considered difficult, high risk or not deemed necessary for effective therapy

Product name & Sponsor	ARTG summary	Functional description	Intended purpose
			<ul style="list-style-type: none"> rate-responsive pacing is indicated to provide increased heart rate appropriate to increasing levels of activity
Micra Introducer - Model MI2355A - Cardiovascular device introducer, non-steerable Medtronic Australasia Pty Ltd	ARTG ID: 221570 Start date: 24/03/2014 Category: Class III GMDN: 57941 Cardiovascular device introducer, non-steerable	The Micra introducer is a single-use, disposable, hydrophilically coated sheath that provides a flexible and haemostatic conduit for the insertion of intravascular devices into the venous system to minimise blood loss. The system comprises two components: a dilator that accommodates a guidewire and an introducer.	The Micra introducer is intended to provide a conduit for the insertion of devices into the venous system and to minimise blood loss associated with such insertions.

AF, atrial fibrillation; AV, atrioventricular; MR, magnetic resonance.

Source: Therapeutic Goods Administration, ARTG Public Summary, accessed 7 July 2021. Verified by assessment group on 17 March 2022.

The applicant specified prerequisites for clinicians prior to Micra VR TPS use, which include a proficiency in femoral venous access and large bore catheter manipulation, and the completion of a dedicated training course (online modules and in-person). The in-person training includes didactic learning, observing Micra VR TPS implant procedures and hands-on procedural training (e.g., implant simulator, cadaver and animal model, videos and demonstration models). The applicant recommends that the first 10 implants, at a minimum, be supported by a Medtronic Micra Technical Expert. The application states that additional support beyond the first 10 implants will be made available.

The next generation Micra LPM device, Micra Atrioventricular (AV) TPS, has been included in the ARTG since October 2021 (ARTG 376750). However, the current application is limited to the Micra VR TPS for pacing of the right ventricle only, without sensing in the atrium. There are currently no other LPMs available in the Australian market. The Nanostim LPM from St Jude Medical (now Abbott) was recalled by the TGA in 2016 due to a battery malfunction specific to that device. According to the applicant and literature searches conducted by the assessment group, other LPMs are still in the early stages of development and are expected to be several years away from being ready for market entry.

6. Proposal for public funding

The proposed population requested for the Micra VR TPS (mode VVIR) is patients requiring permanent pacing with a conventional single-chamber TVPM. This includes patients with sinus node dysfunction (SND) or AV block who require single-chamber pacing of their right ventricle. The Micra VR TPS also provides a treatment option for patients who are eligible for a TVPM but are deemed unsuitable due to venous access issues or prior infections.

The Micra VR TPS is a permanent single-chamber implantable transcatheter LPM that is inserted via the femoral vein and implanted directly into the right ventricular myocardium, negating the need for transvenous leads. The device is programmable and monitors and regulates the patient's heart rate by providing rate-responsive bradycardia pacing to the right ventricle. Similar to TVPMs, the Micra VR TPS has traditional remote monitoring capabilities (via a physical monitor). However, due to its small size (25.9 mm long, 2.8 mm in diameter and weighing 1.75 grams) it is not capable

of Bluetooth® monitoring (via a mobile app). The rate response is controlled through an activity-based sensor.

The applicant proposed four MBS items: one item for the insertion, one item for retrieval and replacement, one item for retrieval and one for explantation of an LPM (see Table 3).

Table 3 Proposed MBS items. ESC amendments in markup (italics and strikethrough).

Category 3 – THERAPEUTIC PROCEDURES	T8 Surgical Operations	Subgroup 6 - Cardiothoracic
MBS item WWWW		
LEADLESS PERMANENT CARDIAC PACEMAKER, SINGLE-CHAMBER VENTRICULAR, percutaneous insertion of, <i>for the treatment of bradycardia</i> , including cardiac electrophysiological services		
<i>(Anaes.) Benefit 75%</i>		
Fee: \$797.45		
MBS item XXXX		
LEADLESS PERMANENT CARDIAC PACEMAKER, SINGLE-CHAMBER VENTRICULAR, percutaneous retrieval and replacement of, including cardiac electrophysiological services, during the same percutaneous procedure.		
<i>(Anaes.) Benefit 75%</i>		
Fee: \$797.45		
MBS item YYYY		
LEADLESS PERMANENT CARDIAC PACEMAKER, SINGLE-CHAMBER VENTRICULAR, percutaneous retrieval of		
<i>(Anaes.) Benefit 75%</i>		
Fee: \$797.45		
MBS item ZZZZ		
LEADLESS PERMANENT CARDIAC PACEMAKER, SINGLE-CHAMBER VENTRICULAR, surgical explantation of		
<i>(Anaes.) (Assist) Benefit 75%</i>		
Fee: \$2984.25		

The fees for the proposed items have been informed by the following existing MBS items that are used to claim the single-chamber TVPM procedure (the nominated comparator for the application):

- MBS item 38350 for insertion, removal or replacement of single-chamber permanent transvenous electrode. Given that all single-chamber TVPM devices provided through the MBS require a lead, the usage data for MBS item 38350 is a reasonable representation of the number of implant procedures as well. However, some of the services provided under MBS item 38350 relate to lead complications, including revisions.
- MBS item is 38353, for insertion, removal or replacement of the TVPM device. This MBS item can be claimed for the insertion of either a dual- or single-chamber pacemaker. According to the survey in Mond 2019,¹ single-chamber TVPMs constituted 21% of all pacemaker services for 2021.
- MBS item 61109 for fluoroscopy is claimed in conjunction with the two previous MBS items (38350 and 38353).
- MBS item 38358 for percutaneous extraction of chronically implanted transvenous leads.

¹ Mond, HG & Crozer, I 2019, 'The Australian and New Zealand Cardiac Implantable Electronic Device Survey: Calendar year 2017, *Heart Lung Circ*, vol. 28, pp. 560-566.

- MBS item 90300, claimed with MBS item 38358, for cardiothoracic surgeon attendance for lead extraction.

The fee for proposed MBS item WWWW (percutaneous insertion of an LPM, including cardiac electrophysiological services) is the same as the combined fee for MBS items 38350 and 38353 (taking the multiple operation rule into account). This also applies to MBS items XXXX (percutaneous retrieval and replacement of an LPM, including cardiac electrophysiological services, during the same percutaneous procedure) and YYYYY (percutaneous retrieval of an LPM).

In Australia, patients with symptomatic bradycardia first seek treatment from a hospital or general practitioner before being referred to a specialist cardiologist. The patient's history, physical examination results and resting electrocardiogram (ECG) are all important components of the medical evaluation required before being considered eligible for single-chamber ventricular pacing (Kusumoto 2019)². Further non-invasive assessments may include an exercise ECG, an ambulatory ECG, imaging, laboratory testing, genetic testing and sleep apnoea testing. When non-invasive examinations are not diagnostic, invasive testing (e.g., implantable cardiac monitors and electrophysiology studies) may be required (Kusumoto 2019).

The healthcare resources required for the insertion of a standard single-chamber TVPM, which include anaesthesia, fluoroscopy, the professional service itself and hospitalisation, are similar to those needed for the insertion of an LPM. The duration of stay is the same for both procedures, with patients generally being admitted overnight. According to an Australian study (Denman et al. 2019)³, the length of time required to insert an LPM or TVPM is similar (around 30 minutes).

No key issues with the proposed descriptors have been raised. However, guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS)² and the European Society of Cardiology (ESC)⁴ note the following regarding key subpopulations who may be more suitable for LPMs:

- The 2018 ACC/AHA/HRS guidelines note that identifying patient populations that will benefit the most from emerging pacing technologies, such as LPMs, will require further investigation as these modalities are incorporated into clinical practice. Moreover, the guidelines warned that the role of these new devices in real-world practice, and their potential interaction with other cardiac devices, is still unclear.
- The 2021 ESC guidelines on cardiac pacing made specific recommendations for LPM as follows:
 - LPMs should be considered as an alternative to TVPMs when no upper extremity venous access exists or when risk of device pocket infection is particularly high, such as patients with a previous infection or those on haemodialysis; and
 - LPMs may be considered as an alternative to standard single-lead ventricular pacing, taking into consideration life expectancy and using shared decision-making.

² Kusumoto, FM, et al. 2019, '2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society', *Circulation*, vol. 140, no. 8, pp. e382-e482.

³ Denman, RA, et al. 2019, 'Leadless permanent pacing: a single centre Australian experience', *Heart Lung Circ*, vol. 28, no. 11, pp. 1677-1682.

⁴ Glikson, M, et al. 2021, '2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy', *Eur Heart J*, vol. 42, no. 35, pp. 3427-3520.

7. Population

One Population, Intervention, Comparator and Outcomes (PICO) set was defined for the proposed technology, the Micra VR TPS, in place of the standard single-chamber (TVPM) (see Table 4). In Australian public hospitals the insertion of the using Micra VR TPS has been performed for several years (first implant 2016) in the proposed patient population.

