# MSAC Application 1749

## Insertion of durable ventricular assist device (VAD) for use as destination therapy

# 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 insertion of left ventricular assist device (LVAD) as destination therapy in patients with refractory heart failure who are not eligible for cardiac transplantation: PICO Set**

| Component | Description |
|---|---|
| Population | Patients with advanced heart failure (HF) despite optimal medical management, with INTERMACS profile 1–4, who are not eligible for cardiac transplantation and in whom left ventricular assist device (LVAD) is used as destination therapy (i.e., final therapy) |
| Intervention | Insertion of an LVAD capable of providing mechanical circulatory support (MCS) for at least six months in addition to guideline-directed medical therapy (GDMT) |
| Comparator/s | GDMT - also referred to as optimal medical management or optimal medical therapy |
| Outcomes | **Effectiveness outcomes**<br>• event-free survival - defined as survival at two years free of disabling stroke or reoperation to replace or remove a malfunctioning device<br>• overall survival<br>• functional status (6-minute walk test and New York Heart Association (NYHA) classification status)<br>• re-hospitalisations<br><u>Patient-reported outcomes</u><br>• quality of life measures - EQ-5D-5L, SF-36, Kansas City Cardiomyopathy questionnaire and Minnesota Living with Heart Failure questionnaire<br>**Safety outcomes**<br>• major adverse events (e.g., stroke, bleeding, infection and thrombosis)<br>• mortality or permanent disability<br>• device malfunction<br>**Health care resources**<br>• procedure duration<br>• procedure success rate<br>• time to hospital discharge<br>• procedure-related and follow-up costs<br>• cost of device and consumables<br>**Cost-effectiveness**<br>• cost per life years gained<br>• cost per quality-adjusted life years (QALY) gained<br>**Total Australian Government health care costs**<br>• total cost to the Medical Benefits Schedule (MBS)<br>• total cost to other healthcare budgets (e.g., Prescribed List, State and Territory Government health budgets, including public hospitals) |
| Assessment questions | What is the comparative safety, effectiveness, cost-effectiveness and total costs of LVAD as destination therapy versus GDMT in patients with advanced HF who are not eligible for cardiac transplantation? |

# Purpose of application

An application requesting amendment of Medicare Benefits Schedule (MBS) items 38615 and 38618 to include the insertion of a durable ventricular assist device (VAD) for use as destination therapy (DT) for advanced heart failure patients was received from Abbott Medical Australia Pty Ltd by the Department of Health.

The clinical claim made in the application is that, compared with guideline-directed medical therapy (GDMT), VAD is superior in terms of effectiveness and safety.

# PICO criteria

### *Population*

The proposed population in this application is patients with advanced heart failure despite optimal medical management (OMM), with INTERMACS profile 1–4, who are not eligible for cardiac transplantation and in whom VAD is used as destination therapy (i.e., final therapy).

#### *Heart Failure*

Heart failure (HF) is a chronic progressive condition due to an abnormality of cardiac structure or function that impairs the heart's ability to pump blood around the body effectively (Australian Institute of Health and Welfare, 2023). HF can result from various diseases and conditions that impair or overload the heart. These include heart attack, high blood pressure, damaged heart valves or cardiomyopathy (Australian Institute of Health and Welfare, 2023).

A systematic review reported a 1.3% prevalence of HF among all ages across 51 countries, and the HF prevalence among all adults was 3.4% (Emmons-Bell et al., 2022). The prevalence of HF is estimated to be 1–2% in Australia, with a higher prevalence observed in older people, the indigenous population and females (Sahle BW et al., 2016). HF contributes to significant resource use and costs to the healthcare systems as patients require frequent hospitalisations and medical appointments (Chan et al., 2016). The annual healthcare cost related to HF in Australia was almost $2.7 billion in 2014 and is estimated to increase to $3.8 billion within 10-15 years (Chan et al., 2016).

#### *Heart failure classification*

There are different classification systems currently used for HF. Generally, the classification systems are based on HF stages, symptoms or left ventricular ejection fraction (LVEF) these include: 1) The American College of Cardiology/American Heart Association (ACC/AHA) classification, which is based on disease stages, 2) the New York Heart Association (NYHA) Classification, which is based on the severity of symptoms; 3) Classification based on LVEF and 4) the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles classification.

#### *1) American College of Cardiology/American Heart Association (ACC/AHA) classification*

The ACC/AHA classified HF into four stages based on the development and progression of the disease: at risk (A), pre-heart failure (B), symptomatic heart failure (C) and advanced HF (D) (Heidenreich et al., 2022). Table 2 provides the HF stages based on ACC/AHA classification.

**Table 2: The ACC/AHA classification based on stages of heart failure**

| Stages | | Definition and criteria |
|---|---|---|
| Stage A | At risk of HF | Patients at risk for HF but without current or prior symptoms or signs of HF and cardiac structural changes or elevated biomarkers of heart disease or positive family history of cardiomyopathy |
| Stage B | Pre-HF | Patients without current or prior symptoms or signs of HF with evidence of one of the following:<br>• Structural heart disease (reduced left or right ventricular systolic function, ventricular hypertrophy, chamber enlargement, wall motion abnormalities and valvular heart disease)<br>• Evidence for increased filling pressures (based on invasive hemodynamic measurements and non-invasive imaging, e.g., Doppler echocardiography)<br>• Patients with risk factors and elevated levels of BNPs or persistently elevated cardiac troponin (in the absence of diagnoses related to biomarker elevations such as acute coronary syndrome, pulmonary embolus, or myopericarditis) |
| Stage C | Symptomatic HF | Patients with structural heart disease with current or prior symptoms of HF |
| Stage D | Advanced HF | Patients with marked HF symptoms interfere with daily life and recurrent hospitalisations despite attempts to optimise GDMT. |

Source: Adapted from Table 3 of (Heidenreich et al., 2022)
Abbreviations: BNP, B-type natriuretic peptide; GDMT, guideline-directed medical therapy; HF, heart failure.

### *2) The New York Heart Association (NYHA) Classification*

The NYHA classification is commonly used to characterise symptoms and functional capacity of patients with symptomatic (stage C) or advanced HF (stage D) (Table 3). It is widely used to determine the eligibility of patients for treatment strategies. It is mainly a subjective assessment by a clinician at baseline after the initial diagnosis and through the continuum of care and can change over time (The Criteria Committee of the New York Heart Association, 1994)

**Table 3: New York Heart Association (NYHA) Classification**

| Class | Patient Symptoms |
|---|---|
| I | No limitation of physical activity. |
| II | Slight limitations of normal physical activity. Comfortable at rest. |
| III | Marked limitation of physical activity. No symptoms at rest |
| IV | Symptoms of heart failure at rest or on any physical activity |

Source: Retrieved from (Atherton et al., 2018), p1137

### *3) HF classification based on left ventricular ejection fraction (LVEF)*

LVEF is an important factor for the classification of patients with HF as it denotes the differing prognosis and response to treatments. Hence, most clinical trials incorporated inclusion criteria based on ejection fraction to select patients (Heidenreich et al., 2022).

