MSAC Application 1717

Extravascular implantable cardioverter defibrillator (EV-ICD) therapy for patients at risk of ventricular arrhythmia

Ratified
PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for extravascular implantable cardioverter defibrillator therapy in patients at risk of ventricular arrhythmia

Component	Description
Population	Patients at risk of ventricular arrhythmia (VA) indicated for implantation of an implantable cardioverter defibrillator (ICD) *This population comprises the following subpopulations:* *a.* Patients who do not have an ICD or who require replacement of an implanted ICD and who are suitable for a transvenous ICD (TV-ICD) or an extravascular ICD (EV-ICD) *b.* Patients with or without an existing ICD, who are ineligible or unsuitable for a TV-ICD or who demonstrate a need for removal of a TV-ICD and replacement with an extravascular ICD (EV-ICD) ***Inclusions:*** *Patients with one of the following: history of haemodynamically significant VAs in the presence of structural heart disease; documented high-risk genetic cardiac disease; ischaemic heart disease with a left ventricular ejection fraction (LVEF) of less than 30% at least one month after experiencing a myocardial infarction (MI) and while on optimised medical therapy; chronic heart failure, classified as New York Heart Association (NYHA) class II or III, with a LVEF of less than 35% despite optimised medical therapy.* ***Exclusions:*** *Patients with a need for long-term bradycardia pacing or cardiac resynchronisation therapy.* ***Notes:*** *Patients not suitable for TV-ICD (part of subpopulation b) include those with structural abnormalities, difficult venous anatomy, high risk of infection (e.g. immunocompromised patients), or who are reluctant to attempt/re-attempt TV-ICD (e.g. younger patients, patients with comorbidities, patients who have undergone previous ICD explant).* *Patients may demonstrate a clinical need for TV-ICD removal (part of subpopulation b) due to the development of venous obstruction, TV lead failure, TV device/lead infection, or to avoid the need for chronic lead extraction.*
Intervention	EV-ICD therapy
Comparator/s	*For subpopulation a:* single chamber TV-ICD therapy *OR* *For subpopulation b:* best available care in the absence of ICD therapy

Component	Description
Outcomes	Technical performance • Lead electrical performance over time • Battery life Safety • Composite of all-cause ICD-related complications • Inappropriate shocks • Serious adverse events • Device-related complications (pocket or lead complications; e.g. lead failure, device/lead infection) • Procedure complications • Replacement procedures or conversion to TV-ICD where appropriate Clinical effectiveness • All-cause mortality • Mortality related to sudden cardiac death (SCD) • Appropriate shocks (to prevent SCD) • Quality of life Healthcare system • Procedure time • Implant success rate • Costs associated with the intervention and comparator, including cost of the procedure, consumables, device, tests, ongoing monitoring and any subsequent interventions required • Costs associated with adverse events for the intervention and comparator • Total Australian Government healthcare costs
Assessment questions	What is the safety, effectiveness and cost effectiveness of EV-ICD versus TV-ICD therapy in patients at risk of VA?

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of extravascular implantable cardioverter defibrillator (EV-ICD) therapy for patients at risk of ventricular arrhythmia (VA) was received from Medtronic Australasia Pty Ltd by the Department of Health.

Implantable cardioverter defibrillators (ICDs) are an established treatment for life-threatening VAs and the prevention of consequent sudden cardiac death (SCD) (Al-Khatib et al., 2018; Philippon et al., 2022; Priori et al., 2015). ICD systems are comprised of a defibrillator generator and one or more leads. Conventionally, a transvenous ICD (TV-ICD) system is used, for which one or more leads are inserted into the heart via the veins (transvenous leads). For the proposed intervention, a single lead is inserted into the substernal space where it is anchored to the fascia (Crozier et al., 2021), remaining outside of the heart and vascular system. This alternative, extravascular lead location is intended to reduce the short- and long-term morbidity associated with transvenous leads.

The applicant requests MBS listing for the insertion, replacement or removal of the extravascular lead component of the EV-ICD system. The applicant advises that existing MBS item 38472 is applicable for the

insertion, replacement or removal of the implantable defibrillator generator component of the EV-ICD system (Applicant, 2022b).

The applicant claims that (Applicant, 2022c):

- the EV-ICD system has noninferior effectiveness (overall survival/appropriate shocks) and noninferior safety (all-cause ICD-related complications/inappropriate shocks) compared to the TV-ICD system
- overall, the EV-ICD system results in noninferior health outcomes compared to the TV-ICD system.

[redacted]

PICO criteria

Population

Ventricular arrhythmias

VAs are abnormal or chaotic heartbeats that originate from ventricles. These types of arrhythmias cause the heart to beat irregularly and/or too fast, which prevents oxygen-rich blood from circulating to the brain and body, and may result in SCD if corrective measures are not taken rapidly (Al-Khatib et al., 2018; Applicant, 2022b).

The most common classifications of VAs are premature ventricular contraction (or premature ventricular complex [PVC]), ventricular tachycardia (VT) and ventricular fibrillation (VF) (Al-Khatib et al., 2018). PVCs are the least harmful subtype, except if there are frequent occurrences over longer periods. Sustained VTs are more likely to be harmful and are defined as VT lasting more than 30 seconds or if haemodynamic instability occurs in less than 30 seconds (Foth et al., 2022). In some cases, VT can progress to VF, a more dangerous condition, where blood cannot be pumped through the ventricles due to limited dilation and contraction of the ventricles (Koplan and Stevenson, 2009; Tung et al., 2010). This can cause the heart to stop beating and may lead to death (Koplan and Stevenson, 2009).

Clinical manifestations of VA range from a total lack of symptoms (especially for non-sustained and benign arrhythmias) to life-threatening sudden cardiac arrest (SCA) and/or SCD (Al-Khatib et al., 2018). The most common symptoms in adults are fatigue, palpitations, dyspnoea, chest pain, dizziness and syncope (Sirichand et al., 2017). Patients can feel either skipped or extra heart beats, or sustained palpitations (Noda et al., 2005; Viskin et al., 2005). This may only last a few seconds. Prolonged episodes can bring feared consequences, including SCD (Koplan and Stevenson, 2009; Tang et al., 2017).

In Australia, the incidence of SCD has been estimated at 70.7 per 100,000 person-years in people ≥35 years of age and 1.1–1.3 per 100,000 person-years in people aged 1–34 years (Bagnall et al., 2016; Feng et al., 2015). The majority of SCDs are attributed to VA; most commonly, to VT and VF (Bayés de Luna et al., 1989).

Who is at risk of ventricular arrhythmias and SCD?

The leading risk factor for developing VA is ischaemic heart disease, also known as coronary heart disease or coronary artery disease (CAD) (Borleffs et al., 2009; Khan et al., 2020). In individuals over 30 years of age, CAD is the main contributor to VT/SCD (Benito and Josephson, 2012). Among children and younger people, congenital heart defects such as congenital heart disease and congenital coronary anomalies are a more

prevalent cause of SCD (Gajewski and Saul, 2010). Other common causes of VA/SCD in younger patients include hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and myocarditis (Bagnall et al., 2016; Gajewski and Saul, 2010; Namboodiri and Francis, 2010).

Patients successfully resuscitated from SCA are at particular high risk of developing SCD, with a mortality rate of up to 45% at 2 years (Santini et al., 2007). Patients who have suffered a prior MI are also at a high risk of VA and arrhythmic mortality (Santini et al., 2007; Yalin et al., 2015). Approximately 10% of MI survivors remain at high risk of death following hospital discharge (mortality rate >25% at 2 years), with SCD secondary to sustained VT or VF accounting for approximately 50% of all deaths in these high-risk patients (Bhar-Amato et al., 2017). The most important independent predictive factor for SCD in patients with a prior MI is left ventricular dysfunction (Santini et al., 2007).

Patients with congestive heart failure can have sudden and unpredictable death from VA despite the use of optimised medical therapies (Bardy et al., 2005). In research studies and clinical practice, the NYHA functional classification has been broadly used to measure heart failure stages based on the severity of symptoms. Research has demonstrated a direct correlation between the risk of VA and NYHA classification; patients with a higher NYHA level may have an increased risk of mortality (Al-Khatib et al., 2018).

While patients with a reduced ejection fraction, a clinical history of heart failure or survivors from cardiac arrest may reflect the highest risk subgroup of patients, a number of SCD events occur in patients who do not have ischaemic cardiomyopathy and sometimes have no structural heart abnormalities (Santini et al., 2007). They include patients with genetically determined structural cardiomyopathies such as hypertrophic and dilated cardiomyopathy and ARVC, as well as patients with channelopathies, such as long QT syndrome, short QT syndrome and Brugada syndrome (Santini et al., 2007). In these patients, SCD often occurs at a young age (Santini et al., 2007).