Table 4 PICO criteria for assessing the transcatheter LPM for the treatment of bradycardia

Component	Description
Population	<p>Patients^a in whom single-chamber ventricular pacing (mode VVIR) is indicated due to one or more of the following conditions:</p> <ul style="list-style-type: none"> • symptomatic paroxysmal or permanent high-grade AV block in the presence of AF • symptomatic paroxysmal or permanent high-grade AV block in the absence of AF, as an alternative to dual-chamber pacing when atrial lead placement is considered difficult, high risk or not deemed necessary for effective therapy • symptomatic SND, 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.
Intervention	<p>Percutaneous transcatheter insertion or retrieval, with or without replacement, and surgical explantation, of a (LPM for single-chamber ventricular pacing):</p> <ul style="list-style-type: none"> • Micra VR Transcatheter Pacing System (Medtronic)
Comparator	Standard single-chamber TVPM
Outcomes ^b	<p>Technical performance</p> <ul style="list-style-type: none"> • pacing performance (sensing, impedance, pacing threshold) • battery life • adaptability (rate response) <p>Patient-relevant effectiveness outcomes</p> <ul style="list-style-type: none"> • mortality (all-cause and cardiovascular) • exercise capacity • change of medication • progression or recurrence of cardiac arrhythmias • switch to an alternative device (a different pacemaker or defibrillator) • symptoms of cardiac arrhythmias (pre-syncope or syncope) • health-related quality of life • patient satisfaction <p>Safety outcomes</p> <ul style="list-style-type: none"> • major procedure-related complications (infection, pericardial effusion, cardiac tamponade/perforation, thromboembolism, vascular complications [bleeding, arteriovenous/atrioventricular fistula, pseudoaneurysm, haematoma]) • right ventricular dysfunction • atrioventricular (tricuspid and mitral) valve regurgitation • pacemaker syndrome • major device-related complications (device dislodgement, device malfunction, battery failure, device infection, pacemaker-induced arrhythmia) • device revision, retrieval, replacement, explantation • any serious adverse event <p>Health care resources</p> <ul style="list-style-type: none"> • procedure duration • implant success rate • time to hospital discharge • procedure-related and follow-up costs (including downstream hospitalisations and device monitoring)

	<ul style="list-style-type: none"> • cost of device and consumables <p>Total Australian Government healthcare costs</p> <ul style="list-style-type: none"> • total cost to the Medicare Benefits Schedule • total cost to other healthcare budgets
<p>Systematic review questions:</p> <p>What is the safety, effectiveness and cost effectiveness of fully implantable LPMs versus single-chamber TVPMs for patients with bradyarrhythmia in whom single-chamber ventricular pacing is indicated?</p>	

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; LPM, leadless pacemaker; SND, sinus node dysfunction; TVPM, transvenous pacemaker; VR, ventricular; VVIR, ventricular demand pacing

Notes: ^a Patients with anatomy that can tolerate a 23 French sheath at the vascular insertion site.

^b The following outcomes were not addressed in the ADAR as no evidence were retrieved from the studies: adaptability (rate response), exercise capacity, change of medication, progression or recurrence of cardiac arrhythmias, symptoms of cardiac arrhythmia (syncope or pre-syncope), and right ventricular dysfunction. However, battery life was reported in a couple of case series studies but this was not mentioned in the application.

The Micra VR TPS is proposed as an alternative or replacement of the current standard of care. According to the applicant, use of the Micra VR TPS will not change the clinical pathway for diagnosis of bradycardia or the work-up prior to pacemaker insertion. Similarly, the applicant states there will be no changes to required medical services associated with use of the intervention following its insertion.

The adapted clinical management described by the applicant is based on feedback from local experts who refer to the 2018 ACC/AHA/HRS guideline on the management of patients with bradycardia (Kusomoto 2019).⁵

The Micra VR TPS is indicated for patients who have experienced one or more of the following conditions (see Table 1):

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

The applicant's experts also specified that the Micra VR TPS would be mainly indicated in patients with AV block. The presence or absence of symptoms is a key factor in determining whether permanent pacing is required in patients with bradycardia associated with AV block. Three additional clinical issues must also be considered: 1) the site of the AV block, especially for patients with infra-nodal disease who are likely to develop complete heart block; 2) significant amounts of right ventricular pacing that are potentially deleterious; and 3) co-existing, associated systemic disease that may lead to progressive AV block or increased risk for ventricular arrhythmias (Kusomoto 2019)⁵.

Only a minority of patients with SND would be considered suitable to receive the Micra VR TPS (to alleviate the symptoms of cerebral hypoperfusion attributed to bradycardia when other potential treatable or reversible aetiologies have been excluded). Moreover, a subset of patients with SND may require atrial pacing at a later point in time. This would require insertion of a TVPM because atrial pacing is not a function of the Micra-VR TPS.

⁵ Kusomoto, FM, et al. 2019, '2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society', *Circulation*, vol. 140, no. 8, pp. e382-e482.

8. Comparator

Standard single-chamber TVPM is the nominated comparator for the assessment, and this is considered the appropriate choice of comparator.

TVPM consists of a pulse generator (containing the battery and the machinery for sensing and timing the electrical impulses) and a lead (an insulated wire that delivers electrical impulses from the pulse generator to the heart). The pulse generator must be inserted through a surgical incision in the chest to create a subcutaneous pocket. A single lead is placed percutaneously into the right ventricle via the subclavian, cephalic or axillary veins and guided transvenously through the tricuspid valve. The position of the wire is checked using fluoroscopy. The lead can either be attached passively with tines (spikes at the end of the wire), which become fixed via granulation tissue formation, or be actively fixed to the myocardium using a screw.

TVPM is currently funded through the MBS items outlined in Table 5:

Table 5 MBS item descriptors related to single-chamber TVPMs

Category 3 – THERAPEUTIC PROCEDURES
<p>38350 (listing date: 01/11/2005) SINGLE CHAMBER PERMANENT TRANSVENOUS ELECTRODE, insertion, removal or replacement of, including cardiac electrophysiological services where used for pacemaker implantation Multiple Operation Rule (Anaes.) Fee: \$664.55 Benefit: 75% = \$498.45 (See para TN.8.60 of explanatory notes to this Category)</p>
<p>38353 (listing date: 01/11/2005) PERMANENT CARDIAC PACEMAKER, insertion, removal or replacement of, not for cardiac resynchronisation therapy, including cardiac electrophysiological services where used for pacemaker implantation Multiple Operation Rule (Anaes.) Fee: \$265.80 Benefit: 75% = \$199.35 (See para TN.8.60 of explanatory notes to this Category)</p>
<p>TN.8.60 The fees for the insertion of a pacemaker (Items 38350, 38353 and 38356) cover the testing of cardiac conduction or conduction threshold, etc related to the pacemaker and pacemaker function. Accordingly, additional benefits are not payable for such routine testing under item 38209 or 38212 (Cardiac electrophysiological studies).</p>

Category 3 – THERAPEUTIC PROCEDURES

38358 (listing date: 01/11/2005)

Extraction of one or more chronically implanted transvenous pacing or defibrillator leads, by percutaneous method, with locking stylets and snares, with extraction sheaths (if any), if:

(a) the leads have been in place for more than 6 months and require removal; and

(b) the service is performed:

(i) in association with a service to which item 61109 or 60509 applies; and

(ii) by a specialist or consultant physician who has undertaken the training to perform the service; and

(iii) in a facility where cardiothoracic surgery is available and a thoracotomy can be performed immediately and without transfer; and

(c) if the service is performed by an interventional cardiologist—a cardiothoracic surgeon is in attendance during the service

(H)

Multiple Operation Rule

(Anaes.) (Assist)

Fee: \$2,089.00 Benefit: 75% = \$1,566.75

(See para TN.8.64, TN.8.214 of explanatory notes to this Category)

TN.8.64

Intravascular Extraction of Permanent Pacing Leads - (item 38358)

For the purposes of item 38358 specialists or consultant physicians claiming this item must have training recognised by the Lead Extraction Advisory Committee of the Cardiac Society of Australia and New Zealand, and the Department of Human Services notified of that recognition. The procedure should only be undertaken in a hospital capable of providing cardiac surgery.

TN.8.214

International guidelines and claiming guide for extraction of leads

International guidelines state that delays from injury to open access to the heart of more than 5–10 minutes are often associated with a fatal outcome. Preparations for this procedure should provide for this rare but life threatening circumstance.

Claiming guide:

When the service to which item 38358 applies is provided to a patient by an accredited interventional cardiologist the following claiming will apply:

Item 38358 is to be claimed by the accredited interventional cardiologist; and

Item 90300 is to be claimed by the standby cardiothoracic surgeon.

When the service to which item 38358 applies is provided to a patient by an accredited cardiothoracic surgeon the following claiming will apply:

Item 38358 is to be claimed by the accredited cardiothoracic surgeon; and

Item 90300 is also claimable by the cardiothoracic surgeon.

Category 1 – PROFESSIONAL ATTENDANCES

Group A37 – Cardiothoracic Surgeon Attendance for Lead Extraction

<p>Category 3 – THERAPEUTIC PROCEDURES</p> <p>90300 (listing date: 01/07/2021)</p> <p>Professional attendance by a cardiothoracic surgeon in the practice of the surgeon's speciality, if:</p> <p>(a) the service is performed in conjunction with a service (the lead extraction service) to which item 38358 applies; and</p> <p>(b) the surgeon is:</p> <p>(i) either performing, or providing surgical backup for the provider (who is not a cardiothoracic surgeon) who is performing, the lead extraction service; and</p> <p>(ii) present for the duration of the lead extraction service, other than during the low risk pre and post extraction phases; and</p> <p>(iii) able to immediately scrub in and perform a thoracotomy if major complications occur (H)</p> <p>Fee: \$895.25 Benefit: 75% = \$671.45</p> <p>(See para TN.8.214 of explanatory notes to this Category)</p>
<p>Category 5 - DIAGNOSTIC IMAGING SERVICES</p> <p>61109 (listing date 31/10/1992)</p> <p>Fluoroscopy in an angiography suite with image intensification, in conjunction with a surgical procedure using interventional techniques, not being a service associated with a service to which another item in this Group applies (R)</p> <p>Bulk bill incentive</p> <p>Fee: \$265.15 Benefit: 75% = \$198.90 85% = \$225.40</p> <p>(See para IN.0.19 of explanatory notes to this Category)</p>
<p>IN.0.19</p> <p>Bulk Billing Incentive</p> <p>Out-of-hospital services (except item 61369) attract higher benefits when they are bulk billed by the provider.</p> <p>For other than items in Group I5 – Magnetic Resonance Imaging (MRI) - benefits for bulk billed services are payable at 95% of the schedule fee for the item. For MRI services, benefits for bulk billed services are payable at 100% of the schedule for the item.</p>

9. Summary of public consultation input

Consultation input was received from two health professionals and one organisation:

- Hearts4Heart

The consultation feedback received was supportive of the application and noted that the advantages of the proposed intervention relate to patient satisfaction and reduction of complications, mainly through the lack of lead and pocket complications.