The ACC/AHA, Heart Failure Association of the European Society of Cardiology (HFA/ESC), and Japanese Heart Failure Society (JHFS) have proposed an updated LVEF-based classification using HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) (Table 4). This updated universal version has resolved the issues with the differences among LVEF-based classifications in their previous guidelines (Bozkurt et al., 2021).

**Table 4: Proposed updated classification of HF based on ejection fraction**

| HF Classification According to EF | LVEF |
|---|---|
| HF with reduced EF (HFrEF) | ≤40% |
| HF with mildly reduced EF (HFmrEF) | 41-49% |
| HF with preserved EF (HFpEF) | ≥50% |
| HF with improved EF (HFimpEF) | HF with a baseline LVEF of ≤40%, a ≥10-point increase from baseline LVEF, and a second measurement of LVEF of >40% |

Source: Adapted from (Bozkurt et al., 2021)*
Abbreviations: HFmrEF, Heart failure with mildly reduced ejection fraction; HFimpEF, heart failure with improved ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction
Notes: *This publication is endorsed by the Cardiac Society of Australia and New Zealand.

### *4) The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles classification*

In addition to the above-mentioned classification systems, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles classifies patients requiring advanced therapies such as long-term mechanical circulatory support (MCS) devices (Crespo-Leiro et al., 2018). INTERMACS is a USA registry established in 2005 for the clinical outcomes of patients who receive an FDA-approved MCS device to treat advanced HF. There are seven INTERMACS profiles and three modifiers that may alter the phenotype of patients of a given profile. The INTERMACS profiles have also been used to define inclusion criteria for clinical trials of MCS devices for advanced HF patients (Bozkurt et al., 2021). The summary of INTERMACS profiles is provided in Table 5.

**Table 5: INTERMACS profiles**

| Profile | Description | The time frame for intervention |
|---|---|---|
| Profile 1 | Critical cardiogenic shock "Crash and burn."<br>Patients with life-threatening hypotension despite inotropic support, critical organ hypoperfusion, frequently confirmed by worsening acidosis and/or lactate levels. | Definitive intervention is needed within hours. |
| Profile 2 | Progressive decline<br>Patients with declining function despite intravenous inotropic support, may be manifested by worsening renal function, nutritional depletion, inability to restore volume balance. Often referred to as "Sliding on Inotropes". | Definitive intervention is needed within a few days. |
| Profile 3 | Stable on inotrope or inotrope-dependent<br>Patients with stable blood pressure, organ function, nutritional status, and symptoms on continuous intravenous inotropic support (and/or a temporary circulatory support device). However, repeated failure to wean from support. This profile is called "Dependent Stability". | Definitive intervention is elective over a period of weeks to a few months. |
| Profile 4 | Frequent Flyer<br>Patients can be stabilized close to normal volume status but experience congestion symptoms at rest or during daily activities. Diuretics doses generally fluctuate at very high levels. More intensive management and surveillance strategies should be needed. | Definitive intervention is elective over a period of weeks to a few months. |
| Profile 5 | Housebound<br>Patients are comfortable at rest and with activities of daily living but unable to do any other activity, living mainly within the house. Patients are comfortable at rest without congestive symptoms but may have underlying refractory elevated volume status along with renal dysfunction. | Variable urgency depends upon the maintenance of nutrition, organ function, and activity |

| Profile | Description | The time frame for intervention |
|---|---|---|
| Profile 6 | Exertion limited<br>Patients without evidence of fluid overload, comfortable at rest and with daily living activities and minor activities outside the home. However, fatigues after the first few minutes of any meaningful activity - Walking wounded | Variable depends upon the maintenance of nutrition, organ function, and activity level. |
| Profile 7 | Advanced NYHA class III symptoms<br>Patient without current or recent episodes of unstable fluid balance, activity limited to mild physical exertion | Cardiac transplantation or MCS may not be currently indicated. |
| **Modifiers for profiles** | | **Possible profiles that can be modified** |
| Temporary Circulatory Support (TCS) | TCS can modify profiles only in hospitalised patients. They include IABP, ECMO, TandemHeart, LVAD, Impella | 1, 2, 3 |
| Arrhythmia (A) | Arrhythmia can modify any profile. | 1–7 |
| Frequent Flyer (FF.) | Frequent episodes of HF characterise patients requiring frequent emergency visits or hospitalisations for diuretics, ultrafiltration, or temporary intravenous vasoactive therapy. | 3 if at home, 4, 5, 6.<br>Rarely for profile 7. |

Source: Adapted from (McDonagh et al., 2022)
Abbreviations: ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; MCS, mechanical circulatory support; NYHA, New York Heart Association
Notes: 2022 AHA /ACC/HFSA HF guidelines describe profile 4 as 'resting symptoms on oral therapy at home and profile 5 as 'exertion intolerant' (Heidenreich et al., 2022)

### *Advanced HF*

Advanced HF (ACC/AHA Stage D), also known as refractory or end-stage HF, is characterised by persistent or progressive symptoms and ventricular dysfunction despite optimal GDMT (Crespo-Leiro et al., 2018; Truby & Rogers, 2020). The prevalence of advanced HF is increasing due to the ageing population and improved survival of HF patients with modern treatments. It has been estimated that 1-10% of the overall HF population comprises advanced HF patients (Crespo-Leiro et al., 2018). The prognosis of advanced HF is poor, with 1-year mortality from 25% to 75% (McDonagh et al., 2022). The Australian HF data were mainly based on self-reported National Health Survey 2017-2018 data. Hence burden of HF is underestimated (Australian Institute of Health and Welfare, 2023) and evidence is limited for the proportion of advanced HF patients from the overall HF population in Australia.

Of note, the application used the wording 'refractory HF' to denote the patient population in line with existing MBS descriptors requested to be amended in this application. However, 'advanced HF' is the most frequently used term in the HF guidelines (Atherton et al., 2018; Heidenreich et al., 2022; McDonagh et al., 2022). Hence the wording 'advanced HF' is used hereafter.

The HFA/ESC position statement on advanced HF 2018 suggested four distinct criteria for defining advanced HF (Crespo-Leiro et al., 2018) (Table 6). These criteria considered that severely reduced LVEF is not mandatory for diagnosing advanced HF as it may also develop in patients with preserved ejection fraction (McDonagh et al., 2022).

**Table 6: Advanced HF criteria as per the HFA ESC 2018 position statement**

| **Updated HFA-ESC criteria for advanced HF.** |
|---|
| All the following criteria must be present despite optimal medical treatment: |
| 1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV]. |
| 2. Severe cardiac dysfunction defined by one or more of these: |
| • LVEF ≤ 30% |
| • Isolated RV failure |
| • Non-operable severe valve abnormalities or congenital abnormalities |
| • Persistently high (or increasing) BNP or NT-proBNP values and severe diastolic dysfunction or LV structural abnormalities |
| 3. Pulmonary Episodes or systemic congestion requiring high-dose intravenous or low-output episodes requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalisation in the last 12 months |
| 4. Severe exercise impairment or low 6MWT (<300 m) or pVO2 (<12–14 mL/kg/min), estimated to be of cardiac origin |

Source: (Crespo-Leiro et al., 2018), table 3, adapted.
Abbreviations: 6MWT, 6-minute walk test; BNP, B-type natriuretic peptide; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO2, peak oxygen consumption; RV, right ventricular.