Significant associations between a number of other conditions and an increased risk of VA have been reported, including cardiac sarcoidosis (Yodogawa et al., 2011), chronic kidney disease (Bonato and Canziani, 2017; Kreuz et al., 2011), systemic sclerosis (Sebestyén et al., 2020), left ventricular hypertrophy (Wolk, 2000) and diabetes (Agarwal and Singh, 2017). People with an electrolyte imbalance that can be due to dehydration, extreme exercise or dieting are also at risk of VAs (Laslett et al., 2020; Pourmoghaddas et al., 2012). Triggers such as electrolyte abnormalities, particularly hypokalaemia and hypomagnesaemia (Laslett et al., 2020; Pourmoghaddas et al., 2012), acute worsening of heart failure and medication-induced pro-arrhythmia (i.e. the aggravation of arrhythmias by anti-arrhythmic drugs) have been identified as potential triggers in some cases. Consequently, known risk factors can assist in distinguishing susceptible populations.

In most cases, no clear cause can be identified for the development of VA.

Prevalence and incidence

Great variability in the incidence of VA has been reported in various studies, based on the indications and in the populations assessed. An early study suggested an approximate 68% prevalence of VA in older patients with CAD worldwide (Aronow et al., 2002). A population-based study from the United States reported an incidence of idiopathic VA (i.e. VA in the absence of structural heart disease) of 51.86 per 100,000 (95% CI 47.72 to 56.01) (Sirichand et al., 2017). The author also noted that the incidence is on the rise and increases with age (Sirichand et al., 2017).

Current management

In the clinic setting, a cardiologist or cardiac specialist will assess each patient's need for an ICD, the necessary functions of the system (i.e. defibrillation, pacing, resynchronisation) and the risks involved (Applicant, 2022b).

Diagnosing the underlying heart disease

Tests prior to ICD implantation may include (but are not limited to) electrocardiogram (ECG), cardiac echocardiogram, cardiac catheterisation, cardiac magnetic resonance imaging (MRI) and/or cardiac biopsy (Applicant, 2022b). The applicant advises that these tests are the same prior to both the proposed intervention and the comparator (Applicant, 2022b).

In patients presenting with wide QRS complex tachycardia, 12-lead ECG is the most reliable means of differentiating VT from supraventricular tachycardia with aberration(Garner and Miller, 2013; Roberts-Thomson et al., 2011). Once a diagnosis of VT is made, the type of underlying heart disease informs the prognosis and management strategy. Typically, patients with structurally normal hearts have a benign prognosis and treatment will be aimed at reducing symptoms, while an ICD will be indicated for most patients with structural heart disease and sustained VT (Pedersen et al., 2014; Roberts-Thomson et al., 2011).

A transthoracic echocardiogram provides assessment of right and left ventricular structure and function, including LVEF (Roberts-Thomson et al., 2011). Cardiac MRI provides detailed structural and functional information and can confirm the presence or absence of myocardial scar or wall abnormalities when structural heart disease is suspected but cannot be definitively diagnosed with an echocardiogram (Pedersen et al., 2014; Roberts-Thomson et al., 2011). In patients with symptoms associated with exertion, suspected CAD or catecholaminergic polymorphic VT, exercise testing is useful to assess for exercise-induced VA (Al-Khatib et al., 2018). In patients who have recovered from unexplained SCA, coronary angiography is useful to confirm the presence or absence of CAD and guide decisions for myocardial revascularisation (Al-Khatib et al., 2018). Myocardial biopsy can assist in the diagnosis of ARVC or myocarditis (Priori et al., 2015; Roberts-Thomson et al., 2011).

Indications for the implantation of an ICD

An ICD may be indicated for secondary prevention in patients who have survived a prior SCA, sustained VT, or syncope caused by VA or for primary prevention in patients who are at increased risk for but have not yet had an episode of sustained VT, VF or SCA (Al-Khatib et al., 2018; Priori et al., 2015).

Australian heart failure guidelines outline the following indications for ICD implantation (Atherton et al., 2018):

- secondary prevention in patients following a resuscitated cardiac arrest, sustained VT in the presence of haemodynamic compromise, and VT associated with syncope and an LVEF <40%
- primary prevention measure in patients at least one month after MI and with an LVEF ≤30%
- primary prevention measure in patients with heart failure with reduced ejection fraction (HFrEF) associated with ischaemic heart disease and an LVEF ≤35%.

Genetic causes have been identified for several cardiac disorders that can cause VAs and SCD (John et al., 2012; Zodgekar et al., 2011). For patients with an inherited cardiac condition, secondary prevention ICD therapy is typically indicated (Al-Khatib et al., 2018; Epstein et al., 2008; Priori et al., 2015) In some conditions, a positive family history of SCD may be an indication for primary prevention implantation. For example, in hypertrophic cardiomyopathy an ICD may be recommended if any one major risk factor—previous cardiac arrest/VT, family history of premature SCD, left ventricular wall thickness ≥30mm, previous episodes of documented non-sustained ventricular tachycardia (NSVT) or unexplained syncope—is present (Cardiovascular Genetics Working Group, 2016). Further indications for primary prevention implantation are emerging. For example, in long QT syndrome there is an emerging indication for primary prevention ICD therapy for post pubertal women with long QT syndrome type 2 and a very long QT interval

(>0.55 seconds) (Waddell-Smith and Skinner, 2016). In dilated cardiomyopathy, there is an emerging indication for ICD therapy in patients with a disease-causing mutation of the Lamin A/C gene and clinical risk factors (Priori et al., 2015).

Follow-up

For patients with a cardiovascular implantable electronic device (CIED), periodic assessment of device function, retrieval of stored health and technical data, and adjustment of the device's programmed settings is essential (Leitch et al., 2022). According to the applicant, specialist follow-up with ECG is required every 6 months (Applicant, 2022b).

This frequency of follow-up is reflected in a recent Cardiac Society of Australia and New Zealand (CSANZ) position statement on the follow-up of CIEDs, which recommends scheduled in-person or remote transmission review checks at least every 6 months for ICDs, in addition to an in-person post-implant check at 2–12 weeks (Leitch et al., 2022). Additional checks may be needed in certain circumstances, such as pre- and post-MRI, over the period of radiation therapy, prior to a surgical procedure, when triggered by a home monitoring alert or in other specific circumstances (Leitch et al., 2022). Periodic in-person review of the underlying cardiac condition is also essential and may occur simultaneously with the scheduled device check or separately (Leitch et al., 2022). According to the position statement, ancillary tests such as a 12-lead ECG are only a required part of patient follow-up in certain circumstances, such as annually in paediatric patients (Leitch et al., 2022).

Proposed population for this PICO

The proposed population is patients at risk of VA who are indicated for ICD therapy for the primary or secondary prevention of VA and consequent SCD.

Specifically, patients who have one of the following are included in the proposed population (Applicant, 2022b):

- history of haemodynamically significant VAs in the presence of structural heart disease
- documented high-risk genetic cardiac disease
- ischaemic heart disease, with a left ventricular ejection fraction (LVEF) of less than 30% at least one month after experiencing a myocardial infarction (MI) and while on optimised medical therapy
- chronic heart failure, classified as New York Heart Association (NYHA) class II or III, with a LVEF of less than 35% (despite optimised medical therapy).

Patients within the overarching population may, according to the applicant, be classified into one of the following three groups (Applicant, 2022a):

a. Patients who do not have an ICD and who are suitable for a TV-ICD or an EV-ICD

b. Patients who do not have an ICD but who are not suitable for a TV-ICD

c. Patients with an existing TV-ICD who demonstrate a clinical need for removal of the TV-ICD and replacement with an EV-ICD or other extravascular device

Further detail on these three subpopulations is provided below.

Patients suitable for a TV-ICD or an EV-ICD

Theoretically, an EV-ICD could be considered for any patient who is suitable for a TV-ICD and does not require long-term bradycardia pacing or CRT. However, it remains unclear whether the proposed intervention is at least non-inferior to the TV-ICD in these patients and thereby whether implantation of an EV-ICD is justified. The assessment will assess whether EV-ICD is non-inferior to the TV-ICD in this subpopulation.

If the EV-ICD is listed, uptake of the device in this subpopulation would be driven by clinician and patient preference. The applicant estimated that, should the service be included on the MBS, as many as 20% of patients suitable for a TV-ICD may instead access the EV-ICD in the first year of listing, increasing to 30% in the third year (Applicant, 2022b).

Patients unsuitable for a TV-ICD

There are some patients who are in clinical need of an ICD but who are not candidates for a TV-ICD or for whom TV-ICD implantation is not ideal due to significant risk of ICD-related morbidity. According to the applicant, patients who are not suitable for TV-ICD include those who have a high risk of infection, venous occlusions, structural abnormalities or difficult venous anatomy (Applicant, 2022a; Applicant, 2022b). In addition, the applicant proposes that patients who are reluctant to attempt or reattempt ICD therapy with a transvenous system can be considered unsuitable for TV-ICD therapy (Applicant, 2022a). These include younger patients, patients with comorbidities, and patients who have undergone a previous ICD explant (Applicant, 2022a; Applicant, 2022b).