Benefits

- Fewer post-implant activity restrictions and no obstructions to shoulder movement.
- Provides an alternative therapy for patients who have failed the traditional current pacemaker, are at risk of infections and for patients who already have a lot of prosthetics, difficulties with lead placement or when a traditional pacemaker might cause additional complications.
- Reduction of lead and pocket complications.
- Patient satisfaction due to absence of a scar, reduced pain & discomfort, and subcutaneous device location.
- Improved quality of life.
- Reduced recovery time and length of hospital stay due to the minimally invasive nature of the procedure.
- Cost savings to the health system.

Disadvantages

- Potential for pain & discomfort during the delivery of the leadless pacemaker to the right ventricle via the femoral vein.
- The use of a large bore (25 Fr) catheter for delivery may increase the risk of bleeding during delivery.

Other

- Feedback supported separate MBS items for retrieval and explantation.
- Feedback from one health professional considered that although the proposed MBS item fee based on the existing fees for pacemaker and lead insertion appeared reasonable, MSAC should consider whether other cardiac catheter-based procedures could be suitable benchmarks: e.g., MBS 38272 Atrial septal defect or patent foramen closure, fee = \$949.25; MBS 38276 Transcatheter occlusion of left atrial appendage, fee = \$949.25.

10. Characteristics of the evidence base

A high-level summary of the included studies is provided in Table 6. The quality assessment was undertaken using the NHLBI quality assessment tool.

Table 6 Key features of the included evidence comparing leadless pacemaker (Micra VR TPS) to TVPM

Trial/Study	N	Study design Risk of bias	Population	Key outcome(s)	Results used in economic model
CED	16,431	Non-randomised observational, PSM Quality appraisal: good*	US Medicare population receiving LPM TVPM patients identified using the ICD-10-PCS for implants occurring in the inpatient setting and Current Procedural Terminology for implants occurring in the outpatient setting	Acute complication rates Survival Chronic complication rates Device-related reintervention rates	Yes**
Cabanas-Grandio 2020	106	Multicentre, non-randomised, consecutive Quality appraisal: poor*	Patients undergoing single-chamber PM implantation from December 2016 to March 2018 The choice of LPM or TVPM was based on clinical criteria and operator availability	QoL at 6 months post-implant	No
Garg 2020	3,329	Multicentre, retrospective cohort with historical control; adjusted mortality analyses Quality appraisal: poor*	Patients who met class I or II guideline recommendations for ventricular pacing, stratified LPM by precluded versus not precluded for TVPM	All-cause mortality Safety, including major complication rates and acute complication rates	No

Trial/Study	N	Study design Risk of bias	Population	Key outcome(s)	Results used in economic model
Pagan 2020	302	Multicentre, non-randomised cohort study Quality appraisal: poor*	Elderly (≥85 years) patients receiving LPM or TVPM.	Procedure-related complication rates	No
Palmisano 2021	154	Single centre, non-randomised, prospective; PSM Quality appraisal: fair*	Allcomers – de novo PM Patients meeting class I or II guideline recommendations for de novo ventricular pacing Choice of PM at clinician discretion. LPMs were preferentially implanted in: patients aged >65 years who had a reasonable life expectancy and functional status of more than one year; patients at high risk of infection; and patients with difficult or no venous access for a TVPM	Procedural data Patient acceptance QoL up to 6 months	No
Martinez-Sande 2020	443	Single centre, non-randomised, prospective cohort, PSM/adjusted Quality appraisal: fair*	Allcomers Patients with an indication for a single-chamber pacemaker implant according to the current guidelines The choice between an LPM or a TVPM was made according to physician discretion	Device-related complications Mortality LPM electrical parameters (pacing capture threshold, sensing, impedance)	No
Tachibana 2020	62	Single centre, non-randomised, retrospective observational Quality appraisal: poor*	Elderly (>85 years) A continuous sample of patients who received single-chamber ventricular pacemaker implantation including TVPM and LPM due to symptomatic bradyarrhythmias from May 2014 to July 2019 TVPMs were mostly implanted prior to Feb 2017; LPMs were implanted after February 2017	Complications Survival rates Electrical parameters	No
Vaidya 2019	163	Multicentre, non-randomised observational Quality appraisal: poor*	Patients from the Mayo Clinic device billing records and device database who received a Micra or Nanostim LPM Matching controls who received a TVPM were identified for each LPM implant from the same cohort of patients	Procedure-related complications	No
Zuchelli 2020	200	Single centre, non-randomised prospective cohort with “matching”	Allcomers Between May 2014 and April 2019, patients who met the class I indication for pacing and	Electrical parameters (including pacing capture thresholds,	No

Trial/Study	N	Study design Risk of bias	Population	Key outcome(s)	Results used in economic model
		Quality appraisal: poor*	were suitable for single-chamber ventricular stimulation Patients who underwent TVPM implantation	impedance, R wave amplitude) Acute and chronic complications Mortality rates	

ICD-10-PCS, International Classification of Diseases, 10th Revision, Procedure Coding System; LPM, leadless pacemaker; PM, pacemaker; PSM, propensity score matched/adjusted; QoL, quality of life; TPS, transcatheter pacing system; TVPM, transvenous pacemaker; VR, ventricular

* Assessment of observational cohort and cross-sectional studies based on NHLBI Study Quality Assessment tool, see Bias assessment.xls (Attachment 3).

** Adjusted rates used for economic model

Methodological considerations of the included studies

A range of databases were searched, and the search strategies appeared to be comprehensive. However, conference abstracts and grey literature were not searched, which could mean that studies were missed. The exclusion of non-comparative studies for the safety section of this application means that there are local data from Australian studies that have not been included.^{6,7}

There were very few details reported about the review methodology, which makes it difficult to verify that robust systematic review methods were followed; specifically, there are no details about the study selection or data extraction processes, and the data extraction spreadsheet is limited.

Eligibility criteria

The way in which the eligibility criteria were applied to select the studies for inclusion in the review is a concern. Five eligibility criteria are listed, but they do not appear to have been followed. Studies that fell outside the stated criteria were included, while others that appeared to meet the criteria were excluded. Specifically, two conference abstracts that utilised national datasets with very large sample sizes were excluded. Without further details about these two larger studies, the outcomes of these two abstracts appear to be similar to those reported in the CED, however there is very little information provided in the abstracts to adequately compare whether the composite outcomes reported in the CED are comparable to the outcomes reported in the abstracts.

Synthesis of evidence

The applicant has reported the results of the CED study separately from the other studies, which were deemed supportive. While methodologically this is not common practice, the sheer size of the CED study means that the additional data reported by the much smaller supportive studies

⁶ Chieng, D, Lee, F, Ireland, K & Paul, V 2020, 'Safety and efficacy outcomes of combined leadless pacemaker and atrioventricular nodal ablation for atrial fibrillation using a single femoral puncture approach', *Heart Lung Circ*, vol. 29, no. 5, pp. 759-765.

⁷ Denman, RA, et al. 2019, 'Leadless permanent pacing: a single centre Australian experience', *Heart Lung Circ*, vol. 28, no. 11, pp. 1677-1682.

would not be sufficient to alter the results of the CED study. The economic section of the report relies solely on data from the CED study.

The adjustment of the baseline characteristics in the application is an area of uncertainty. Neither the protocol nor the statistical analysis plan clearly states which variables were used to undertake the adjustment, so the accuracy of this cannot be verified. Several outcomes for both safety and efficacy reported in the application show an unadjusted rate that is significantly in favour of TVPM, with a corresponding adjusted rate that shows no differences between the LPM and TVPM groups (including rates of overall complications at 30 days, complications at two years⁸ and re-intervention⁸). The validity of these results relies entirely on the adjustment for confounding having been performed accurately. Without further details about how the adjustment was undertaken, it is difficult to substantiate the claims about the Micra VR TPS for these outcomes.

The synthesis of the supportive studies is inappropriate, as all outcomes have been meta-analysed despite the applicant stating that the studies have heterogeneous populations, outcome definitions and lengths of follow-up. There are several analyses and forest plots showing a single study, even though the applicant states in the methods that meta-analysis will only be applied when there is more than one study available. The majority of the outcomes reported from these meta-analyses have wide confidence intervals, indicating imprecision, and should not be relied on for decision making. For this reason, the safety and effectiveness results reported below focus largely on the CED study; the supportive studies have not been considered in this summary.

Bias and confounding

Bias was assessed in the CED study using the NHLBI Study Quality Assessment tool. The quality assessment seems appropriate. However, the applicant claims to have assessed bias for some studies at the outcome level, when in fact the risk of bias assessment was only conducted for the CED study as a whole.

Confounding was a significant issue in the CED study. Propensity score overlap weights were used to account for differences in population characteristics between the treatment groups at baseline, which is appropriate given the study design.

11. Comparative safety

The safety outcomes discussed here are those from the CED study.