### *Management of advanced HF*

HF patients with persistent or progressive symptoms and ventricular dysfunction despite optimal GDMT (Please see the section 'comparator' for more details on GDMT) are eligible for advanced HF therapies (Crespo-Leiro et al., 2018). A timely referral is crucial for decisions on advanced therapies and improving patient outcomes (Atherton et al., 2018). HF patients with possible warning signs (e.g., persistent NYHA class IIIB to IV or persistently elevated natriuretic peptides, very low ejection fraction) should be referred to an advanced HF specialist (Heidenreich et al., 2022; McDonagh et al., 2022). The acronym 'I-Need-Help' has been suggested to assist in decision-making on the timely referral of advanced HF patients (Baumwol, 2017).

**I-Need-Help**

I=Intravenous inotropes

N=NYHA class IIIb to IV or persistently elevated natriuretic peptides

E=End-organ dysfunction

E=EF≤35%

D=Defibrillator shocks

H=Hospitalisations >1

E=Edema despite escalating diuretics

L=Low SBP ≤90 mmHg, high heart rate

P=Prognostic medication, progressive intolerance or down-titration of GDMT

The management of advanced HF patients includes short-term and long-term treatment. Advanced HF patients may need short-term management with pharmacological therapies such as intravenous vasoactive drugs and short-term MCS such as intra-aortic balloon counter-pulsation (IABP), extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO) while waiting for the long term management strategies (Crespo-Leiro et al., 2018). The long-term management of advanced HF includes advanced therapies (e.g., long-term MCS or cardiac transplantation) or palliative care (Atherton et al., 2018).

Conventional cardiac surgeries are indicated in certain patients with advanced HF. For example, coronary artery bypass grafting, in addition to medical therapy, could significantly reduce mortality and hospitalisations compared to medical therapy alone among patients with an LVEF ≤35% and coronary artery disease amenable to surgical revascularisation (Crespo-Leiro et al., 2018).

Observational cohort studies have shown that cardiac transplantation could reduce morbidity and mortality among advanced HF patients (Heidenreich et al., 2022). However, careful selection of patients is essential for cardiac transplantation. The Transplantation Society of Australia and New Zealand (TSANZ) clinical guidelines for organ transplantation recommend offering cardiac transplant only to end-stage heart disease patients who have exhausted all alternative options and are expected to gain survival benefits with a reasonable chance of returning to an active lifestyle (Transplantation Society of Australia and New Zealand, 2023).

Long-term MCS strategies for advanced HF patients include implanting durable MCS devices such as LVAD and total artificial heart (TAH) (McDonagh et al., 2022), noting TAH is not available in Australia. Randomised controlled trials (RCTs) and observational studies have shown improved survival and quality of life among advanced HF patients treated with long-term MCS compared to optimal medical management (Rose et al., 2001). Long-term MCS devices are indicated in selected patients when GDMT is insufficient or short-term MCS have not led to cardiac recovery or improvement or to keep the patient alive until transplantation (McDonagh et al., 2022).

Patients receiving advanced HF therapies require immediate post-operative and long-term follow-up with a multidisciplinary team. This team may include a surgical team, a nutritionist, a physiotherapist, a psychiatrist, and a general practitioner (Crespo-Leiro et al., 2018). Optimal care of advanced HF patients also includes palliative care at the end of life and whenever appropriate. Palliative care also involves shared care through a multidisciplinary team, including specialised advanced HF services, primary care providers and specialist palliative care services (Crespo-Leiro et al., 2018).

### *VAD as an MCS strategy for the management of advanced HF patients*

VAD is the most common MCS device used for treating advanced HF, and the indications for VAD implantation can be categorised into four broad areas (Atherton et al., 2018).

- bridge to transplantation (BTT) - for advanced HF patients who are awaiting cardiac transplantation e.g., Left ventricular assist device (LVAD) or biventricular assist device (BiVAD)
- bridge to candidacy (BTC) - for advanced HF patients who are not eligible for cardiac transplantation at the time of VAD implantation but who are expected to become eligible for cardiac transplantation following a period of VAD support (usually LVAD)
- bridge to recovery (BTR) - for patients with acute severe HF complicating myocarditis or following cardiac surgery
- destination therapy (DT) - for advanced HF patients who are ineligible for cardiac transplantation (LVAD).

BTR refers to using MCS to keep a patient alive until cardiac function recovers sufficiently to remove MCS. The 2022 AHA/ACC/HFSA guidelines recommend using temporary MCS, including percutaneous and extracorporeal VAD (such as ECMO), as BTR (Heidenreich et al., 2022). Hence, BTT, BTC and DT are the main indications for durable VAD.

LVAD is the most common durable VAD device (Birks & Mancini, 2022). Of note, two VADs; LVAD and right ventricular assist device (RVAD) can provide long-term MCS for patients with biventricular failure. However, due to the complexity of biventricular VAD, patients who require biventricular support typically have worse outcomes than those who require only LVAD support. Therefore, BiVAD is intended as BTT, not DT (Birks &

Mancini, 2022). Hence, LVAD is the device of choice for DT, and the clinical guidelines and clinical trials refer to the DT intervention as LVAD.

Of note, the application used both durable VAD and LVAD interchangeably to define the population and intervention relevant to this application considering the availability of both LVAD and RVAD and in line with the MBS item descriptors requested to be amended in this application. 'Durable' was also used in the application to distinguish from short-term/temporary MCS/VAD. Hence, hereafter 'durable VAD' is used to describe the details in common and 'LVAD' is used to specify the details relevant to LVAD.

*LVAD for patients not eligible for cardiac transplantation.*

LVAD as DT is indicated for advanced HF patients who are not eligible for cardiac transplantation (Atherton et al., 2018; McDonagh et al., 2022). The 2018 NHFA/CSANZ HF guidelines did not provide eligibility criteria for durable VAD but made recommendations for the consideration of durable VAD implantation. The 2022 AHA/ACC/HFSA guidelines included eligibility criteria for durable VAD as BTT and DT. The 2021 ESC HF guidelines provided eligibility criteria for LVAD as BTT, BTC and DT. Hence, the patients who are eligible for LVAD and who are not eligible for cardiac transplantation should be considered for LVAD as DT.

Of note, the application provided inclusion and exclusion criteria for cardiac transplantation as the population of interest in this application is advanced HF patients who are indicated for VAD as DT and are not eligible for cardiac transplantation. However, there are common exclusion criteria (e.g., inability to comply with complex medical therapy and non-adherence and unstable psychosocial background) that contraindicate both cardiac transplantation and LVAD implantation among advanced HF patients (McDonagh et al., 2022).

A summary of the proposed population, eligibility criteria for LVAD for DT across HF guidelines and the inclusion criteria of the pivotal MOMENTUM 3 RCT quoted in the application is provided in Table 7.