International literature defining patient selection for another extravascular ICD system—the subcutaneous ICD (S-ICD)—provides some detail on patients who may be unsuitable for a transvenous system or in whom an extravascular system may be preferred. According to international guidelines, the S-ICD may be a useful alternative when venous access is difficult, in patients at high risk for infection (e.g. patients with a prior device infection, end stage renal disease, diabetes mellitus or who are chronically immunosuppressed), after the removal of a transvenous ICD for infections, or in young patients with a long-term need for ICD therapy (Al-Khatib et al., 2018; Priori et al., 2015).

Transvenous lead placement may be made difficult or impossible due to congenital anomalies precluding venous access or acquired stenosis or obstruction of the central veins (Cappelli et al., 2014). For patients with a history of device infections, the risk of relapse is very high (Cappelli et al., 2014), therefore an extravascular system may be preferred. In younger patients with preserved venous access, an extravascular device may be preferred owing to the effect of growth on endocardial leads and the possibility of saving venous vasculature (Cappelli et al., 2014).

Lead failure, vascular problems and infection are more common in the paediatric population than in adults, likely due to their higher activity level, smaller body size, and growth (Priori et al., 2015). Lead failure is more often seen in patients who are younger, have better preserved left ventricular function and are female (Kleemann et al., 2007). A major cause of lead failure is insulation failure, the risk of which increases with time after implantation, and which is therefore more common in patients with longer life expectancy (Kleemann et al., 2007). Higher activity in younger patients and restricted anatomy in female patients may also increase the risk of insulation failure (Kleemann et al., 2007). In children, growth can cause complications such as infection and lead malfunction (Hata et al., 2017).

In patients with inherited cardiac diseases, the risk of inappropriate shocks and ICD-related complications such as lead failure and/or fracture has been found to increase concordantly with the number of device replacements (Olde Nordkamp et al., 2013). Patients with a high life expectancy may face multiple lead and device replacements and thus, a substantial risk of future ICD-related morbidity (Olde Nordkamp et al., 2013).

According to the applicant, unsuitability for TV-ICD (due to TV-ICD being not feasible or not ideal) is a rare occurrence and may affect between 5–8% of patients with an indication for ICD implantation (Applicant, 2022b; Applicant, 2022c).

Need for removal of a TV-ICD

According to the applicant, patients may demonstrate a need for removal of a TV-ICD and replacement with an extravascular system when any of the following apply: development of a venous obstruction, transvenous lead failure or transvenous device/lead infection (Applicant, 2022a). Furthermore, patients may demonstrate a clinical need to switch to an extravascular system to avoid the need for chronic lead extraction (Applicant, 2022a).

Transvenous lead extraction may be needed due to infection (e.g. isolated pocket infections, bacteraemia, or endocarditis), lead dysfunction, lead related complications (e.g. thromboembolic events, superior vena cava syndrome, arrhythmias or perforation), venous access issues (up to 25% of patients with transvenous leads develop some degree of stenosis), chronic pain, or for other reasons (Bongiorni et al., 2018).

Recently implanted leads may be explanted using simple traction techniques; however, leads that have been implanted for longer durations (i.e. chronically implanted leads) develop fibrous adhesions and require more complex extraction tools (Bongiorni et al., 2018; Mazzone et al., 2013) Lead removal may be defined as an extraction procedure when at least one of the leads being removed has been implanted for more than one year or if specialised equipment or removal via a route other than the implanted vein is required, regardless of implant time (Bongiorni et al., 2018).

Among 3,555 consecutive European patients who underwent transvenous lead extraction between 2012 and 2014, an in-hospital procedure-related major complication rate of 1.7% (95% confidence interval [CI]: 1.3 to 2.1) and a procedure-related mortality rate of 0.5% [95% CI: 0.3 to 0.8) (Bongiorni et al., 2017) were reported. Procedure-related complications and deaths were found to be more common in female patients and for leads that had been implanted for more than 10 years (Bongiorni et al., 2017)

Volume of ICD implantations in Australia

The incidence of ICD insertion in the Australian private sector can be estimated from historic Medicare statistics. The applicant reported that in 2021 there was a total of 1,962 claims for the MBS items associated with TV-ICD lead services (former items 38384 and 38390 and current item 38471) and 1,828 claims for the MBS items associated with TV-ICD generator implant/replacements/removals (former items 38387 and 38393 and current item 39472) (Applicant, 2022b). These figures were verified during drafting of the PICO confirmation (Australian Government Services Australia, 2022).

Trial populations

An important consideration is whether there is an evidence base to support the intervention for the intended population.

To date, data pertaining to the permanent implantation of EV-ICD are available from a single pilot study (Crozier et al., 2020), with data from a second study (a prospective, multicentre, single-arm, premarket clinical study) expected to be available later this year, according to the applicant (Applicant, 2022b). According to *ClinicalTrials.gov*, the primary completion date was 28 April 2022 and the estimated study completion date is 31 July 2023 (ClinicalTrials.gov, 2022). An additional study, the EV-ICD continued access study, is also listed on *ClinicalTrials.gov*. This trial is expected to begin in August 2022, with an estimated primary complete data of 28 July 2023 (ClinicalTrials.gov, 2021).

Earlier studies on the EV-ICD system were acute feasibility studies in which an investigational system was implanted to test the feasibility of defibrillation, sensing and/or pacing from the substernal position, then removed (Boersma et al., 2019; Chan et al., 2017; Sholevar et al., 2018).

The EV-ICD pilot study enrolled 26 patients with a class I or IIa indication for implantation of an ICD according to current international guidelines (Al-Khatib et al., 2018; Priori et al., 2015) and without an indication for

bradycardia pacing or cardiac resynchronisation (Crozier et al., 2020). Implantation was attempted in 21 patients between 22 and 77 years of age (Crozier et al., 2020).

Patients with a class I or IIa indication for implantation of an ICD who were at least 18 years of age and who did not have an indication for bradycardia pacing or cardiac resynchronisation were eligible for enrolment in the EV-ICD pivotal study (Crozier et al., 2021). According to *ClinicalTrials.gov,* 365 participants were enrolled (ClinicalTrials.gov, 2022).

The trial populations appear to be relatively consistent with the proposed population. Upon the trial completion and study publication, the EV-ICD pivotal study will be able to provide more information and clinical data for the EV-ICD system. Nevertheless, patients that may most benefit from an extravascular system may not be fully captured. The pivotal study was limited to patients at least 18 years of age, without an existing system, medical condition or abnormality which might increase procedure risk or infection risk.

Available data will remain limited to non-comparative data collected over a relatively short follow-up period (up to approximately 3.5 years, depending on the time of enrolment) (Crozier et al., 2021).

PASC noted that subpopulation a should correspondingly be defined as: patients who do not have an ICD or who require replacement of an implanted ICD and who are suitable for a TV-ICD or an EV-ICD. PASC noted that the application does not suggest a change to the current indication for ICD therapy given that it proposes to utilise the existing item number for generator insertion.

PASC noted that subpopulations b and c could be combined into a single subpopulation, defined as: patients who are ineligible or unsuitable for a TV-ICD or who demonstrate a need for removal of a TV-ICD and replacement with an extravascular system.

PASC noted that subpopulations b and c, combined, represent quite a small and heterogeneous population, thus getting evidence on this small group of patients will be challenging. It was also noted that the study cohort in the larger pivotal trial may include some patients from this subpopulation but data have not been published yet, and they may be considered as non-comparative data. PASC further noted that, if this application was to be approved, it would be unlikely to significantly increase the total number of ICD implants because only a small number of patients belong to the second subpopulation (i.e. patients currently ineligible or unsuitable for a TV-ICD), and the procedure is provided by accredited specialists. PASC considered that some of the second subpopulation may receive a S-ICD.

Intervention

The intervention for this application is EV-ICD therapy.

Overview

An ICD is a small, battery-powered device placed in the chest to detect and stop life-threatening VAs. A defibrillator generator is connected to one or more leads which relay information about the heart's activity back to the defibrillator and carry electrical impulses from the defibrillator to the heart. Over several decades, various ICD devices have been put forward with different implantation sites for both the leads and the defibrillator generator (Gebran and Refaat, 2021).

Despite the clinical efficacy of traditional transvenous ICD (TV-ICD) systems, they are associated with various lead-related complications, such as device/lead infection, lead dislodgement and venous obstruction (Baddour et al., 2012; Gebran and Refaat, 2021). The EV-ICD system, with its lead implanted in the substernal area, offers an alternative to the traditional transvenous system (Crozier et al., 2021).