Acute complications at 30 days

The ADAR presents data for acute complications at 30 days post-implantation for the CED study (Relative Risk (RR) 1.04, 95% confidence interval [CI] 0.93 to 1.16). While there were no differences in the overall complication rates between the Micra VR TPS and TVPM groups, this composite outcome was derived from several acute complications that warranted further discussion by the applicants. It would have been more helpful to focus on complications by type rather than overall complication rates, so that any trade-offs can be clearly seen. The results, summarised by complication type, are reported in the Table 7 below.

⁸ Chi-square tests were calculated by the commentary

Table 7 Acute complications (within 30 days) in CED study – unadjusted and adjusted

Events	Unadjusted rates (%)						Adjusted rates (%)				
	LPM (n=5746)	TVPM (n=9662)	RD % (95% CI)	P value (calculated by applicant)_	RR (95% CI) ^e	p-value (recalculated by ASERNIP-S) ^e	LPM (n=5746)	TVPM (n=9662)	RD % (95% CI)	P value	RR (95% CI) ^c
Overall complications	484 (8.4)	707 (7.3)	1.11 (0.22 to 1.99)	0.02	1.15 (1.03 to 1.29)	0.0129	442 (7.7)	715 (7.4)	0.3 (-0.6 to 1.3)	0.49	1.04 (0.93 to 1.16)
Embolism and thrombosis	202 (3.5)	286 (3.0)	0.56 (-0.03 to 1.14)	0.07	1.19 (0.99 to 1.42)	0.0571	184 (3.2)	300 (3.1)	0.1 (-0.5 to 0.7)	0.81	1.03 (0.86 to 1.24)
DVT	145 (2.5)	176 (1.8)	0.70 (0.22 to 1.19)	0.003	1.39 (1.11 to 1.72)	0.0033	126 (2.2)	193 (2.0)	0.3 (-0.2 to 0.7)	0.27	1.10 (0.88 to 1.37)
Pulmonary embolism	72 (1.3)	128 (1.3)	0.07 (-0.30 to 0.44)	0.74	0.95 (0.71 to 1.26)	0.7037	69 (1.2)	126 (1.3)	-0.1 (-0.5 to 0.3)	0.52	0.92 (0.69 to 1.23)
Thrombosis due to cardiac device	≤10 ^a	≤10 ^a	NE	0.64	NE	NE	≤10 ^a	≤10 ^a	0 (0 to 0)	0.52	NA
Embolism due to cardiac device	≤10 ^a	0	NE	NA	NE	NE	≤10 ^a	NA	NA	NA	NA
Events at puncture site	78 (1.4)	31 (0.3)	1.04 (0.72 to 1.36)	<0.001	4.23 (2.79 to 6.41)	<0.0001	69 (1.2)	29 (0.3)	0.8 (0.5 to 1.2)	<0.001	4.00 (2.60 to 6.17)
Arteriovenous fistula	40 (0.7)	≤10 ^a	NE	<0.001	NE	NE	29 (0.5)	NA	NA	0.003	NA
Vascular aneurysm	49 (0.9)	24 (0.3)	0.60 (0.35 to 0.86)	<0.001	3.43 (2.11 to 5.59)	<0.0001	52 (0.9)	19 (0.2)	0.7 (0.4 to 0.9)	<0.001	4.60 (2.72 to 7.77)
Cardiac effusion and/or perforation	47 (0.8)	38 (0.4)	0.42 (0.16 to 0.69)	<0.001	2.08 (1.36, 3.19)	0.0008	46 (0.8)	39 (0.4)	0.4 (0.1 to 0.7)	0.004	4.07 (2.39 to 6.94)
Device-related complications ^b	81 (1.4)	247 (2.6)	1.15 (0.71 to 1.58)	<0.001	0.55 (0.43 to 0.71)	<0.0001	80 (1.4)	242 (2.5)	-1.1 (-1.5 to -0.6)	<0.001	0.56 (0.43 to 0.71)
Other complications	136 (2.4)	169 (1.8)	0.62 (0.15 to 1.09)	0.01	1.35 (1.08 to 1.69)	0.0080	121 (2.1)	164 (1.7)	0.4 (-0.1 to 0.9)	0.10	1.24 (0.98 to 1.57)

Events	Unadjusted rates (%)						Adjusted rates (%)				
	LPM (n=5746)	TVPM (n=9662)	RD % (95% CI)	P value (calculated by applicant)_	RR (95% CI) ^e	p-value (recalculated by ASERNIP-S) ^e	LPM (n=5746)	TVPM (n=9662)	RD % (95% CI)	P value	RR (95% CI) ^c
Device-related AMI	≤10 ^a	≤10 ^a	NE	0.71	NE	NE	≤10 ^a	≤10 ^a	0.0 (0 to 0.1)	0.40	NA
Post-procedural haematoma	30 (0.5)	40 (0.4)	0.11 (-0.12 to 0.33)	0.33	1.26 (0.79 to 2.02)	0.3356	29 (0.5)	39 (0.4)	0.1 (-0.1 to 0.3)	0.45	1.25 (0.77 to 2.02)
Post-procedural haemorrhage	32 (0.6)	11 (0.1)	0.44 (0.24 to 0.65)	<0.001	4.89 (2.47 to 9.70)	<0.0001	29 (0.5)	10 (0.1)	0.4 (0.2 to 0.6)	<0.001	4.88 (2.38 to 10.00)
Intraoperative cardiac arrest	20 (0.4)	24 (0.3)	0.1 (-0.08 to 0.28)	0.30	1.40 (0.77 to 2.53)	0.2644	17 (0.3)	29 (0.3)	0.1 (-0.2 to 0.3)	0.51	0.99 (0.54 to 1.79)
Pericarditis	51 (0.9)	23 (0.2)	0.65 (0.39 to 0.91)	<0.001	3.73 (2.28 to 6.09)	<0.0001	46 (0.8)	29 (0.3)	0.6 (0.3 to 0.9)	<0.001	2.67 (1.68 to 4.24)
Vascular complication	38 (0.7)	16 (0.2)	0.50 (0.27 to 0.72)	<0.001	3.99 (2.23 to 7.16)	<0.0001	34 (0.6)	19 (0.2)	0.4 (0.2 to 0.6)	<0.001	3.01 (1.72 to 5.27)
Hemothorax	0	0	0	NA	NE	NE	NA	NA	NA	NA	NA
Pneumothorax	0	77 (0.8)	0.80 (0.62 to 0.98)	NA	0.01 (0.00 to 0.18)	0.0014	NA	77 (0.8)	NA	NA	NA

Abbreviations: AMI, acute myocardial infarction; NA, not applicable. NE, not estimable from the data reported; LPM, leadless pacemaker; TVPM, transvenous pacemaker; CI=confidence interval; RD=risk difference.

a Cells with 10 or less patients were suppressed to protect beneficiary privacy as required by the US Centres of Medicare & Medicaid Services.

b Includes complications related to the mechanical integrity of the device or codes explicitly stating device relatedness (eg, device dislodgement, device infection, device pocket complication). See Table 1 in the Supplement for details.

c Calculated.

d Risk difference and associated 95% CIs calculated using the University of Illinois, Chicago risk reduction calculator. araw.mede.uic.edu/cgi-bin/nntcalc.pl

e Relative risk and associated 95% CIs and p-values calculated using MedCalc Software Ltd. Relative risk calculator. https://medcalc.org/calc/relative_risk.php (Version 20.106)

Bold denotes statistical significance

Source: commentary report

The most important complication is cardiac perforation. Patients receiving a Micra VR TPS patients were reported to be twice as likely to experience this complication than those receiving a TVPM (0.8% vs 0.4%; RR 1.98, 95% CI 1.30 to 3.03; P = 0.0016).

In November 2021 the United States Food & Drug Administration (FDA) published a letter to healthcare providers⁹ detailing the risk of major complications related to cardiac perforation during implantation of the Micra VR TPS. The letter stated that *“the Medtronic Micra leadless pacemaker premarket clinical studies suggested major complications related to cardiac perforation appeared to be more severe for patients who received a leadless pacing system compared to patients who received a transvenous pacemaker... 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.”* The FDA intend to evaluate post-market studies to provide additional information in the future.

Post-procedural complications at two years

The ADAR reported results at two years after device implantation from the CED study, but these were provided as an overall composite outcome made up of several individual complications. There were significantly more complications in the TVPM group compared to the Micra VR TPS at two years with adjusted rates of 6.5% and 4.6% respectively (hazard ratio 0.69, 95% CI 0.60 to 0.81, p<0.0001). However, it would have been more helpful to focus on complications by type rather than overall complication rates. The results are reported in Table 8:

⁹ United States Food and Drug Administration (U.S. FDA) 2021, *Leadless pacing systems: Risk of major complications related to cardiac perforation during implantation – Letter to health care providers* [Online], U.S. FDA. Available: <https://www.fda.gov/medical-devices/letters-health-care-providers/leadless-pacing-systems-risk-major-complications-related-cardiac-perforation-during-implantation> [Accessed 29 March 2022].