**Table 7: Eligibility criteria for VAD for DT**

| Proposed Population in the application | Recommendation for VAD based on 2018 NHFA/CSANZ HF guidelines | Patients eligible for durable VAD* based on the 2017 AHA scientific statement and 2022 AHA/ACC/HFSA guidelines | Patients eligible for LVAD based on the 2021 ESC HF guidelines | Population included in the MOMENTUM 3 RCT |
|---|---|---|---|---|
| | | **Indications** | **Indications** | **Inclusion criteria** |
| Patients with advanced HF despite optimal medical management,<br>• with INTERMACS profile 1–4<br>• who are not eligible for cardiac transplantation<br>• in whom VAD is used as DT | No specific eligibility criteria included. However following recommendations were suggested.<br>• Referral to a specialist centre for consideration of VAD implantation should be considered in patients with intractable, severe HF despite GDMT and pacemaker therapy, and who do not suffer from major comorbidities, to decrease mortality.<br>• Implantation of a VAD as a BTT should be considered in patients actively listed for cardiac transplantation who become inotrope-dependent or who progress to needing acute mechanical circulatory support.<br><br>INTERMACS:<br>Highlighted the importance of approving DT as an approved indications for VAD implantation in Australia as the DT is the most common indication for VAD implantation globally reported in recent INTERMACS registry data | Combination of the following:<br>• Frequent hospitalisations for heart failure<br>• NYHA class IIIb–IV functional limitations despite maximal therapy<br>• Intolerance of neurohormonal antagonists<br>• Increasing diuretic requirement<br>• Symptomatic despite CRT<br>• Inotrope dependence<br>• Low peak $vO_2$ (<14–16)<br>• End-organ dysfunction attributable to low cardiac output<br><br>INTERMACS:<br>Eligibility criteria are not based on INTERMACS profiles. However, 2022 AHA/ACC/HFSA guidelines reported that MCS implantation in INTERMACS profile 1 patients has been associated with poorer outcome, while profiles 5 to 7 patients might be too well to have significant benefit, depending on their symptom burden. | Advanced HF patients,<br>• With the persistence of severe symptoms despite optimal medical management and device therapy,<br>• Without severe right ventricular dysfunction and/or severe tricuspid regurgitation,<br>• and who have at least one of the following:<br>LVEF <25% and unable to exercise for HF or cardiopulmonary exercise testing, with peak $vO_2$ <12 mL/kg/min and/or <50% predicted value<br>≥_3 HF hospitalisations in the previous 12 months without an obvious precipitating cause<br>Dependence on i.v. inotropic or temporary MCS<br>Progressive end-organ dysfunction<br><br>INTERMACS:<br>Eligibility criteria are not based on INTERMACS profiles. However, 2021 ESC HF guidelines recommended that the durable VAD should be considered in | • Age ≥ 18 years and able to give consent<br>• Body Surface Area (BSA) ≥ 1.2 m2<br>• NYHA Class III with dyspnea upon mild physical activity or NYHA Class IV<br>• LVEF ≤ 25%<br>• Inotrope dependent or<br>• Cardiac Index (CI) < 2.2 L/min/m2, while not on inotropes with one of the following:<br>On OMM based on current HF practice guidelines for at least 45 out of the last 60 days and are failing to respond<br>Advanced HF for at least 14 days AND dependent on intra-aortic balloon pump (IABP) for at least 7 days,<br>• Females of child-bearing age must agree to use adequate contraception<br><br>INTERMACS:<br>• Eligibility criteria did not based on INETRMACS profiles<br>• included advanced HF patients with all INTERMACS profiles (1-7). |

| Proposed Population in the application | Recommendation for VAD based on 2018 NHFA/CSANZ HF guidelines | Patients eligible for durable VAD* based on the 2017 AHA scientific statement and 2022 AHA/ACC/HFSA guidelines | Patients eligible for LVAD based on the 2021 ESC HF guidelines | Population included in the MOMENTUM 3 RCT |
|---|---|---|---|---|
| | | | • Patients with INTERMACS profiles 2-4<br>• INTERMACS profile 5-6 patients when they have high-risk characteristics | • However, only a small number of patients with 5-7 profiles (n=25)<br>• A subgroup analysis showed no significant difference in the primary endpoint across INTERMACS profiles |
| | | **Contraindications** | **Contraindications** | **Exclusion criteria** |
| | | Absolute<br>• Irreversible hepatic disease<br>• Irreversible renal disease<br>• Irreversible neurological disease<br>• Medical non-adherence<br>• Severe psychosocial limitations<br>Relative<br>• Age>80 y for DT.<br>• Obesity or malnutrition<br>• Musculoskeletal disease that impairs rehabilitation<br>• Active systemic infection or prolonged intubation<br>• Untreated malignancy<br>• Severe PVD<br>• Active substance abuse<br>• Impaired cognitive function<br>• Unmanaged psychiatric disorder<br>• Lack of social support | • major contraindications (i.e., long-term oral anticoagulation, infection, severe renal dysfunction, ventricular arrhythmias),<br>• unstable psychosocial background | • Patients were excluded from the trial if biventricular circulatory support was expected to be necessary or if irreversible end organ dysfunction or active infection was present. |

Source: Adapted from (Cook et al., 2017; Heidenreich et al., 2022; McDonagh et al., 2022)

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; BTT, bridge to transplant; CRT cardiac resynchronisation therapy; DT, destination therapy; ESC = European Society of Cardiology; GDMT, guideline directed medical therapy; HF, heart failure; HFSA, Heart Failure Society of America; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IV, intravenous; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; NYHA, New York Heart Association; OMM, optimal medical management; PVD, peripheral vascular disease; VAD, ventricular assist device; $vO_2$, oxygen volume.

Notes: * durable VAD defined as durable MCS indicated for bridge to transplant and destination therapy in the 2017 AHA scientific statement.

The REMATCH RCT and the ROADMAP observational study provided evidence on the comparative safety and effectiveness of LVAD therapy as DT compared to GDMT among advanced HF patients. The REMATCH trial included patients in NYHA class III or IV for at least 28 days (Rose et al., 2001). The ROADMAP study included advanced HF patients who were not dependent on intravenous inotropic support (Estep et al., 2015; Rogers et al., 2015).

The application suggested defining patients suitable for LVAD as DT to be INTERMACS profile 1-4 based on the MOMENTUM 3 trial (Mehra et al., 2019). However, INTERMACS profiles included in the MOMENTUM 3 RCT and ongoing RCTs differed from the suggested INTERMACS profiles in this application. The MOMENTUM 3 trial included advanced HF patients with INTERMACS profiles (1-7). A subgroup analysis of MOMENTUM 3 that included a small number of patients with 5-7 profiles (n=25) showed no significant difference in the primary endpoint across INTERMACS profiles (Mehra et al., 2019). The ongoing Swedish Evaluation of Left Ventricular Assist Device as Permanent Treatment in End-stage Heart Failure (SweVAD) (ClinicalTrials.gov Identifier: NCT02592499) RCT, which is evaluating LVAD as DT compared to the OMM, is at the participant recruitment stage. The SweVAD trial recruits advanced HF patients in NYHA IIIB-IV, INTERMACS profile 2-6 (exclude INTERMACS 1), whereas ongoing AMbuVAD study includes patients with INTERMACS 4-6.