Function

EV-ICDs can help manage life-threatening arrhythmias, especially those that can lead to SCA. If an abnormal heart rhythm is detected, the EV-ICD device will deliver an electric shock (defibrillation) to restore a normal heartbeat (Applicant, 2022b). In addition to defibrillation, the EV-ICD system can provide anti-tachycardia pacing (ATP), post-shock pacing and short-duration pause-prevention pacing (Thompson et al., 2022). These functions are described below. The EV-ICD system does not provide long-term bradycardia pacing (Applicant, 2022c).

- Defibrillation: an electric shock is delivered to restore normal heart rhythm in the event of life-threatening rapid VAs (VF/fast VT) (Stevenson and Voskoboinik, 2018).
- ATP: pacing faster than the arrhythmia, which can sometimes break the circuit and terminate the arrhythmia (Stevenson and Voskoboinik, 2018), avoiding the need for a defibrillation shock.
- Post-shock bradycardia pacing: provides haemodynamic support during bradycardia following a defibrillation shock (Thompson et al., 2022).
- Short-duration pause-prevention pacing: prevents morbidity and mortality associated asystole (Thompson et al., 2022).

The EV-ICD system also monitors the patient's heart rhythm to detect any disturbance. When a patient's heartbeat is abnormal, the EV-ICD records the electrical patterns of the heart to assist doctors with future management (Swerdlow et al., 2021).

CSANZ recommends a hybrid of in-person checks and remote monitoring for CIEDs (Leitch et al., 2022). Remote monitoring (i.e. ICD interrogations that occur outside of the physician's office) reduces the number of in-person checks and may be particularly beneficial in rural and regional communities and in elderly patients with mobility issues (Leitch et al., 2022). Both scheduled transmissions (i.e. interrogations at predetermined time intervals) and alert transmissions (i.e. in the case of abnormal lead parameters, arrhythmias, battery depletion) can be sent to the physician from a remote location; however, programming changes cannot be made remotely (Leitch et al., 2022). The EV-ICD does not currently have remote monitoring capabilities, however the applicant has advised that when the product is made available commercially, it will have remote monitoring capabilities (Applicant, 2022c).

Device features

The EV-ICD system is the product of a development program initiated by Medtronic in 2012 (Thompson et al., 2022; van Dijk and Boersma, 2021). The system comprises a defibrillator generator and an extravascular high voltage lead, as depicted in Figure 1.

Figure 1 EV-ICD defibrillator generator and quadripolar lead with passive fixation

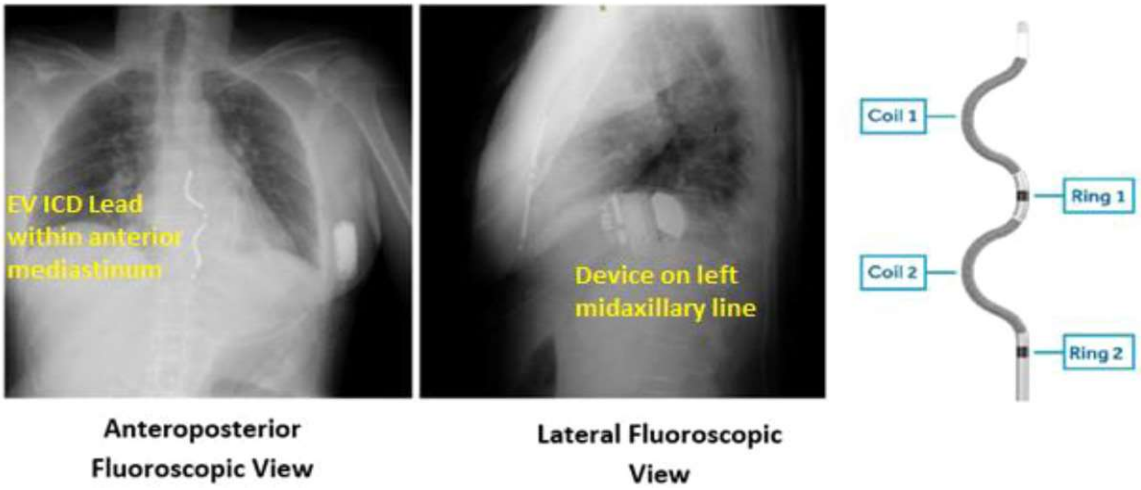
Abbreviations
EV-ICD = extravascular implantable cardioverter defibrillator
Source:
(Crozier et al., 2021)

The EV-ICD defibrillator generator is a small device (33 cm^3) about the size of a TV-ICD defibrillator and capable of delivering up to 40 J of defibrillation energy (Crozier et al., 2021). It is implanted in a pouch under the skin near the serratus anterior muscle in the left midaxillary line (Crozier et al., 2021). The applicant advises that the generator is similar in function and design to the TV-ICD generator such that the creation of a new MBS item for the insertion of the generator component of the EV-ICD is not necessary (Applicant, 2022b). There is a difference in implant location (further discussed in the Comparator(s) section); however, MBS item 38472 is applicable for the insertion, replacement or removal of an implantable defibrillator generator irrespective of the generator location.

The EV-ICD lead is positioned in the substernal space (i.e. between the sternum and the pericardium), remaining outside the heart and vasculature (Crozier et al., 2021). The lead is positioned just over the right ventricle, facilitating sensation, short-term pacing and defibrillation of the heart (van Dijk and Boersma, 2021). It has an epsilon shape allowing for passive fixation (Crozier et al., 2021). The lead is secured to the rectus fascia using an anchoring sleeve and sutures (Crozier et al., 2020; Thompson et al., 2022).

As shown in Figure 2, the EV lead comprises 2 sets of ring electrodes and 2 coil electrodes/segments. The ring electrodes are intentionally oriented towards the left lateral border of the sternum to optimise sensing and pacing, while the coils are positioned closer to the right side to facilitate defibrillation (Thompson et al., 2022). The 2 coil electrodes can be coupled to form an overall 8 cm defibrillation coil (Boersma et al., 2019). Three vectors are available for sensing and pacing: ring 1 to ring 2, ring 1 to coil 2, and coil 1 to coil 2. Among them, coil 1 to coil 2 is a high voltage vector while the others are low voltage (Boersma et al., 2019).

Figure 2 EV-ICD-defibrillator generator and lead positioning under fluoroscopy and EV-ICD distal lead construction



Abbreviations
EV-ICD = extravascular implantable cardioverter defibrillator
Source
(Thompson et al., 2022)

Implantation procedure

The surgical process of implanting an EV-ICD system involves multiple steps including introducer sheath and tunnelling tool placement, EV-ICD lead insertion, acute sensing assessment and device placement. General anaesthesia is recommended, and access to external defibrillation pads is required in case there is a need for rescue defibrillation (Crozier et al., 2021). Authors of the EV-ICD pivotal study provide the following description of the implantation procedure (Crozier et al., 2021):

'To access the substernal space, an incision (approximately 3 cm) will be made between the inferior point of the xiphoid and the left costal margin. Blunt dissection is then performed beyond the rectus fascia and through the diaphragmatic attachments. The dedicated implant tunnelling tool will be placed within a peel-

away introducer heath and then be introduced and advanced utilizing lateral fluoroscopy to ensure the tip of the tunnelling tool is in close proximity to, or direct contact with, the posterior surface of the sternum to avoid cardiac injury…The EV ICD lead will be inserted into the substernal space via the peel-away introducer sheath once the tunnelling tool is removed. After deployment of the lead, acute sensing measurements will be collected… The lead will then be anchored to the fascia in the subxiphoid incision. The proximal portion of the lead will be tunnelled to a left lateral subcutaneous device pocket near the midaxillary line.'

The applicant advised that the sternal tunnelling tool (Medtronic Epsila EV Model EAZ101) can deliver the introducer and lead into the anterior mediastinum, while a transverse tunnelling tool (Medtronic Epsila Model EAZ201) is required to connect the proximal lead to the device pocket (Applicant, 2022b). Both are single-use consumables (Applicant, 2022b).

In the EV-ICD pilot study, the median total time for substernal lead placement (time from first incision until final lead placement) across the 21 patients undergoing attempted implantation was 25 minutes (interquartile range [IQR]: 21 to 35 minutes) (Crozier et al., 2020). Median total procedure time (time from first incision until final suture) was 85 minutes (IQR: 78 to 104 minutes) and median fluoroscopy time was 4.2 minutes (Crozier et al., 2020).

Training and accreditation

According to the applicant, insertion, removal or replacement of the EV-ICD leads will be performed by a cardiothoracic surgeon or an electrophysiology cardiologist (Applicant, 2022b). According to the applicant, cardiothoracic surgeons must have completed the Cardiothoracic Surgery Program and be eligible to be a Fellow of the Royal Australasian College of Surgeons or otherwise qualified to practice cardiothoracic surgery in Australia while electrophysiology cardiologists must have completed the Advanced Training Curriculum in Cardiology and be eligible to be a Fellow of the Royal Australasian College of Physicians or otherwise qualified to practice interventional cardiology in Australia (Applicant, 2022b).