Table 8 Adjusted and unadjusted rates of device-related complications at 2-years in CED: LPM vs TVPM

Events	LPM (n=6,219)			TVPM (n=10,212)			LPM vs TVPM			
	Observed Events (%) ^a	2-Year Unadjusted CIF Estimates (95%CI)	2-Year Weighted CIF Estimates (95% CI)	Observed Events (%) ^a	2-Year Unadjusted CIF Estimates (95%CI)	2-Year Weighted CIF Estimates (95% CI)	Unadjusted p-value	Adjusted HR (95% CI)	Adjusted RRR (95% CI)	Adjusted P value
Overall complications	285 (4.6%)	4.9% (4.4% - 5.5%)	4.6% (4.2%, 4.9%)	631 (6.2%)	6.5% (5.9% - 7.1%)	6.5% (6.1%, 6.9%)	0.0001	0.69 (0.60, 0.81)	31% (19%, 40%)	<.0001
Embolism and thrombosis	≤10*	NA*	NA*	23 (0.2%)	0.2% (0.2% - 0.3%)	0.2% (0.2%, 0.2%)	0.23	0.54 (0.25, 1.17)	46% (-17%, 75%)	0.12
Thrombosis due to cardiac device	≤10*	NA*	NA*	≤10*	NA*	NA*	0.29	0.49 (0.20, 1.19)	51% (-19%, 80%)	0.12
Embolism due to cardiac device	≤10*	NA*	NA*	≤10*	NA*	NA	0.89	0.86 (0.15, 5.02)	14% (-402%, 85%)	0.87
Device-related complications	155 (2.5%)	2.5% (2.1% - 2.9%)	2.4% (2.2%, 2.5%)	500 (4.9%)	4.8% (4.6% - 5.0%)	4.8% (4.7%, 5.0%)	<.0001	0.48 (0.40, 0.58)	52% (42%, 60%)	<.0001
Breakdown	80 (1.3%)	1.4% (1.1%-1.8%)		191 (1.9%)	2.0% (1.8%-2.3%)		0.01			
Dislodgement	23 (0.4%)	0.4% (0.3%-0.6%)		121 (1.2%)	1.2% (1.0%-1.4%)		<.0001			
Other mechanical complications	55 (0.9%)	0.9% (0.7%-1.2%)		104 (1.0%)	1.1% (0.9%-1.3%)		0.45			
Infection	≤10*	NA		60 (0.6%)	0.6% (0.5%-0.8%)		<.0001			
Device pain	0 (0.0%)	0.0% (0.0-0.1%)		*	*		<.0001			
Device stenosis	24 (0.4%)	0.4% (0.3%-0.6%)		30 (0.3%)	0.3% (0.2%-0.5%)		0.27			
Pocket complications	N/A	N/A		131 (1.3%)	1.4% (1.2%-1.6%)		N/A			

Events	LPM (n=6,219)			TVPM (n=10,212)			LPM vs TVPM			
	Observed Events (%) ^a	2-Year Unadjusted CIF Estimates (95%CI)	2-Year Weighted CIF Estimates (95% CI)	Observed Events (%) ^a	2-Year Unadjusted CIF Estimates (95%CI)	2-Year Weighted CIF Estimates (95% CI)	Unadjusted p-value	Adjusted HR (95% CI)	Adjusted RRR (95% CI)	Adjusted P value
Other complications	141 (2.3%)	2.2% (2.0% - 2.5%)	2.1% (2.0%, 2.3%)	142 (1.4%)	1.4% (1.2% - 1.6%)	1.4% (1.3%, 1.6%)	<.0001	1.48 (1.15, 1.91)	-48% (-91%, -15%)	0.002
Pericarditis	100 (1.6%)	1.7% (1.4% - 2.0%)	1.6% (1.4%, 1.9%)	76 (0.7%)	0.8% (0.6% - 1.0%)	0.8% (0.7%, 0.9%)	<.0001	2.05 (1.50, 2.80)	-105% (-180%, -50%)	<.0001
Hemothorax	43 (0.7%)	0.7% (0.6% - 1.0%)	0.6% (0.5%, 0.8%)	71 (0.7%)	0.7% (0.6% - 0.9%)	0.7% (0.6%, 0.9%)	0.97	0.87 (0.57, 1.33)	13% (-33%, 43%)	0.51

Abbreviations: N/A, not applicable. LPM, leadless pacemaker; TVPM, transvenous pacemaker; CI=confidence interval; CIF, cumulative incidence function; RRR, relative risk reduction.

^a Raw percentage defined as number of events divided by number of patients.

* Cells with 10 or less patients were suppressed to protect beneficiary privacy as required by the US Centres of Medicare & Medicaid Services.

Source: Commentary report

Re-interventions at two years

Patients implanted with a LPM had significantly fewer overall reinterventions over 2-years compared with patients implanted with a TVPM (Table 9), with the adjusted rates of 3.1% vs. 4.9%, respectively ($p=0.003$). It should be noted that reinterventions were combined in a composite score that included revision, replacement, upgrade and removal. In terms of the individual outcomes, LPM patients experienced significantly fewer revisions (adjusted HR [95% CI]: 0.20 [0.08, 0.50], $p=0.01$), removals (0.05 [0.01, 0.20], $<.0001$) and upgrades to CRT (0.70 [0.51, 0.96], $p=0.025$); whereas fewer replacements were observed in TVPM patients (2.50 [1.40, 4.46], $p=0.002$). The applicant does not explain why almost three times as many patients in the LPM group had a replacement compared to TVPM patients. There is no definition of replacement, or any details related to this including whether the original (presumably faulty) LPM remained in situ while a second device was deployed.

Table 9 Unadjusted and Adjusted rates of reintervention rates at 2-years in CED: LPM vs TVPM

Events	LPM (n=6,219)			TVPM (n=10,212)			LPM vs TVPM			
	Observed Events (%) ^a	2-Year unadjusted CIF Estimates (95% CI)	2-Year Weighted CIF Estimates (95% CI)	Observed Events (%) ^a	2-Year unadjusted CIF Estimates (95% CI)	2-Year Weighted CIF Estimates (95% CI)	Unadjusted p-value	Adjusted HR (95% CI)	Adjusted RRR (95% CI)	Adjusted P value
Any re-intervention	169 (2.7%)	3.0% (2.4%-3.8%)	3.1% (2.8%-3.4%)	494 (4.4%)	4.8% (4.2%-5.3%)	4.9% (4.5%-5.4%)	0.006	0.62 (0.45, 0.85)	38% (15%-55%)	0.003
System re-intervention										
Revision	≤10*	NA*	NA*	56 (0.6%)	0.6% (0.4%-0.8%)	0.6% (0.4%-0.8%)	0.0003	0.20 (0.08, 0.50)	80% (50%-92%)	0.001
Lead-related reinterventions	N/A	N/A	N/A	65 (0.6%)	0.7% (0.5%-0.9%)	0.7% (0.5%-0.9%)	N/A	N/A	N/A	N/A
Replacement	68 (1.1%)	1.1% (0.8%-1.5%)	1.1% (0.9%-1.3%)	44 (0.4%)	0.4% (0.3%-0.7%)	0.4% (0.3%-0.6%)	0.0016	2.50 (1.40, 4.46)	-150% (-346%--40%)	0.002
System switch (replacement with opposite type of device)	18 (0.3%)	0.3% (0.2%-0.5%)	0.4% (0.2%-0.5%)	26 (0.3%)	0.3% (0.2%-0.4%)	0.3% (0.2%-0.4%)	0.6776	1.28 (1.34, 2.50)	-28% (-150%--34%)	0.463
Removal	≤10*	NA*	*	75 (0.7%)	0.8% (0.6%-1.0%)	0.8% (0.7%-1.1%)	<.0001	0.05 (0.01, 0.20)	95% (80%-99%)	<.0001
Upgrade										
Dual-chamber	22 (0.4%)	0.4% (0.3%-0.6%)	0.4% (0.3%-0.6%)	66 (0.7%)	0.7% (0.6%-0.9%)	0.8% (0.6%-1.0%)	0.0458	0.58 (0.33, 1.02)	42% (-2%-67%)	0.06
CRT	57 (0.9%)	1.1% (0.8%-1.5%)	1.2% (1.0%-1.4%)	140 (1.4%)	1.6% (1.4%-1.8%)	1.7% (1.4%-1.9%)	0.0162	0.70 (0.51, 0.96)	30% (4%-49%)	0.025

Abbreviations: N/A, not applicable. LPM, leadless pacemaker; TVPM, transvenous pacemaker; CI=confidence interval; CIF, cumulative incidence function; RRR, relative risk reduction.

^a Raw percentage defined as number of events divided by number of patients.

* Cells with 10 or less patients were suppressed to protect beneficiary privacy as required by the US Centres of Medicare & Medicaid Services.

Source: Commentary report.

Missing outcomes

There are several other important complications that appear to be missing from the included studies and therefore cannot be commented on. Ventricular fibrillation is a major concern and should have been reported as a complication. Rates of pleural effusion and intra-procedure cardioversion or defibrillation should also have been reported.

Limitations of the safety data

The main safety data reported by the applicant is a composite outcome comprising several different complications. Combining rare and common complications into a composite outcome does not provide a true estimation of risk. The composite complication outcomes reported in the CED study cover a spectrum of severity, and several outcomes are related to the type of patient more so than to the type of device implanted. For example, pulmonary embolism has a background rate in the general population independent from the placement of a pacemaker. Similarly, the likelihood of developing deep vein thrombosis after the procedure may be more related to a patient's level of mobility than to the type of pacemaker that was implanted. It would have been more helpful to focus on outcomes that are clearly related to device placement.

While there are several methodological problems with the data presented, particularly in the composite outcomes, these may not have had a substantial impact on the results. While the propensity score matched adjustment of the overall complication rate made a difference from a statistical point of view (changing the result from statistically significant to non-significant), the unadjusted rates of overall complications at 30 days' follow-up (8.4% for the Micra VR TPS and 7.3% for the TVPM) were not substantially different between the treatment groups. Considering the significant baseline differences between treatment groups in the CED study, it seemed likely that the unadjusted complication rates would also be vastly different. However, the complication rates differed by only 1.1%. Statistical adjustment (via logistic regression) cannot adjust for all confounders, and any unmeasured confounders will persist in the data. When adjusted, the difference in the overall complication rates between the Micra VR TPS and the TVPM groups changed from 1.1% to 0.3%. Thus, it is likely that the real difference in the complication rates is less than 0.3%.