The recent INTERMACS report confirmed that profiles 5, 6, and 7 account for less than 3% of continuous-flow LVAD implants (Yuzefpolskaya et al., 2023). Nevertheless, the 2021 ESC HF guidelines suggested that LVAD should be considered in patients with INTERMACS profiles 2-4 and the INTERMACS profile 5-6 patients when they have high-risk characteristics (McDonagh et al., 2022). INTERMACS profile 1 patients with no irreversible end-organ failure other than cardiac and recovering from while on short-term MCS may also qualify for long-term MCS (McDonagh et al., 2022). However, implantation of MCS among INTERMACS profile 1 showed poorer outcomes (Heidenreich et al., 2022). Hence, confining patients with INTERMACS profiles 1–4 in this application would exclude INTERMACS profile 5-6 patients when they have high-risk characteristics.

*PASC queried the appropriateness of using INTERMACS profiles 1-4 to define the population relevant to this application, given that there is a possibility of excluding patients who may benefit from LVAD as DT. PASC noted that data from the INTERMACS register indicates that LVAD as DT is predominantly used in patients with an INTERMACS profile of 1-4. However, a 2019 publication indicated that the benefit (percentage of patients alive at 12 months) is in patients with an INTERMACS profile of 4-7 (Kittleson et al., 2020). PASC noted this could reflect that these were a healthier group of patients. The applicant advised that INTERMACS profiles are primarily used to select patients with the highest clinical need for this ~~highly expensive~~ high-cost yet lifesaving treatment, rather than exclude patients. The applicant's clinical experts acknowledged the evidence that LVAD as DT is of a benefit in patients with an INTERMACS profile of 5-7 but stated that the benefits from LVAD as DT were more prominent for patients with INTERMACS profiles 1-4, when patient outcomes with LVAD as DT are compared with GDMT. PASC queried the feasibility of providing LVAD as DT to patients with INTERMACS profile 1, as these are patients who require definitive intervention within hours and may be too unstable to transport to one of the four specialised quaternary centres. The applicant's clinical experts responded that the number of patients presenting with INTERMACS profile 1 who require LVAD as DT would be very small. Patients with INTERMACS profile 1, if deemed suitable may receive other short term MCS such as ECMO as a bridge to transplant or if not eligible for transplant, then as a bridge prior to LVAD as DT. Overall, PASC considered it appropriate to use INTERMACS profiles 1-4 to define the population.*

### *LVAD as destination therapy*

The 2018 NHFA/CSANZ HF guidelines highlighted the importance of approving DT as an indication of VAD implantation in Australia (Atherton et al., 2018). Currently, BTT, BTC and BTR are the approved indications for VAD implantation in Australia, despite DT being the most predominant indication for LVAD internationally (Atherton et al., 2018). The recent INTERMACS annual report also reported a marked increase in VAD implantation as DT over the recent years (56.5% in 2018 vs 81.1% in 2021) (Yuzefpolskaya et al., 2023). Furthermore, LVAD as DT is an approved indication by the National Institute of Health and Care Excellence and other international health technology assessment agencies such as the Ontario Health Technology Assessment (Health Quality Ontario, 2016; National Institute for Health and Care Excellence, 2015). Furthermore, the Department received statements from The Cardiac Society of Australia and New Zealand stating that treating advanced HF patients using LVAD as DT has merit and warrants appropriate consideration from MSAC. Hence, the suggested indication for VAD in this application is appropriate.

### *Estimated size of the proposed population in Australia*

Currently, VAD is MBS listed for BTT, BTC and BTR in Australia (MBS items 38615 and 38616). The application suggested estimating the incidence of patients who could receive LVAD as DT based on the relative number of patients receiving VAD as BTT or BTC as a potentially reliable approach. Based on MBS utilisation statistics, an average of 30 VAD procedures were funded via the MBS (items 38615, 38618) in Australia during 2010-2020. The VAD procedures funded under these MBS items in 2021 and 2022 were 30 and 28, respectively. However, the MBS items relevant for VAD insertion (items 38615 and 38618) also include BTR indications, such as acute post-cardiotomy and cardiorespiratory support. Hence, the VAD procedures for BTT and BTC would be slightly less than the total number of procedures funded under these MBS items.

The recent INTERMACS annual report based on the USA data showed an increasing number of patients receiving VAD for DT (56.5% in 2018 vs 81.1% in 2021) (Yuzefpolskaya et al., 2023). However, during the 2012-2021 period, 21.9% BTT, 26.9% BTC and 50.4% DT procedures were reported. Furthermore, the early period 2012-2017 DT procedure represented, on average, approximately 49% of VAD procedures per year in the INTERMACS registry. The applicant considered the percentage reported during the early period of DT introduction in registry data would be more applicable to the adoption of DT for the first time on the MBS in Australia. Thus, it can be expected that the DT procedures will be similar to the combined number of procedures for BTT and BTC (i.e., 50% DT, 50% BTT/BTC) per year in Australia. The application estimated up to 30 procedures of VAD as DT being conducted on the MBS each year when the indication for DT has been established after several years of availability. The applicant considered that the estimation is appropriate based on MBS utilisation data and assuming that each procedure is conducted in a unique patient and systems of referral to identify patients potentially eligible for DT are similar between the USA and Australia.

*PASC queried whether the INTERMACS registry included any Australian patients and whether the Australian patient population may be different to the American patients in the INTERMACS registry. The applicant stated that patients potentially eligible for LVAD as DT should be similar between the USA and Australia. Furthermore, the applicant's clinical experts indicated that the establishment of a registry similar to the INTERMACS for Australia is in progress.*

The insertion of VAD is currently limited to specialised quaternary centres, which may place capacity and capability constraints to deliver the service in Australia. This could lead to the number of VAD insertion for DT procedures that can be performed in the Australian setting being significantly less than the estimate of 30 procedures per year. The application confirmed that four quaternary hospitals for adults and one children hospital perform heart transplants and implant LVADs in Australia. Therefore, access to LVAD in the proposed population is limited by capacity constraints due to Australia's low number of implant centres.

Considering that VAD implantation and patient assessment are already well-established for the current MBS items (VAD for BTT or BTC), the applicant raises the question of what would be appropriate accreditation for clinicians and hospitals for the additional DT population. Further, the applicant suggested continued liaison with local experts will determine the necessity for accreditations of centres and clinicians to ensure appropriate patient care in the expanded patient population (Application: Proposed MBS item).