In addition, implanting physicians require theoretical and practical training in EV-ICD implantation and therapy to establish skills in safe access and tunnelling within the substernal space (Applicant, 2022b; Crozier et al., 2021; van Dijk and Boersma, 2021). The applicant (Medtronic Australasia Pty Ltd) advises that they intend to provide this training (Applicant, 2022b).

Details pertaining to the medical device

The proposed health technology involves the implantation of a medical device. The medical device associated with the intervention is not yet listed on either the ARTG or the Prosthesis List. Currently, there is only a first generation of the device available (Applicant, 2022c).

PASC agreed that the intervention is EV-ICD. PASC noted that the intervention has many similarities to the comparator with the fundamental difference being the location of the ICD lead which is placed in a substernal location, making the procedure for lead placement significantly more complex than for TV-ICD lead placement.

[redacted]

The Applicant noted that the first generation EV-ICD system is expected to have remote monitoring capability facilitated by a home monitor.

PASC noted the Department's advice that this is an in-hospital service only and no current hospital access is available for this service.

PASC noted the Department's advice that this service is unlikely to be provided at rural sites and will be provided at major city and regional sites similar to TV-ICD.

PASC noted that some clinical questions about the intervention that remain to be resolved are:

- *What is the likelihood that patients with EV-ICD will require change to TV-ICD or cardiac resynchronisation therapy (CRT)?*
- *Whether additional tools would be required as part of the overall service package (for example tunnelling tools) and whether these would be included in the costs (of the EV-ICD device) or would there be additional costs for the patient?*
- *Whether the anaesthesia time required for the service will be equivalent to that required for TV-ICD for insertion, replacement and removal?*
- *Whether additional services will be required at implant or replacement (e.g. division of adhesions)?*
- *What are the appropriate credentialling guidelines for practitioners undertaking this procedure and whether this would differ for cardiothoracic surgeons vs electrophysiologists?*
- *Whether the lead and generator can be implanted purely for anti-tachycardia pacing?*
- *Whether the lead and generator can be inserted solely for post-shock pacing or short-duration pause-prevention pacing?*
- *Whether the proposed services require imaging for positioning and safety reasons and if so, which modality would be used?*

Comparator(s)

The applicant has nominated TV-ICD therapy as the comparator, noting single-chamber TV-ICD is the main comparator (Applicant, 2022a; Applicant, 2022b). Other extravascular ICD devices, notably the S-ICD, were not included in the nominated comparator.

There are existing MBS items for TV-ICD therapy. MBS item 38471 (formerly MBS items 38384 and 38390) is associated with TV-ICD lead insertion, while MBS item 38472 (formerly MBS items 38387 and 38393) is associated with TV-ICD generator insertion, removal or replacement (Applicant, 2022b; Australian Government Department of Health, 2022a).

The nominated comparator is the relevant comparator for subpopulation a. For subpopulations b and c, best available care in the absence of ICD therapy is a more appropriate comparator. An overview of each is provided below.

TV-ICDs

For several decades, patients at risk of VA have been managed through TV-ICD therapy (Al-Khatib et al., 2018; Priori et al., 2015).

Conventional single-chamber TV-ICDs comprise a generator and a transvenous lead inserted into the right ventricle of the heart. Additional leads may be inserted into the right atrium (for dual-chamber ICD) or into the left ventricle (for CRT). In the majority of cases, the generator is placed in a pocket in the pectoral region below the left clavicle (Marquie et al., 2007).

Insertion of the TV-ICD is clinically similar to the insertion of an EV-ICD; however, the TV-ICD leads need to be inserted into the vasculature of the heart. One or two leads are implanted and attached to the heart tissue, depending on the types of ICD being used (i.e. single- or dual-chamber). The other ends of the leads are connected to the generator, which is positioned in a small pocket located between the skin and the chest

muscle (Kobe et al., 2017). The procedure usually takes about an hour (Lenarczyk et al., 2018). Either general anaesthesia or local anaesthesia and sedation are carried out based on local guidelines (Marquie et al., 2007).

The comparator and the proposed intervention have similar functions in that they can provide defibrillation, ATP and post-shock pacing; however, the TV-ICD can provide chronic pacing therapy (Thompson et al., 2022) A comparison between the proposed intervention and a single-chamber TV-ICD device is provided below (Table 2).

Table 2 Comparison between the proposed intervention and the TV-ICD system

	Extravascular ICD	**Transvenous ICD †**
Lead location	Anterior mediastinum (substernal)	Endovascular/endocardial
Generator location	Left midaxillary region	Pectoral
Potential for cardiac injury/perforation during implantation	Yes	Yes
Maximum delivered energy (J)	40	40
Anti-tachycardia pacing	Yes	Yes
Chronic pacing therapy	Available as short-duration pause-prevention pacing therapy	Available as chronic pacing therapy
Post-shock pacing	Yes	Yes
Generator volume (cm^3)	33	33
Generator mass (g)	77	79

Abbreviations
ICD = implantable cardioverter defibrillator
Notes
† = Comparison made with Cobalt™ XT single chamber ICD (Medtronic plc)
Source
Adapted from Table 1 in Thompson et al. (2022)

Lead-associated problems persist after the implantation and may require lead replacement or extraction (Brunner et al., 2014; Kleemann et al., 2007). While ICD generators can be explanted, TV-ICD leads are not easy to remove because extensive scarring and fibrosis occurs around the lead in the blood vessels and the heart (Maisel, 2007). Significant in-hospital mortality has been reported related to vascular complications during lead extractions (Brunner et al., 2014). Nevertheless, fibrosis can also occur around extravascular leads. For example, fibrotic adhesions around the parasternal coil of S-ICD leads have been reported (Behar et al., 2020).

Best available care in the absence of ICD therapy

There is a small group of patients who may benefit from an ICD but for whom TV-ICD implantation is not feasible or not ideal (i.e. subpopulations b and c). For these patients, the comparator would be best available care in the absence of ICD therapy. The effectiveness of the EV-ICD system could be compared to natural disease history/risk of SCD in the absence of ICD therapy (Applicant, 2022c).

Best available care in the absence of ICD therapy may include therapies to prevent arrhythmia occurrence or recurrence (anti-arrhythmic drugs; catheter ablation) as well as therapies to treat the underlying heart disease and comorbidities (e.g. heart failure medications). It is important to note that these therapies, which may also be provided alongside ICD therapy, are intended to reduce the occurrence of arrhythmias rather than treat life-threatening arrhythmias as they occur (as per the ICD).

Anti-arrhythmic medications are often categorized by the Vaughan Williams 4-level schema and include fast sodium channel blockers (class I), beta blockers (class II), repolarisation potassium current blockers (class III) and non-dihydropyridines calcium channel blockers (class IV) (Al-Khatib et al., 2018). Except for beta

blockers, there is no randomised controlled trial (RCT) evidence that the use of anti-arrhythmic medications in the management of VA improves survival (Al-Khatib et al., 2018; Priori et al., 2015). Generally, anti-arrhythmic medications are not an alternative to ICD therapy but may be used as an adjunctive therapy in arrhythmia-prone patients to reduce the morbidity associated with ICD shocks (Larson et al., 2022; Priori et al., 2015).

Catheter ablation has evolved into an important treatment option for patients with scar-related heart disease who present with VT or VF (Priori et al., 2015). Catheter ablation may be used as an alternative or adjunct to anti-arrhythmic medications (Pedersen et al., 2014), and may lower the risk of VT recurrence, ICD shocks and hospitalisations in comparison to medical therapy (Ravi et al., 2022).

A fundamental aspect of VA management and the prevention of SCD is the effective management of the underlying heart disease and comorbidities (Priori et al., 2015). For example, for patients with heart failure and reduced left ventricular function, appropriate medical therapy (e.g. beta-blockers, angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists) is important to reduce the risk of SCD (Al-Khatib et al., 2018).

Rationale

Single- versus dual-chamber TV-ICD devices

Single-chamber TV-ICD is the most relevant comparator; however it has not been specified within the comparator definition.

According to Australian heart failure guidelines (Atherton et al., 2018):

'Generally single-chamber ICDs are recommended with an atrial lead included only if there is a separate bradycardia indication because dual chamber devices are associated with a higher rate of complications, device replacement and expense.'

Nevertheless, there is no clear consensus regarding the use of a single or dual chamber device in patients without an indication for bradycardia pacing. Whilst a single chamber device may be chosen to reduce complication risk, a dual chamber device may be preferred for other reasons (presumed better discrimination between supraventricular arrhythmias and VAs; to prevent another procedure to place an atrial lead should a bradycardia pacing indication develop) (Zeitler et al., 2018) One meta-analysis of RCTs found no significant difference in outcomes between single and dual chamber devices when there is no indication for bradycardia pacing (Zeitler et al., 2018).