Based on the adjusted analysis, 330 LPMs would have to be implanted to produce one extra (most likely non-lethal) complication. The 30-day mortality reported in the CED study was around 4% in both treatment groups (reported in the next section on efficacy), which makes a 0.3% difference in complication rates acceptable. However, whether these mortality and complication rates are applicable to the Australian context is unknown.

12. Comparative effectiveness

Effectiveness outcomes are reported in Table 10. The outcomes are split into those reported by the CED study and those reported by the supportive studies.

Mortality

There were no differences in mortality outcomes at 30 days or two years after implantation between the Micra VR TPS and TVPM groups. This is unsurprising given that the loss of pacemaker function is unlikely to be a lethal event in this patient group. However, the ADAR did not report procedural or cardiac mortality rates.

Quality of life

Quality of life results (SF-36 scores) were reported in two supportive studies, both of which reported significant differences in favour of the Micra VR TPS (four of ten SF-36 domains for both studies and an additional five domains in one study). Neither study reported measures of variance for changes from baseline, consequently it was not possible to verify whether the outcomes reported were significantly different from baseline values for either treatment group.

Electrical parameters

Electrical parameters (not shown in Table 7) were reported by six supportive studies. The applicants also included several case series studies, despite the methods stating that these study types were excluded. While it is likely that the pacing thresholds remained stable over time, the applicant claims that this endured over the longer term. However, this is not substantiated because the follow-up periods for most studies were less than six months.

Table 10 Summary of evidence table

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TVPM	Risk with LPM				
Mortality - any (CED) follow up: 24 months	325 per 1,000	317 per 1,000 (301 to 336)	HR 0.97 (0.91 to 1.04) [Mortality - any (CED)]	1,6431 (1 non-randomised study)	⊕⊕○○ Low	LPM results in little to no difference in mortality rates based on the CED study.
Mortality – any Supportive studies	135 per 1,000	72 per 1,000 (41 to 126)	RR 0.53 (0.30 to 0.93)	948 (4 observational studies)	⊕○○○ Very low ^{a,b}	The evidence is very uncertain about the effect of LPM on any mortality rates based on supportive studies. Although a benefit in favour of LPM is observed, the risk of confounding compromises the results.
SF-36 Physical component summary at 6 months Supportive study	The mean SF-36 Physical component summary at 6 months was 38.8	MD 3.2 higher (1.91 higher to 4.49 higher)	-	154 (1 observational study)	⊕⊕○○ Low	LPM may increase the SF-36 score at 6 months - Physical component summary.
SF-36 Mental component summary at 6 months Supportive study	The mean SF-36 Mental component summary at 6 months was 43.4	MD 5.8 higher (1.7 higher to 9.9 higher)	-	154 (1 observational study)	⊕⊕○○ Low	LPM may increase the SF-36 score at 6 months - Mental component summary.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**, confidence interval; **HR**, hazard Ratio; **LPM**, leadless pacemaker; **MD**, mean difference; **RR**, risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

a. Possible selection bias, some differences in baseline characteristics which was not adjusted for in the majority of the studies.

b. Some heterogeneity in the results.

Key limitations of the effectiveness data

Missing outcome data

No data was provided in the application relating to battery longevity, even though there are case series studies reporting battery life. In the absence of data, it seems reasonable to assume that the high pacing thresholds of the Micra VR TPS will affect battery longevity.

The lack of data regarding strategies to replace the Micra VR TPS once it reaches the end of its service life is also concerning. No data was provided in the application on retrieval of the device. The Micra VR TPS is designed to be left in situ and to be encapsulated over time. The potential inability to retrieve an implanted device, or the damage that may be caused by retrieving it, may limit the use of the device in selected patients. The process for device retrieval or reimplantation with a second device is unclear, particularly regarding the number of Micra VR TPS devices that can be retained in the heart. It is assumed that electrical interaction between the functioning and non-functioning pacemakers is unlikely, but no long-term data was provided to confirm this.

Limitations of the effectiveness evidence

The applicant claims use of the Micra VR TPS results in noninferior effectiveness and superior safety, compared with the TVPM. Focussing solely on the methodology of the review, the clinical claim may be overstated given the uncertainty in the evidence reported in the summary of evidence tables, which describe the certainty as low or very low for all outcomes. There is insufficient evidence available to conclusively say that the Micra VR TPS is noninferior in terms of efficacy or superior in terms of safety.

However, The Micra VR TPS is already in use worldwide to varying degrees, which means there is unlikely to be a randomised controlled trial (RCT) conducted on its use. The outcomes of greatest interest (cardiac perforation) occur with such low frequency that even a meta-analysis of very large RCTs may not be able to provide definitive answers on the level of risk for this complication.

There appear to be pros and cons related to using the Micra VR TPS device. On the one hand there are important risks to consider, including higher rates of cardiac perforation than for TVPMs, but on the other hand device-related complications are lower with the Micra VR TPS.

Applicability

The applicant does not discuss patient selection, and there were no published studies or guidance identified that address how clinicians might choose which device a patient should receive. It is clear that selection criteria were being applied because patients who received the Micra VR TPS in the CED study were younger and had significantly more comorbidities than patients who received the TVPM.

In the United Kingdom, an expert advisory group recently produced recommendations for leadless pacemakers for the Medicines & Healthcare products Regulatory Agency (MHRA).¹⁰ They stated that *“patients should have a clear indication for bradycardia pacing, a clear and explicit reason documented for the choice of a leadless device over a conventional pacemaker and that*

¹⁰ Medicines & Healthcare products Regulatory Agency (MHRA) Expert Advisory Group 2021, *Leadless cardiac pacemaker therapy: design of pre- and post-market clinical studies. Recommendations from MHRA Expert Advisory Group Version 3: Updated January 2021* [Online], MHRA. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/956252/Leadless-EAG-guidance.pdf [Accessed 29 March 2022].

careful attention should be paid to contraindications, such as patient habits and venous abnormalities likely to result in complications from the large sheaths required for device delivery". The guidance also recommends that due to the higher incidence of tamponade, LPMs should be implanted in high volume centres with on-site cardiac surgery until robust data confirms that the risk of tamponade is as low as that for conventional pacing.

Clinical claim

The clinical claim made by the applicant is that, compared with TVPM, the use of a Micra VR TPS results in noninferior effectiveness (favouring the Micra VR TPS for quality-of-life outcomes) and superior safety with respect to complication rates over time.

13. Economic evaluation

A cost-utility analysis is presented in the submission that compares the Micra VR TPS to TVPMs in the Australian healthcare system. This approach is appropriate given the claim of clinical superiority. A Markov model was developed in Excel which included alive and dead states. Within the alive state, events are included for infection, pericarditis, revision, lead-related re-intervention, replacement and removal. The events were assigned disutility values derived from the literature. The economic analysis included a two-year time horizon presented in the sensitivity analysis, which captures the maximum follow-up available from the CED study. This study was the source for clinical outcome rates in the model. An extrapolated analysis was also included with a 12-year time horizon. This time period was considered to reflect the battery life of the Micra VR TPS device. A summary of the model elements is provided in Table 11.

Table 11 Element of the economic model included in the evaluation

Component	Description
Perspective	Australian health system
Population	Patients with SND or AV block that require single-chamber pacing of their right ventricle
Comparator	TVPM
Type of economic evaluation	Cost-utility analysis
Source of evidence	Clinical and device-related events based on the CED study
Time horizon	2 years base and 12 years extrapolated (the assumed battery life)
Outcome	Quality-adjusted life-years (QALYs)
Methods used to generate results	Markov model
Health states	Alive and dead (infection, pericarditis, revision, lead-related re-intervention, replacement and removal events included in the alive state)
Cycle length	1 year
Discount rate	5% per annum
Software packages used	Excel

Source: Submission, Table 4 (pp.8) and compiled for the commentary

Abbreviations: AV, atrioventricular block; LPM, leadless pacemaker; QALYs, quality-adjusted life years, TVPM, transvenous pacemaker; SND, sinus node dysfunction

Incremental costs and effectiveness

The incremental cost-effectiveness ratio (ICER) over two years was estimated to be \$ [REDACTED] per quality-adjusted life-year (QALY) gained (see Table 8). The extrapolated 12-year time frame was associated with the Micra VR TPS generating 0.0832 additional QALYs over the TVPM; the ICER was \$ [REDACTED] per QALY gained.

Table 12 Results of the economic analysis

Step	Micra VR TPS	TVPM	Increment	ICER
Step 1 – Comparative study data, 2-year time horizon (CED study maximum follow-up)				
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	
Outcome (QALYs)	[REDACTED]	[REDACTED]	[REDACTED]	\$ [REDACTED]
Step 2 – Time frame extrapolated with additional modelling (12-year battery life)				
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	
Outcome (QALYs)	[REDACTED]	[REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Submission and compiled for the commentary

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; TPS, Transcatheter Pacing System; TVPM, transvenous pacemaker; VR, ventricular

There are some uncertainties and evidence gaps in the economic model. The absence of a lead and pocket for the Micra VR TPS was assumed to result in improved patient quality of life, although the included value of utility improvement was not based on specific evidence. This assumption has a very large impact on the results (accounting for 42% of the total QALY benefits) and is not supported by evidence.

A stepped sensitivity analysis was presented in the submission, with a two-year analysis being used to reflect the maximum follow-up in the CED study and an extrapolated 12-year analysis being used to represent the predicted battery life of a Micra VR TPS. There is uncertainty about this length of extrapolation for battery life because the Duray (2017)¹¹ study only includes 12 months of data. The calculated ICERs are sensitive to this assumption, as outlined in the following table.