*PASC queried the evidence for, and accessibility of, LVAD as DT for children versus adults, noting only one centre in Australia could provide LVAD as DT for children. The applicant's clinical experts advised that it would be very uncommon for a child or a teenager to receive LVAD as DT because clinicians advocate for cardiac transplantation to achieve the best long-term outcome for children. However, if a child was ineligible for cardiac transplant (i.e., absolute contraindication, such as malignancy or a genetic disorder for malignancy) then the child might be eligible for LVAD as DT. The applicant's clinical experts estimated that this would be less than one child per year.*

*PASC also raised concerns over accessibility issues for regional and remote patients given that the insertion of LVAD is currently limited to specialised quaternary centres and there is a high level of device care required to live with the LVAD. As such, PASC queried whether the travel required would reduce remote patients' eligibility for LVAD as DT and subsequently ability to access the follow up care. The applicant's clinical expert acknowledged that the specialists and multidisciplinary teams for VAD insertion and post-operative management are located in the specialised quaternary centres but confirmed the specialised quaternary centres receive patient referrals from local expert teams across Australia. The clinical experts also stated that there is a well-established back referral system to local expert centres for further management. Moreover, VAD as DT is more effective if patients are able to operate independently in their home environment with appropriate care and family support.*

### *Intervention*

#### *Overview*

The proposed medical service is a therapeutic technology, which involves the insertion of a VAD to provide MCS for at least six months as DT for advanced HF patients who are not eligible for cardiac transplantation. The available evidence is mixed regarding whether VAD for DT is or is not in addition to the GDMT (i.e., some studies include OMM in the intervention arm along with VAD whereas other studies do not).

*PASC noted that there is conflicting evidence on whether the LVAD is in addition to the GDMT or not. PASC noted that LVAD as DT might reduce some pharmacological treatments, but most adjunct care will continue. Therefore, PASC considered that the intervention should be LVAD as DT in addition to the GDMT.*

Over the years, different types of LVADs have been introduced. An overview of LVAD characteristics from first to third-generation devices is provided in Table 8.

**Table 8: Overview of LVAD characteristics – first through third-generation devices**

| | First generation | Second generation | Third generation | |
|---|---|---|---|---|
| Example | HeartMate XVE | HeartMate II | HeartWare | HeartMate 3™ |
| Flow type | Pulsatile | Axial-continuous | Centrifugal | Fully magnetically levitated centrifugal |
| Implant site | Abdomen | Abdomen/chest | Pericardium | Pericardium |
| Electrical source | Pneumatic | Electric | Electric | Electric |
| | Not on ARTG | No longer included on ARTG; however, accessories are included on the ARTG still (e.g., HeartMate II system controller, ARTG 292290) | HeartWare is included on ARTG (ARTG 181875). However, this device is no longer available in the market as Medtronic cease the supply of HeartWare globally due to safety issues. | **ARTG ID**: 300895<br>**Start date**: 16/03/2018<br>**Category**: Medical device AIMD<br>**GMDN**: 47533 Implantable ventricular circulatory assist system<br>**Sponsor:** Abbott Medical Australia Pty Ltd<br>**Intended purpose:**<br>The HeartMate 3™ LVAS is intended to provide long-term haemodynamic support in patients with advanced, refractory left ventricular HF. It is intended either for temporary support, such as a BTT, or DT. The HeartMate 3™ is intended for use inside or outside the hospital. |

Source: Adapted from (Griffin & Katz, 2014) and Therapeutic Goods Administration, ARTG Public Summary, accessed 12th June 2023.
Abbreviations: ARTG, Australian Register of Therapeutic Goods; BTT, bridge to cardiac transplantation; DT destination therapy; GMDN, Global Medical Device Nomenclature; HF, Heart Failure; HVAD, HeartWare Ventricular Assist Device; LVAS, Left ventricular circulatory assist system.

LVAD is the most common type of durable VAD and the device of choice for the DT (Please see more details in the section: population: VAD as an MCS strategy for the management of advanced HF patients).

HeartMate 3™ is the most recent and current generation LVAD available in Australia. It is a third-generation, fully magnetically levitated centrifugal-flow LVAD, listed on the Australian Register of Therapeutic Goods (ARTG) and the current Prescribed List (PL). HeartWare is another third-generation continuous flow LVAD; however, it is not fully magnetically levitated like the HeartMate 3™. Although HeartWare is registered in the ARTG (ARTG 181875), it is no longer listed in the PL or used globally. Medtronic ceased the distribution and sale of the HeartWare VAD System in June 2021 due to a growing body of observational clinical comparisons showing a higher frequency of neurological adverse events and mortality among HeartWare VAD System patients as compared to those who receive other commercially available LVAD (Medtronic, 2021; U.S. Food and Drug Administration, 2021). Therefore, the application has provided details related to the HeartMate 3™ system as the nominated intervention.

HeartMate II is a second-generation LVAD with a continuous axial flow pump, whereas HeartMate 3™ is a fully magnetically levitated, continuous flow, centrifugal pump. The axial vs centrifugal refers to the blades' rotation within the pump and how blood is transported through the pump. The MOMENTUM 3 RCT compared the safety and effectiveness of HeartMate 3™ and HeartMate II as a bridge to transplantation or as DT among advanced HF patients. The results showed that HeartMate 3™ was associated with less frequent pump replacement and was superior with survival free of disabling stroke or reoperation to replace or remove a malfunctioning device compared to HeartMate II (Mehra et al., 2019). Considering the superior outcomes of HeartMate 3™, the most recent generation device, the device-specific details provided in the application were specific to HeartMate 3™.

### *HeartMate 3™ Left Ventricular Assist System (LVAS)*

The HeartMate 3™ LVAS comprises a set of equipment and materials to provide therapeutic benefits to advanced heart failure patients. The LVAS (Figure 1) includes an LVAD, a blood pump, and an extracorporeal controller, including controls, attachments, interfaces, power sources, supporting equipment, labelling, and tools required to provide the intended therapeutic benefit.

1. **LVAD**: The HeartMate 3™ LVAD is a fully magnetically levitated, centrifugal flow rotary heart pump (Figure 2). The inflow cannula of the LVAD attaches to the apex of the left ventricle, and its sealed outflow graft connects to the ascending aorta. It is implanted in the thorax of the advanced HF patient.
2. **Driveline**: consists of two cables, the pump cable (that extends from the LVAD through the skin) and the modular cable (which connects the pump cable to the system controller)
3. **System controller**: An extracorporeal interface device that receives power from the power module, the portable power unit, or portable batteries and appropriately transfers the power to the LVAD. The system controller is the primary user interface. It has several important functions, including operating condition display, the source for audible and visible alarms, transfer event/period log and alarm information and battery backup in the case of full power disconnection. The system controller supplies the power to LVAD by one of three sources: 1) the power module, 2) the mobile power unit connected to an AC electrical outlet, or 3) two HeartMate 3™ 14 Volt Lithium-Ion direct current batteries. The emergency backup battery in the reserve backup system controller is charged every six months.