PASC noted that the comparators for subpopulation a is the single chamber TV-ICD; a technology which has been established for more than 30 years.

Other extravascular ICD devices

Similar to the proposed intervention, the S-ICD system is designed to provide defibrillation therapy without entry into the vasculature of the heart (Thompson et al., 2022). Similar to the EV-ICD, the generator is implanted in the left midaxillary region, while the lead is tunnelled subcutaneously in the parasternal region (Philippon et al., 2022; Thompson et al., 2022). The extrathoracic lead location does not allow for ATP and, moreover, requires higher energy defibrillation (up to 80 J) and a larger generator (Thompson et al., 2022).

International guidelines recommend that the S-ICD can be considered a useful alternative to the TV-ICD for patients in whom ATP, bradycardia pacing or pacing as part of CRT is neither needed nor anticipated, particularly when venous access is difficult, in patients at high risk for infection, after the removal of a transvenous ICD for infections, or in young patients with a long-term need for ICD therapy (Al-Khatib et al., 2018; Priori et al., 2015).

Australian heart failure guidelines note that S-ICDs may be considered in younger people for primary prevention (Atherton et al., 2018). CSANZ position statements/guideline updates for ARVC, familial long QT syndrome and people with Fontan circulation suggest that S-ICDs may have important advantages given the high morbidity associated with ICD placement in young cohorts, but they identify some drawbacks, notably a significant inappropriate shock rate, shorter battery longevity, lack of ATP pacing that may terminate VT painlessly, and lack of potential to discriminate atrial tachycardia from VT (Hamilton-Craig et al., 2020; Waddell-Smith and Skinner, 2016; Zentner et al., 2020).

The S-ICD generator is listed on the ARTG and Prosthesis Lists (ARTG entry: 286705; Prosthesis List Billing code BS329); however, the lead is listed on the ARTG but not the Prosthesis List (ARTG entry: 291908) (Australian Government Department of Health - Therapeutic Goods Administration, 2022; Australian Government Department of Health, 2022b).

MSAC has considered applications requesting listing of the S-ICD lead (electrode) on 2 occasions (MSAC Applications 1374 and 1374.1) (Australian Government Medical Services Advisory Committee, 2014; Australian Government Medical Services Advisory Committee, 2021). In the initial instance, MSAC did not support public funding because of uncertain comparative long-term safety, clinical effectiveness and thereby cost effectiveness (Australian Government Medical Services Advisory Committee, 2014). On resubmission, MSAC deferred its advice on the creation of a new MBS item (Australian Government Medical Services Advisory Committee, 2021):

'MSAC considered the evidence demonstrated that S-ICD therapy had a different safety profile to the comparator transvenous ICD (TV-ICD) therapy. MSAC was inclined to accept that S-ICD had similar clinical effectiveness, but noted longer-term data remains lacking. MSAC anticipated there may be a subpopulation of patients with a high clinical need who would benefit from the device – however, considered that this subpopulation needs to be clearly defined in an MBS descriptor and that data for effectiveness in this subpopulation were lacking.'

PASC raised the issue that the comparator for subpopulations b and c (now combined) could be either best available care in the absence of ICD therapy or possibly the S-ICD.

The Applicant argued that the comparator for subpopulations b and c (now combined) should be best available care in the absence of ICD therapy given the S-ICD has different functionality compared with the EV-ICD (i.e. the EV-ICD provides ATP, which the S-ICD does not) and it is not within the MBS system (MSAC deferred the advice on creating a new MBS item for insertion of a subcutaneous lead for the S-ICD therapy because there was not enough evidence to be certain that the S-ICD is at least as clinically effective as a TV-ICD and the economic impact was also uncertain. More data have been required for potential future decisions).

PASC noted that the S-ICD is currently performed in a large portion of patients who are not suitable for a TV-ICD, either in the public hospital system, or in the private hospital system, despite a lack of MBS funding. Currently, the lead component of the S-ICD is not listed on the Prosthesis List.

PASC requested further justifications from the Applicant before deciding whether it was reasonable to exclude the S-ICD as a comparator.

Outcomes

Technical performance

Technical performance outcomes include:

- lead electrical performance over time
- battery life.

Patient-relevant outcomes

Safety outcomes include:

- composite of all-cause ICD-related complications and inappropriate shocks
- inappropriate shocks
- serious adverse events
- device-related complications (pocket or lead complications; e.g. lead failure, device/lead infection)
- procedure complications
- replacement procedures or conversion to TV-ICD if appropriate.

Primary effectiveness outcomes include:

- all-cause mortality
- mortality related to SCD
- appropriate shocks (to prevent SCD)
- quality of life.

Healthcare system outcomes

Healthcare system outcomes include:

- procedure time
- implant success rate
- costs associated with the intervention and comparator, including cost of the procedure, anaesthesia time, consumables, device, tests, ongoing monitoring, and of any subsequent interventions required (i.e. lead or generator replacement or removal)
- costs associated with adverse events for the intervention and comparator
- total Australian Government healthcare costs.

Rationale

The outcomes listed above largely reflect those nominated by the applicant (Applicant, 2022b); however, regarding effectiveness outcomes, mortality related to SCD was added, and procedure time was redefined as a healthcare system outcome. The list of cost items to be considered was expanded to capture the cost of any subsequent interventions and of any adverse events. Implant success rate and technical performance outcomes such as device longevity were also added.

Mortality related to SCD has been added as a disease-specific outcome, in conjunction with all-cause mortality.

The costs of any subsequent interventions and of any adverse events are important components, which could differ between the intervention and comparator. Complications of the intervention and comparator including pain, inappropriate shocks, lead failure and infection may require lead or generator replacement, lead reintervention and/or other treatment strategies (e.g. antibiotics to treat an infection). Furthermore, generator replacement would be required upon battery depletion.

Outcome measures reported in the EV-ICD trials

To date, data pertaining to the permanent implantation of EV-ICD is available from a single pilot study (Crozier et al., 2020), with data from a second study (the EV-ICD pivotal study) expected to be available later this year, according to the applicant (Applicant, 2022b). Both the pilot and pivotal studies were single arm studies; therefore, all available data on the intervention will be non-comparative.

Primary safety endpoints have been freedom from major complications related to the EV-ICD system or procedure at 90 days (Crozier et al., 2020), and up to 6-month post implant (Crozier et al., 2021). In both studies, the primary efficacy endpoint has been defibrillation success at implant (i.e. the device's ability to detect and convert induced episodes of VF, polymorphic VT and/or rapid VT) (Crozier et al., 2020; Crozier et al., 2021). While defibrillation success at implant demonstrates feasibility of the system, it is not a primary effectiveness outcome.

In the premarket clinical study, secondary objectives include characterisation of appropriate and inappropriate shocks; electrical performance (pacing capture thresholds, pacing impedance, sensing amplitudes) over time; extra-cardiac pacing sensation; asystole pacing; ATP performance with spontaneous arrhythmias; and a summary of adverse events (Crozier et al., 2021).