Table 13 Sensitivity analyses (time horizon)

Analyses	Incremental cost	Incremental QALY	ICER
2 year analysis	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
3 year analysis	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
5 year analysis	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
10 year analysis	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
12 year analysis	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Submission, Table 61.

ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year.

Key drivers of the model are summarised in Table 14.

¹¹ Duray, GZ et al.; Micra Transcatheter Pacing Study Group 2017, 'Long-term performance of a transcatheter pacing system: 12-Month results from the Micra Transcatheter Pacing Study', *Heart Rhythm*, vol. 14, pp. 702-709.

Table 14 Key drivers of the model

Description	Method/Value	Impact: 12-year ICER: \$/QALY gained
Long term disutility for TVPM based on presence of lead and pocket	The submission included a disutility in the TVPM cohort equivalent to a patient experiencing approximately one month of post-procedural QoL decrement (0.0608 ÷ 12). The utility improvement based on lead and pocket absence were not supported by specific evidence. Clinical feedback during the commentary indicated that an LPM could result in higher QoL, but the exact magnitude of improvement is unclear.	High; favors the intervention This assumption has a very large impact on the results (42% of total QALY benefits). Omitting this disutility for TVPM results in the ICER increasing to \$████ per QALY gained.
Post-procedural disutility	The -0.0304 disutility was derived from Palmisano (2021). The submission selected this study over Cabanas-Grandio (2019) to derive the estimated disutility for TVPM because it used propensity score matching.	Moderate in the 12-year projection; favours the comparator. Use of the alternative value generates an ICER of \$████. Omission of the -0.0304 disutility in the 2-year follow-up multi-variate sensitivity analysis has a large impact given the limited period of follow-up after implementation.
Extrapolation	An extrapolated 12-year analysis which is claimed to correspond with the battery life of an LPM was included. There is uncertainty about this extrapolation as the Duray (2017) ¹² study includes only 12 months of data. The predicted battery life of 12.1 years was based on usage conditions at 12 months, where the LPMs in 89% of patients had a projected longevity of 10 years.	High; favors the intervention At 5 and 10 years, the calculated ICERs are \$████ and \$████ per QALY gained, respectively.
Cost of pacemaker infection treatment	There were large differences between the Barwon Health service and state-wide Victorian estimates of pacemaker infection treatment costs presented in Roder (2019) ¹³ . The cost for an admission to treat infection was \$98,097 in the Barwon Health service, which was far higher than the \$19,403 per infection estimated for all of Victoria.	High; favors the intervention Including the Victoria-based cost indexed to an inflation rate of 1.13 generated an ICER= \$████
Cost of LPM system	The overall cost of the Micra VR system which includes the LPM device, a single-use delivery catheter to deliver, deploy and test device placement and a single-use introducer (23 French sheath) is a relatively expensive unit cost and was specified as a single unit cost for the device and consumables.	A 10% variation in the system unit cost results in the ICER ranging from \$████ to \$████. The lack of disaggregation of cost of the Micra device and consumables creates uncertainty but the direction is unclear.

ICER, incremental cost-effectiveness ratio; LPM, leadless pacemaker; QALY, quality-adjusted life-year; QoL, quality of life; TVPM, transvenous pacemaker.
Source: Commentary report.

14. Financial/budgetary impacts

The financial implications to the MBS resulting from the proposed listing of LPM are summarised in Table 15. The submission provided a financial analysis using a market share approach. The LPM is assumed to substitute for the TVPM using Medicare statistics for MBS item 38350, the current MBS-funded service procedure for transvenous leads associated with single-chamber pacemakers. This approach is reasonable as all single-chamber pacemakers require a lead. An

¹²Duray, GZ et al.; Micra Transcatheter Pacing Study Group 2017, 'Long-term performance of a transcatheter pacing system: 12-Month results from the Micra Transcatheter Pacing Study', *Heart Rhythm*, vol. 14, pp. 702-709.

¹³ Roder, C, Gunjaca, V, Otome, O, Gwini, SM & Athan, E 2020, 'Cost and outcomes of implantable cardiac electronic device infections in Victoria, Australia', *Heart Lung Circ*, vol. 29, no. 7, pp. 140-146.

additional validation analysis was also included which used pacemaker sales data reported in the Australian and New Zealand Cardiac Implantable Electronic Device Survey.

It is evident that the submission calculated the new item to have a cost neutral impact on the MBS. The requested item is for transcatheter insertion, retrieval or removal at a cost of \$797.45, which would substitute for the existing items MBS item 38350 for insertion, replacement or removal of lead (current MBS fee \$664.55) and MBS item 38353 for insertion, replacement or removal of pacing device (\$132.90; current MBS fee of \$265.80 adjusted for multiple operation rule x 50%).

Table 15 Net financial implications of an LPM to the MBS

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of LPM						
Number of single-chamber PM patients, projected	3,509	3,623	3,736	3,850	3,964	4,078
Number of people who receive an LPM						
LPM costs, 75% benefit	\$█	\$█	\$█	\$█	\$█	\$█
Fluoroscopy costs (MBS item 60503), 75% benefit	\$█	\$█	\$█	\$█	\$█	\$█
Cost to the MBS	\$█	\$█	\$█	\$█	\$█	\$█
Change in use and cost of TVPM						
Change in use of TVPM						
MBS item 38350 for insertion, replacement or removal of lead	█\$█	█\$█	█\$█	█\$█	█\$█	█\$█
MBS item 38353 for insertion, replacement or removal of pacing device	█\$█	█\$█	█\$█	█\$█	█\$█	█\$█
MBS item 60503 for fluoroscopy	█\$█	█\$█	█\$█	█\$█	█\$█	█\$█
Total, full benefit	█\$█	█\$█	█\$█	█\$█	█\$█	█\$█
Total, 75% benefit	█\$█	█\$█	█\$█	█\$█	█\$█	█\$█
Net financial impact to the MBS	0	0	0	0	0	0

LPM, leadless pacemaker; PM, pacemaker; TVPM, transvenous pacemaker

The submission requested four separate listings for LPMs (i.e., insertion, retrieval only, replacement and retrieval, and explantation), although financial impact is only calculated for insertion. It is noted in the submission that most LPM-related procedures on the MBS will be for the insertion procedure. This is likely to be the case over the next six years given device failure rates and the estimated life of the device. It is unclear in the submission whether insertion, retrieval and replacement require different amounts of time or differential fees. Justification of equivalent item costs for each should have been provided.

The base-case analysis assumes an uptake rate of █ in Year 1, increasing to █ in Year 6. There is a high degree of uncertainty about uptake of LPMs. Consequently, maximum adoption rates of █ and █ are included as sensitivity analyses in the critique. As the new and current items have the same unit cost value, changes in uptake are also cost neutral.

The major cost impact for LPMs is for prostheses costs to private health insurers. LPMs have a higher prosthesis unit cost than TVPMs. TVPM unit costs include the pacing device (\$3,948, Prostheses List group 08.04.03) and lead (\$831, Prostheses List group 08.08.09), while the

LPM unit cost is \$ [REDACTED]. Thus, the aggregate national prostheses costs to health insurers are forecast to increase by \$ [REDACTED] in Year 1, rising to \$ [REDACTED] in Year 6.

15. Other relevant information

Nil

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues

Comparative safety – Short-term safety is generally non-inferior and may improve with increasing expertise with the percutaneous transcatheter delivery of the device. For longer-term safety it was demonstrated from low quality evidence that leadless pacemaker (LPM) was superior with respect to reduced device-related complications and re-interventions 2-years post-implantation.

Comparative effectiveness – The data showed consistent findings of noninferiority with regards to mortality and improvement in health-related quality of life (mental and physical domains), but it is informed from low to very low-quality evidence (GRADE).

Economic issues

Time horizon – A key driver of the economic model was the time horizon of the model based on assumed battery life of 12 years. Using the trial follow-up time increased the ICER to \$ [REDACTED] per QALY, up from \$ [REDACTED] in the base case.

The lifetime model needs to be considered. If lifetime, ~48% of people would need another device at 12 years at an older age (89 years of age) accruing additional costs, but there would be fewer additional QALYs gained from this point, meaning the ICER would likely be higher.

Modelled incremental effectiveness based on assumption – Long term disutility of transvenous pacemaker (TVPM) is a key driver of cost effectiveness but not based on evidence. Removing the disutility results in an ICER of \$ [REDACTED].

Financial issues

The major financial impact will be on the prostheses costs to private health insurers because LPMs have a higher prosthesis unit cost than TVPMs.

MBS costs are equivalent (apart from extraction), and listing should be cost neutral to the MBS for insertion.

Policy relevant information issues

Credentiailling for removal of leadless pacemaker should be consistent with CSANZ's recommendations for explantation.

Ceiling for the total number of LPM devices should be consistent with CSANZ's recommendations, which will likely change as the technology evolves.

ESC discussion

ESC noted that this is an application from Medtronic Australasia Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of percutaneous transcatheter insertion (initial or otherwise),

percutaneous retrieval with or without replacement and surgical explantation of a LPM for the treatment of bradycardia that requires single-chamber ventricular pacing.

ESC noted that consultation feedback was received from a single individual in support of the application. ESC noted this feedback, highlighting that possible advantages of LPM would include patient satisfaction due to the absence of a scar, which would be valuable for younger patients.