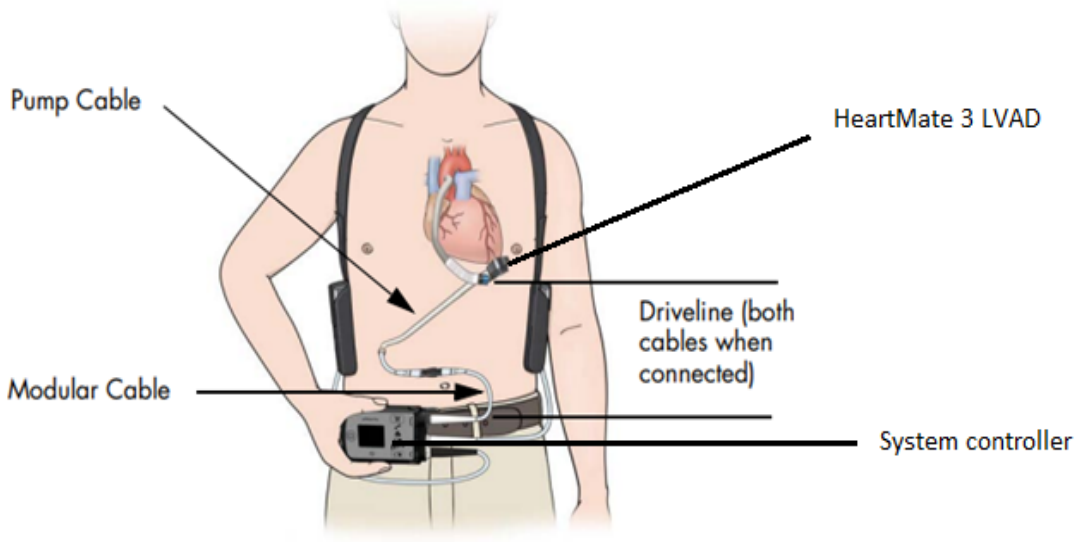


**Figure 1: Overview of LVAS equipment**
Source: Figure 3, p9 of MSAC 1749 application PICO Set
Abbreviations: LVAD Left Ventricular Assist Device; LVAS Left Ventricular Assist System

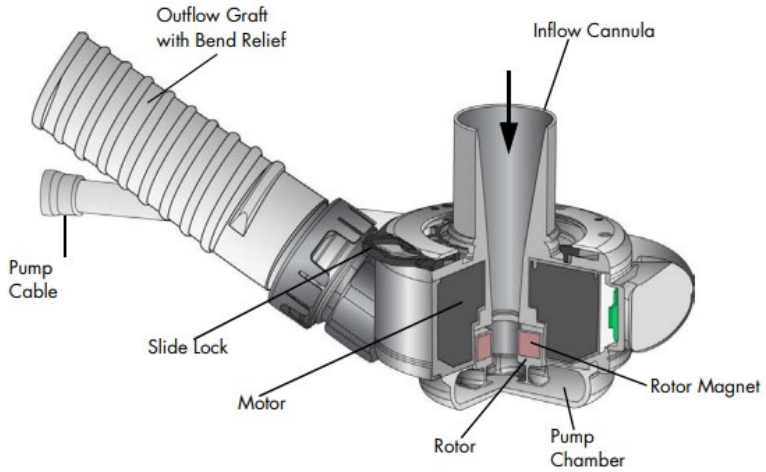


**Figure 2: VAD components**
Source: Figure 2, p9 of MSAC 1749 application PICO Set
Abbreviations: LVAD Left Ventricular Assist Device; LVAS Left Ventricular Assist System

### *Mechanism of action and treatment procedure*

LVAD is designed to perform some or all the workload of the left ventricle and intended to restore the patient's systemic perfusion.

The HeartMate 3™ LVAD is a centrifugally configured device so that the paths of the entering and exiting flow stream are perpendicular to the pump's axis. It uses a rotary blood pump to generate flow, and the rotor assembly is fully magnetically levitated within the flow stream. The pump is driven by an external power source via a Driveline. It has the capacity to generate a blood flow of up to 10 litres per minute. Blood enters the pump from the left ventricle through an Inflow Cannula. The blades on the spinning rotor then move the blood through the pump to an Outflow Cannula and ultimately to normal circulation.

*Implant procedures*

The LVAD is implanted via an open chest procedure by a cardiothoracic surgeon, either via median sternotomy or thoracotomy. Hence, it is an inpatient procedure performed either in public or private hospitals.

The key steps for the LVAD implantation include opening the chest, creating the driveline exit site, attaching the sealed outflow graft to the aorta, preparing the ventricular apex site, inserting the pump in the ventricle, attaching the sealed outflow graft to the pump, de-airing the pump to remove residual air and securing the pump and connections.

The inflow cannula is placed utilising left ventricle apical cannulation with the pump placed within the pericardial space between the ventricular apex and the diaphragm. The sealed outflow graft is anastomosed to the ascending aorta, and the pump cable exits either the right or left upper quadrant of the abdomen and connects to the external equipment. A midline chest incision is made not to extend below the xiphoid process. The pericardium is opened and reflected laterally to allow exposure of the LV apex. In creating the driveline exit site, the tunnel created for the pump cable should be as long as possible to maximise ingrowth along the cable's polyester velour covering and to minimise the risk of exit site infection. The pump cable has been designed to allow velour or silicone to cross the exit site. It is recommended that the velour-covered portion of the pump cable remains inside the patient and that only the silicon-covered portion crosses the exit site to reduce infection. The backup battery in the system controller is installed as a post-implant procedure.

The intervention relevant to the PICO set is the insertion of a LVAD capable of providing mechanical circulatory support as DT. The MOMENTUM 3 RCT showed evidence of the comparative safety and effectiveness of the HeartMate 3™ device compared to the HeartMate II second-generation device among advanced HF patients who received LVAD as BTT or DT (Mehra et al., 2019).

There is limited evidence on the direct comparison of safety and effectiveness of HeartMate 3™ and the application's comparator. However, there are two ongoing clinical trials that could provide direct evidence on the comparative safety and effectiveness of HeartMate 3™ versus OMM. The Swedish Evaluation of Left Ventricular Assist Device as Permanent Treatment in End-stage Heart Failure (SweVAD) (ClinicalTrials.gov Identifier: NCT02592499) RCT, which aims to evaluate the safety and effectiveness of HeartMate 3™ as DT compared to OMM among n=80 end-stage HF patients (NYHA IIIB-IV, INTERMACS profile 2-6), is at the participant recruitment stage (estimated primary completion date December 2023 and study completion date December 2025). The ongoing AmbuVAD (ClinicalTrials.gov Identifier: NCT04768322) RCT also evaluates HeartMate 3™ as BTT, BTC or DT compared to GDMT among n=92 ambulatory advanced HF patients (NYHA III-IV, INTERMACS profile 4-6; estimated primary completion date February 2026 and study completion date February 2027). The REMATCH RCT provided evidence on the comparative safety and effectiveness of HeartMate 3™ vented electrical device LVAD therapy as DT compared to OMM among advanced HF patients (Rose et al., 2001). The ROADMAP observational study also compared old-generation LVAD devices (HeartMate II) as DT versus OMM in advanced HF patients who did not dependent on intravenous inotropic support (Estep et al., 2015; Rogers et al., 2015).