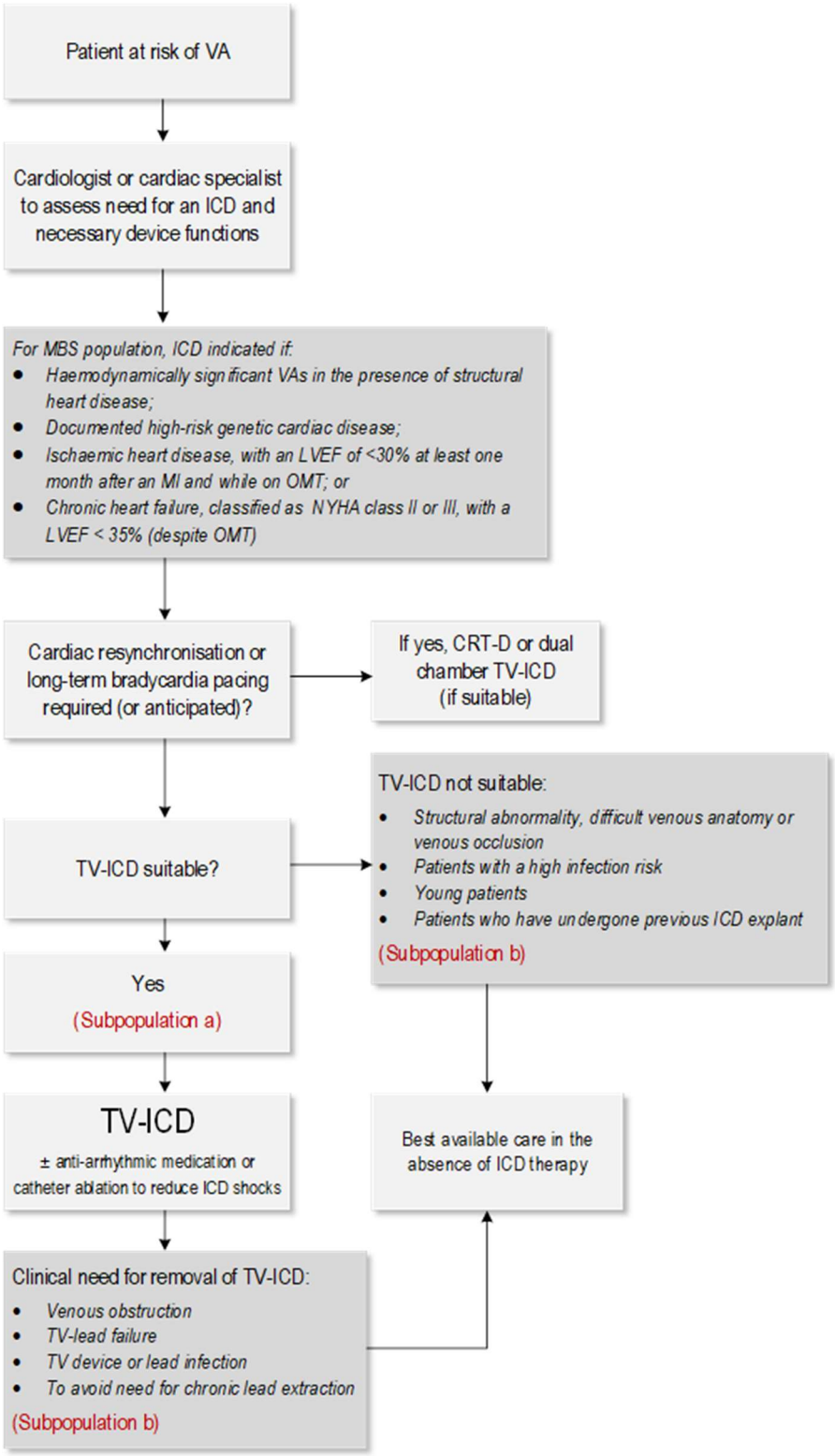
PASC accepted the applicant's suggestion that the outcome 'pacing performance over time' should be changed to 'lead electrical performance over time'. PASC further accepted the applicant's suggestion that the outcome 'cardiovascular-related mortality' should be changed to 'mortality related to SCD'. These outcomes are being collected in the ongoing trial.

PASC agreed with the remaining outcome measures.

Clinical management algorithms

Below are the current (Figure 3) and proposed (Figure 4) clinical management pathways for patients at risk of VA.

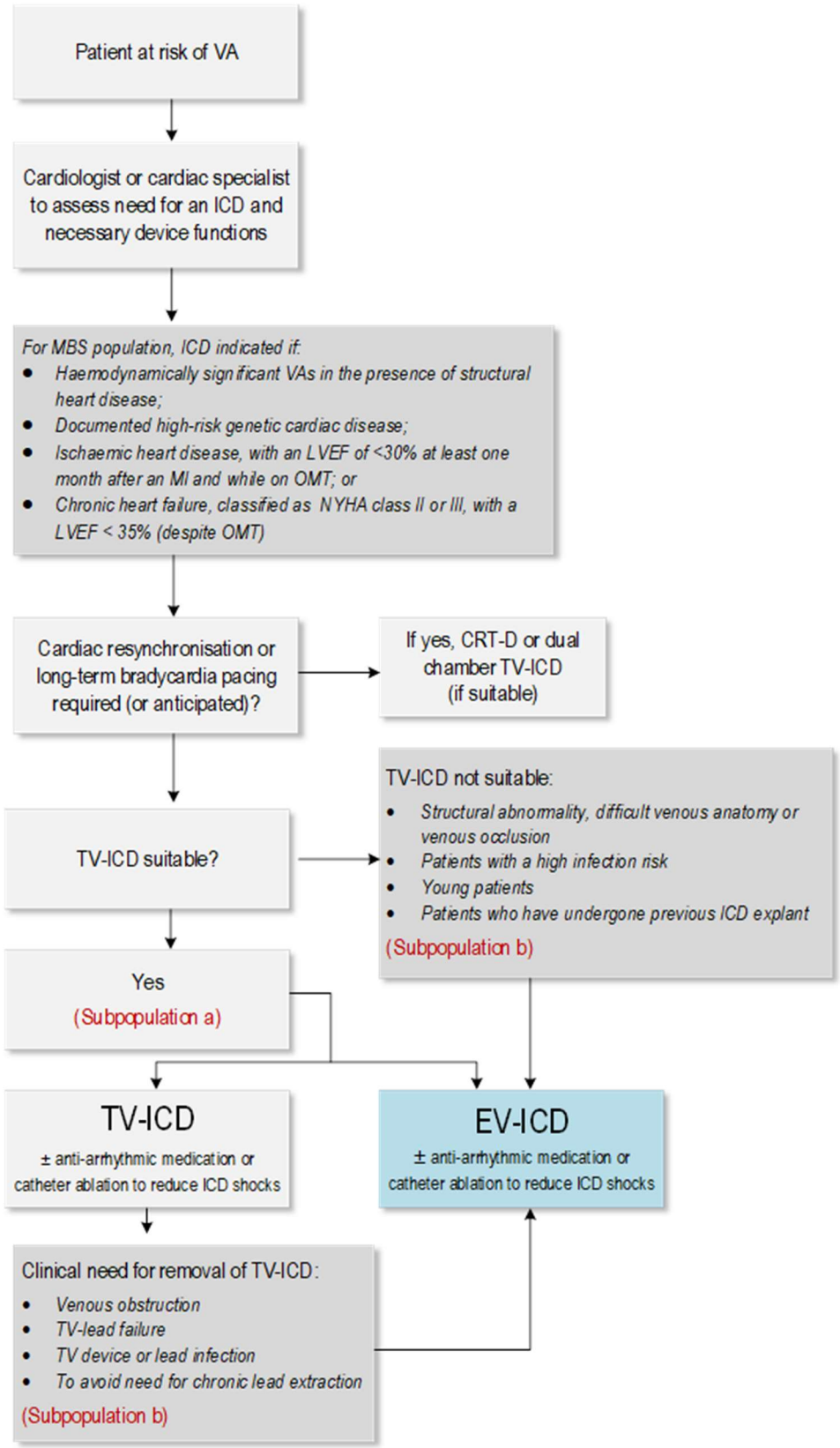
Figure 3 Current clinical management algorithm for patients at risk of VA



Abbreviations

CRT-D = cardiac resynchronisation therapy defibrillator, **ICD** = implantable cardioverter defibrillator, LVEF = left-ventricular ejection fraction; MBS = Medicare Benefits Schedule; MI = myocardial infarction; NYHA = New York Heart Association; OMT = optimal medical therapy; TV-ICD = transvenous implantable cardioverter defibrillator; **VA** = ventricular arrhythmia

Figure 4 Proposed clinical management algorithm for patients at risk of VA



Abbreviations

CRT-D = cardiac resynchronisation therapy defibrillator, **EV-ICD** = extravascular implantable cardioverter defibrillator, **ICD** = implantable cardioverter defibrillator, LVEF = left-ventricular ejection fraction; MBS = Medicare Benefits Schedule; MI = myocardial infarction; NYHA = New York Heart Association; OMT = optimal medical therapy; TV-ICD = transvenous implantable cardioverter defibrillator; **VA** = ventricular arrhythmia

Anti-arrhythmic medications, cardiac ablative surgery and/or ICD therapy are used to mitigate the risk of SCD in patients at risk of VAs.

In some patients, medication and/or cardiac ablative surgery may be sufficient (e.g. patients with symptomatic PVCs and structural heart disease; patients with NSVT in the absence of structural heart disease; patients with idiopathic VT) (Pedersen et al., 2014). Others will be indicated for ICD implantation to treat life-threatening VAs as they occur (e.g. patients with structural heart disease and sustained VT; patients with sustained polymorphic VT in the absence of a completely reversible cause) (Pedersen et al., 2014).

ICDs are implanted to mitigate against the risk of SCD by terminating episodes of VA; however, they cannot reduce the rate of arrhythmia recurrences (Chik and Marchlinski, 2015); therefore anti-arrhythmic medication and/or catheter ablation may also be required to reduce appropriate ICD shocks.

Patients with a separate indication for long-term bradycardia pacing or CRT are not suitable for the proposed intervention.

As noted by the applicant, there are currently some patients who are unsuitable for TV-ICD (part of subpopulation b). Under the current management algorithm, these patients would receive no ICD therapy (note the S-ICD is not relevant to this application). Furthermore, some patients who have a TV-ICD may demonstrate a clinical need for TV lead removal (part of subpopulation b). Again, there is currently no MBS-subsidised extravascular system for these patients. As shown in the proposed management algorithm (Figure 4), the proposed intervention provides a device-based management option for these patients (i.e. for subpopulations b and c) in addition to best available care.