ESC noted that the proposed population includes a difficult group of patients to treat because of complications (e.g., infections). ESC noted that the applicant-developed assessment report (ADAR) focused on insertion of the device (Micra VR TPS). ESC noted that removal of the device is not mentioned in the purpose of application or in subsequent clinical or economic evaluations, despite being stated in the application title and proposed MBS items.

ESC noted the Department's advice for the item descriptor and agreed with:

- The addition of the clinical indication for the procedure “for the treatment of bradycardia” in the insertion item (WWWWW) noting previous PASC advice that this application is specifically intended for a single indication – the treatment of bradyarrhythmia –and there are many other reasons why people receive pacemakers
- The addition of a "Hospital only" (75%) rebate for all items, as this procedure is only appropriate to be performed in the in-hospital setting.

ESC advised that the word “surgical” should be removed from the item descriptor for explantation (ZZZZZ) because it suggests that the procedure should be performed by surgeons; however, the procedure is mostly performed by cardiologists. In addition, ESC considered that the credentialing for removal of LPMs should be consistent with the CSANZ recommendations regarding explantation.

ESC considered that the same remote monitoring items (MBS item 11719 and 11720) for TVPM would apply to LPM.

ESC considered that it was appropriate that the proposed fees be benchmarked on the current fees for the comparator transvenous pacemaker (TVPM), despite some differences in the procedures (such as use of the femoral vein for access as opposed to the cephalic or subclavian vein for a TVPM lead; and no requirement for additional insertion of a subcutaneous generator). This would ensure one technique wasn't financially incentivised over the other. ESC also noted that proceduralists experienced in LPM insertion would be able to perform the procedure in a shorter time than taken to insert a TVPM.

ESC noted that the applicant has separated the data from the CED study from the data of the studies considered to be supportive. The Commentary noted that the large sample size of the CED study meant that any data reported by the much smaller supportive studies would not be sufficient to alter the impact of the results of the CED study in a systematic review, if all studies were included. The applicant reports the supportive studies separately from the CED study “on the basis of these studies being small in sample size, heterogeneous with respect to population, and less robust in the designs.” However, the Commentary noted this is not appropriate for a systematic review. With the exception of Tachibana (2020) (which does not meet the inclusion criteria for sample size), the supportive studies meet these eligibility criteria.

The *a priori* eligibility criteria appear to have been amended during the study selection process to include only particular publication types (no conference abstracts) and only studies with demographic specific (heterogeneous studies - presumably compared to the CED study - were excluded) and “large” sample sizes. The Commentary considered this inappropriate and stated

that this undermined the validity of systematic review methodology, which should include all studies meeting the eligibility criteria to minimise study selection bias.

ESC noted that confounding was a significant issue with the CED study. Propensity score overlap weights were used to adjust for differences in population characteristics between the treatment groups at baseline, which ESC considered was appropriate given the study design however may not adjust for all group differences if there are unobserved confounders.

ESC noted that only the CED study was used to evaluate safety. ESC noted that despite significant baseline differences between treatment groups in the CED study (LPM group were less healthy), that the unadjusted rates of overall complications at 30 days' follow-up (8.4% for the Micra VR TPS and 7.3% for the TVPM) were not substantially different between the treatment groups. The ADAR presented the adjusted rates for acute complications at 30 days post-implantation for the CED study (relative risk [RR] 1.04, 95% confidence interval [CI] 0.93 to 1.16). While there were no differences in the overall complication rates between the Micra VR TPS and TVPM groups, this composite outcome was derived from several acute complications that warranted further discussion by the applicant. ESC noted that the commentary stated that it would have been more helpful to focus on complications by type rather than overall, so that any trade-offs can be clearly seen.

The ADAR reported results at 2 years after device implantation from the CED study, but these were provided as an overall composite outcome made up of several individual complications. There were significantly more complications in the TVPM group compared to the Micra VR TPS at 2 years, with adjusted rates of 6.5% and 4.6%, respectively (hazard ratio 0.69, 95% CI 0.60 to 0.81, $p < 0.0001$). ESC noted that, when the data was adjusted, that the difference in the overall complication rates between the Micra VR TPS and the TVPM groups changed was small.

ESC noted that patients implanted with an LPM had significantly fewer overall reinterventions over 2 years compared with patients implanted with a TVPM, with the adjusted rates of 3.1% versus 4.9%, respectively ($p = 0.003$). ESC noted that reinterventions was defined as a composite score that included revision, replacement, upgrade and removal. In terms of the individual outcomes, LPM patients experienced significantly fewer revisions (adjusted HR [95% CI]: 0.20 [0.08, 0.50], $p = 0.01$), removals (0.05 [0.01, 0.20], $p < 0.0001$) and upgrades to cardiac resynchronisation therapy (CRT) (0.70 [0.51, 0.96], $p = 0.025$), whereas fewer replacements were observed in TVPM patients (2.50 [1.40, 4.46], $p = 0.002$). ESC noted that the applicant does not explain why almost three times as many patients in the LPM group had a replacement compared to TVPM patients. There is no definition of replacement, or any details related to this including whether the original (presumably faulty) LPM remained in situ while a second device was deployed. Overall, ESC considered that short-term safety (30 days post-implantation) is generally non-inferior, and that it may improve over time with increasing expertise with the percutaneous transcatheter delivery of device. For longer-term safety, it was demonstrated from low quality evidence that LPM was superior in respect to reduced device-related complications and re-interventions 2-years post-implantation.

Regarding effectiveness, ESC noted that low to very low-quality evidence (GRADE) showed consistent findings of noninferiority with regards to mortality and improvement in quality of life (mental and physical domains), but it was unknown if the quality of life scores (using 36-Item SF-36) were clinically significant as no MCID was provided in the ADAR.

ESC noted that the economic modelling was a cost-utility analysis with most evidence from the CED study. ESC considered that the use of the simple Markov model using alive and dead states

was reasonable. ESC noted there was a small difference in SF-36 scores which were converted to EQ-5D utility values by using a mapping equation developed by Ara and Brazier (2008).

ESC noted that the ADAR did not discuss patient selection, but it was clear that selection criteria were being applied because patients who received the Micra VR TPS in the CED study were younger and had significantly more comorbidities than patients who received the TVPM. ESC noted that the starting age of the model was assumed to be 77 years old and 41.8% being female, as informed by Australian data from Ranasinghe (2019), compared with the mean age of about 80 years old across the two study arms and 44% were female in the CED study. ESC considered it was unclear how this would affect the model or applicability to the Australian population.

ESC noted that the time horizon (assumed based on 12-year battery life) is a major driver of the model. The incremental cost-effectiveness ratio (ICER) for trial follow-up (2-year) was \$ [REDACTED] per quality-adjusted life year (QALY), reduced to \$ [REDACTED] in the base case (12-year). In the pre-ESC response, the applicant provided data from routine monitoring of device information such as battery longevity and electrical parameters. The median projected longevity when standardised from implant was [REDACTED] with [REDACTED] of devices having a projected longevity exceeding [REDACTED]. ESC considered that although the length of the battery life (12 years) is supported by evidence, the model should have considered a lifetime analysis; after 12 years, ~48% of patients would require another device at an older age. Additional costs would be accrued with this next device, but fewer additional QALYs would be gained from this point and would likely further drive up the ICER.

ESC also noted that the other key drivers were mainly in favour of the intervention. The long-term disutility of TVPM is based on an assumption rather than specific evidence; its impact is high as this assumption is driving the incremental difference in benefit between model arms (accounting for 42% of the total QALY benefits). Removing the disutility results in an ICER of \$ [REDACTED]. ESC also noted that the ICER was sensitive to the cost of pacemaker infection treatment. Overall, ESC considered that the ICER may be much higher than the base-case estimate. Given the high and uncertain ICER, ESC queried whether there may be a subpopulation with greater need and may benefit more with an LPM, and potentially with more favourable cost-effectiveness.

ESC noted that the base-case analysis assumes an uptake rate of [REDACTED] in Year 1, increasing to [REDACTED] in Year 6. Although this is uncertain, the impact on the MBS estimates remain the same.

ESC noted that the major financial impact will be on the prostheses costs to private health insurers because LPMs have a higher prosthesis unit cost than TVPMs. The TVPM unit costs include the pacing device (\$3,948, Prostheses List group 08.04.03) and lead (\$831, Prostheses List group 08.08.09), whereas the LPM unit cost is \$ [REDACTED]. The pre-ESC response that the applicant clarified that LPM had three individual components (i.e., the LPM device, a single use delivery catheter, and a single-use introducer) which were all part of the Micra VR TPS system priced at \$ [REDACTED]. ESC noted that the aggregate national prostheses costs to health insurers are forecast to increase by \$ [REDACTED] in Year 1, rising to \$ [REDACTED] in Year 6. ESC also noted that increased uptake will increase these estimates (unlike the MBS costs).

ESC questioned whether there should be a ceiling on the maximum number of LPM devices per lifetime. There is evidence in animal models that up to three Micra LPM devices can be accommodated in the right ventricle at the same time. It is likely that in the future, the devices may be miniaturised further, thus a ceiling number of implantations may be reasonable through a CSANZ consensus document. ESC considered that the number of LPM devices should be consistent with CSANZ recommendations and the Department should consult with the CSANZ.

17. Applicant comments on MSAC's Public Summary Document

Medtronic is pleased that MSAC has supported MBS funding of single-chamber leadless pacemakers for the treatment of bradyarrhythmia for patients with a clinical need for leadless pacemakers due to the safety advantages compared with transvenous-pacemakers. This decision is likely to lead to improved clinical outcomes for a multitude of patients due to the elimination of pocket and lead related complications. We look forward to working with all stakeholders to further improve patient access to this innovative minimally invasive pacing therapy. Medtronic's first priority is for the safety of its patients.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)