PASC agreed with most of the current and proposed clinical management algorithms. In the current algorithm, PASC noted that, if the TV-ICD is not suitable, then the patient would receive best available care in the absence of ICD therapy, or potentially, the S-ICD could be considered.

Proposed economic evaluation

Based on the applicant's clinical claim of noninferior safety and effectiveness, and considering the matrix in Table 3, it is likely that a cost-minimisation analysis (CMA) will be required.

Table 3 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Noninferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

Abbreviations
CEA = cost-effectiveness analysis, **CMA** = cost-minimisation analysis, **CUA** = cost-utility analysis
Notes
? = Reflects uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
a = 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
b = An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

PASC agreed that it is reasonable to present a single clinical claim of non-inferiority for the overarching population, even if for subpopulations b and c (now combined), a superiority claim could be suggested. PASC noted that the amount of available comparative data is limited, making any kind of subgroup analysis challenging.

No changes to the proposal for a cost-minimisation analysis were noted by PASC.

Proposal for public funding

The applicant proposes the creation of 2 new MBS items for the insertion of, and the removal or replacement of, the EV lead component for the EV-ICD system (Applicant, 2022a). The applicant notes that existing MBS item 38472 (Insertion, replacement or removal of implantable defibrillator generator, if the patient …) is applicable for the insertion, removal or replacement of the generator used for the EV-ICD system (Applicant, 2022b).

Separate items are proposed for the insertion of an EV lead and the removal or replacement of an EV lead given differences in the complexity, and thereby proposed fee, of the procedures. Initial insertion of an EV lead (for ICD-naïve patients or following the removal of a TV lead) requires a complex substernal tunnelling procedure which, according to the applicant, increases procedure time and requires advanced specialist training (Applicant, 2022a). This tunnelling procedure is not required when the extravascular leads are removed or replaced (Applicant, 2022a).

The MBS items proposed by the applicant are shown below. Amendments made by the assessment group are shown in red.

PASC suggested that MBS item 38467, which is for the insertion, removal or replacement of myocardial electrode and (access items) 18260, 38418, 38448, 38456, should be restricted from co-claiming with this proposed service.

PASC agreed that the revised MBS item descriptors are clear. PASC agreed to change the terminology from " (per applicant proposal) to "substernal" to avoid confusion with other extravascular systems, such as the S-ICD system.

Category 3 – Therapeutic Procedures – Surgical Operations
MBS item *XXXX SUBSTERNAL ~~EXTRAVASCULAR~~ DEFIBRILLATOR LEAD (WITH CAPACITY FOR PACING), insertion of, if the patient has one of the following: (a) a history of haemodynamically significant ventricular arrhythmias in the presence of structural heart disease; (b) documented high-risk genetic cardiac disease; (c) ischaemic heart disease, with a left ventricular ejection fraction of less than 30% at least one month after experiencing a myocardial infarction and while on optimised medical therapy; (d) chronic heart failure, classified as New York Heart Association class II or III, with a left ventricular ejection fraction of less than 35% (despite optimised medical therapy); other than a service to which item 38212, 38350, 38353 or 38467 applies (H) Multiple Operation Rule (Anaes.) (Assist.)
Fee: $1,095.30 Benefit: 75% = $821.50 **Note**: this item will apply when a transvenous lead is replaced with an extravascular lead

Note: this item will apply when a transvenous lead is replaced with an extravascular lead

Category 3 – Therapeutic Procedures – Surgical Operations
MBS item *XXXX SUBSTERNAL~~EXTRAVASCULAR~~ DEFIBRILLATOR LEAD (WITH CAPACITY FOR PACING), removal or replacement of Note: For extravascular lead replacement procedures, this MBS item will be claimed only once during a single procedure to remove and replace an extravascular lead. other than a service to which item 38212, 38350, 38353 or 38467 applies (H) Multiple Operation Rule (Anaes.) (Assist.)
Fee: $664.55 Benefit: 75% = $498.45

Note: This item will apply when an extravascular lead is replaced with an extravascular lead.

The eligible population for the proposed service comprises patients with one of the following:

a) a history of haemodynamically significant ventricular arrhythmias in the presence of structural heart disease
b) documented high-risk genetic cardiac disease
c) ischaemic heart disease, with a LVEF of less than 30% at least one month after experiencing an MI and while on optimised medical therapy
d) chronic heart failure, classified as NYHA class II or III, with a LVEF of less than 35% (despite optimised medical therapy).

These criteria mirror those defined in the descriptors for existing MBS items 38471 and 38472, which currently apply for the comparator, TV-ICD, and reflect the terminology recommended by the Cardiac Services Clinical Committee as part of the MBS review (Cardiac Services Clinical Committee, 2018). For most patients currently eligible to receive MBS-subsidised TV-ICD, the proposed technology provides an alternative treatment option to the TV-CD.

In addition, the proposed technology provides an additional treatment option for a small group of patients indicated for ICD therapy but in whom transvenous lead insertion is either not feasible or not ideal. Listing of the proposed service could thus expand the size of the MBS-subsidised ICD population.

Proposed fee

The applicant has proposed a fee of $1,095.30 for the insertion of an EV lead. This fee is informed by the fee for existing MBS item 38471 (Insertion of implantable defibrillator, including insertion of patches for the insertion of one or more transvenous endocardial leads …). The applicant notes that while there are some differences between TV and EV lead placement, they expect resource use and procedure times to be similar, justifying a similar MBS fee.

PASC noted that, compared with implantation of a transvenous lead, implantation of a substernal lead would probably be more expensive, due to the procedure being more complex and taking longer to complete. It was questioned whether a higher MBS fee was required for implantation of the substernal lead.

PASC noted that if the existing transvenous lead is still functional, transitioning from a TV-ICD to an EV-ICD and implanting a new EV-ICD lead will be an additional cost, compared to those who choose to continue their TV-ICD. In such cases, the abandoned functional transvenous lead could be either abandoned (i.e. left in situ) or extracted to reduce the intravascular lead burden/avoid future issues {Bongiorni, 2018 #102;Sidhu, 2018 #107}.

The applicant has proposed a fee of $664.55 for the removal or replacement of an EV lead, which requires fewer resources (shorter procedure/trained specialist time) than the insertion procedure. This fee is informed by the fee for existing MBS item 38350 (SINGLE CHAMBER PERMANENT TRANSVENOUS ELECTRODE, insertion, removal or replacement of …).

Service provision

EV-ICD procedure is an in-hospital service that may be provided in either an inpatient public or inpatient private hospital setting. According to the EV-ICD pivotal study protocol: *'implants will be performed by a trained investigator with cardiothoracic surgical backup available, and general anaesthesia is recommended for the procedure'* (Crozier et al., 2021).

The applicant proposes that MBS funding will only be available for cardiothoracic surgeons or electrophysiology cardiologists (Applicant, 2022b). Implanting physicians require additional theoretical and practical training in EV-ICD implantation and therapy to establish skills in safe access and tunnelling within the substernal space (Applicant, 2022b; Crozier et al., 2021; van Dijk and Boersma, 2021).

The applicant advises that the insertion of an extravascular lead will, in the majority of cases, be delivered only once in a lifetime, noting a new generator can be connected to an existing EV lead (Applicant, 2022b). Some patients may require removal or replacement of the EV-ICD lead, and possible conversion to a TV-ICD system.

The choice between the intervention and comparator may impact the number of replacement procedures for the defibrillator generator (MBS item 38472) required. For example, the battery life of the EV-ICD system may differ to that of the comparator, impacting the number of generator replacements due to battery depletion. The frequency of pocket-related complications requiring generator replacement or removal may also differ. Differences in the frequency of generator replacements/removals should be considered.

PASC noted leakage was unlikely to be an issue.

PASC noted that a remaining question to be resolved was whether electrophysiologists should be credentialled with the Cardiac Society of Australia and New Zealand and listed under a new specification code with Services Australia for the purposes of billing. PASC noted that credentialling restrictions are not currently in place for the TV-ICD MBS item.

TGA and Prosthesis List applications

[redacted]

Summary of public consultation input

PASC noted that a letter of support was received from hearts4heart. This organisation was in support of the application as an alternative option to TV-ICD for patients where insertion of a TV-ICD is not ideal or feasible.

Next steps

PASC acknowledged that the application would progress as an ADAR. The applicant acknowledged that an application to MSAC can be lodged before relevant therapeutic goods are listed on the ARTG provided that there is evidence that they have commenced the TGA process, but confirmation of ARTG listing is required before MSAC can complete its own appraisal of the corresponding medical service.

[redacted]

Applicant Comments on the Ratified PICO Confirmation

Population

The applicant stated that they agree with the description for the Population under consideration to be described as noted by PASC.

Intervention

The applicant agreed, stating that they intend to address the clinical questions in the ADAR.

Proposed Economic Evaluation

The applicant agreed that a CMA is the appropriate methodology to support an overall claim of non-inferiority of EV-ICD with the nominated comparators.

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