*PASC raised concerns about the limited evidence for direct comparison of safety and effectiveness of HeartMate 3™ and the GDMT and noted the two ongoing trials (SweVAD and AmbuVAD). The applicant acknowledged the lack of direct comparative evidence but emphasised the uncertainty about the study completion time of the ongoing SweVAD RCT, which is evaluating the HeartMate 3™ and the comparator. Hence, the applicant suggested that it is not worthwhile to delay the assessment of HeartMate 3™, given*

*that LVAD as DT is the only option available for patients who are not eligible for heart transplantation, therefore, considered to be the lifesaving therapy for the proposed patient population.*

*PASC noted that the LVAD patients require care in specialised MCS +/- transplant centres, pre-VAD assessment (estimated hospital stay of 9 days), general anaesthetic and sternotomy or thoracotomy for insertion, intensive care support, recovery care and rehabilitation (average hospital stay of 31 days), ongoing pharmacological therapy, regular review and device monitoring. The applicant's clinical expert also claimed that VAD as DT involved more than just insertion of the device and there is a network of post implantation support services including specialist VAD nurses required on an ongoing basis. PASC noted this and considered that these pre and post care should be reflected in the proposed economic evaluation, in addition to the implantation surgery.*

### *Comparator(s)*

The application proposed GDMT, also referred to as OMM or optimal medical therapy (OMT), as the comparator for LVAD as DT. Continuing with the GDMT is the option available for the long-term management of advanced HF patients who are not eligible for a heart transplant. Hence, the proposed comparator is appropriate for the intervention of LVAD as DT in patients with advanced HF who are not eligible for cardiac transplantation.

*PASC noted and accepted the proposed comparator.*

The term GDMT incorporates clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments (Heidenreich et al., 2022). Research studies and international health technology assessments have used OMM and OMT to denote GDMT (Health Quality Ontario, 2016; McDonagh et al., 2022). The OMM in the comparator arm of the REMATCH RCT refers to the management of end-stage HF patients based on guidelines developed by the medical committee, with the aim of minimising HF symptoms and optimising organ perfusion (Rose et al., 2001). Of note, the management of advanced HF would have been different in the REMATCH study (Rose et al., 2001) in terms of pharmacological agents compared to the current GDMT therapy, as it was conducted more than 20 years ago. The OMM in the comparator arm of the ROADMAP observational study referred to drug management (Estep et al., 2015; Rogers et al., 2015). The OMM for the control group in the ongoing SweVAD RCT includes pharmacological management, device therapies (e.g., implantable cardioverter defibrillator) or surgical interventions whenever indicated, whereas the ongoing AMBU-VAD RCT comparator group will receive GDMT alone, where GDMT includes pharmacological management only. The intervention group of the AMBU-VAD study will receive LVAD in addition to the GDMT.

The pharmacological management of GDMT includes different categories of drugs. The consensus statement on the current pharmacological management of HF in Australia recommended quadruple therapy with renin-angiotensin-system inhibitors [angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blockers (ARBs)/ angiotensin and angiotensin receptor II blocker - neprilysin inhibitor (ARNI)], beta-blocker (BB), mineralocorticoid receptor antagonist (MRAs), and sodium-glucose cotransporter 2 inhibitors (SGLT2is) as the first line treatment in patients with HFrEF (Sindone et al., 2022). This consensus statement was based on the 2018 NHFA/CSANZ HF guidelines (Atherton et al., 2018), the updated evidence after the 2018 guidelines and recent updates of international HF guidelines such as 2022 AHA/ACC/HFSA HF guidelines (Heidenreich et al., 2022). Initiating first-line treatment with all four drugs simultaneously may not be feasible in some patients. It is recommended that medications are started sequentially in these patients, and the sequence would be determined by clinical or other factors (e.g., drug availability) (Bozkurt, 2022). Once the starting dose is initiated, it is required to up-titrate the dose to the target or maximum tolerated dose

(National Heart Foundation of Australia, 2018). The available evidence from the clinical trials determines each drug's optimum or target dose (Atherton et al., 2018; Heidenreich et al., 2022). The up-titration frequency could be every 1 to 2 weeks depending on the patient's signs, symptoms, and clinical indicators (Bozkurt, 2022). The first line therapy can also be followed by further additional therapies such as hydralazine nitrates depending on the requirement of the patient as well as treatment for comorbidities such as iron deficiency, diabetes, atrial fibrillation and ischemic heart disease (Heidenreich et al., 2022).

The 2018 NHFA/CSANZ guidelines did not give specific recommendations for patients with HFpEF. However, the recent consensus statement suggested SGLT2 inhibitor (empagliflozin) in patients with HFpEF to decrease cardiovascular mortality or hospitalisation (Sindone et al., 2022).

Of note, the application mentioned inotropes under comparator. However, inotropes may be indicated for use in advanced HF patients either as palliative care for those who are ineligible for either MCS or cardiac transplantation despite optimal GDMT and device therapy or bridge to therapy for those who are refractory to GDMT and device therapy and are awaiting MCS or cardiac transplantation. The 2022 AHA/ACC/HFSA guidelines indicate that the long-term use of intravenous inotropic agents may be harmful for reasons other than palliative care or as a bridge to advanced therapies (Heidenreich et al., 2022). Hence inotropes alone could not be considered comparators in this application.

#### *Existing MBS listing for the comparator*

The comparator mainly includes pharmacological management and the relevant drugs for the GDMT (National Heart Foundation of Australia, 2018) listed under the pharmaceutical benefits scheme (PBS).

Non-pharmacological treatments may include ventilation, pacing, angioplasty, ECMO or haemofiltration. The majority of patients will receive pharmacological therapy, but these other interventions are likely to be used in addition to pharmacological management for the most severely affected patients as required.

### *Outcomes*

The outcome measures used in LVAD studies are outlined below. The main primary endpoints in these studies are survival at two years free of disabling stroke, reoperation to replace or remove a malfunctioning device and all-cause mortality. Please see Table 9 for more details.

**Effectiveness outcomes**

- event-free survival- defined as survival at two years free of disabling stroke or reoperation to replace or remove a malfunctioning device
- overall survival
- functional status (6 Minutes walking test and New York Heart Association (NYHA) classification status)
- re-hospitalisations

**Patient-reported outcomes**

- quality of life measures - EQ-5D-5L, SF-36, Kansas City Cardiomyopathy Questionnaire and Minnesota Living with Heart Failure questionnaire

**Safety outcomes**

- major adverse events (e.g., stroke, bleeding, infection and thrombosis)
- mortality or permanent disability
- device malfunction

**Health care resources**

- procedure duration

- procedure success rate
- time to hospital discharge
- procedure-related and follow-up costs
- cost of device and consumables

**Cost-effectiveness**

- cost per life years gained
- cost per quality-adjusted life year (QALY) gained

**Total Australian Government health care costs**

- total cost to the Medical Benefits Schedule (MBS)
- total cost to other healthcare budgets (e.g., Prescribed List; State and Territory Government health budgets, including public hospitals)

*PASC noted possible overlapping between the event free survival and mortality or permanent disability outcomes.*

*PASC also raised concerns over needing timeframes for the re-hospitalisation, device malfunction and mortality or permanent disability outcomes. The applicant's clinical expert claimed that the timeframes for these outcomes depend on clinical scenario rather than LVAD procedure. Further, the applicant's clinical expert claimed that the 30-days mortality may be due to reasons other than the LVAD procedure itself. PASC accepted this claim and considered that it is appropriate to include outcomes without definitive timeframes.*

## Clinical management algorithms

The details of the clinical management pathways are included in the section Population: diagnosis and management. Figure 3 illustrates the current clinical management pathway.

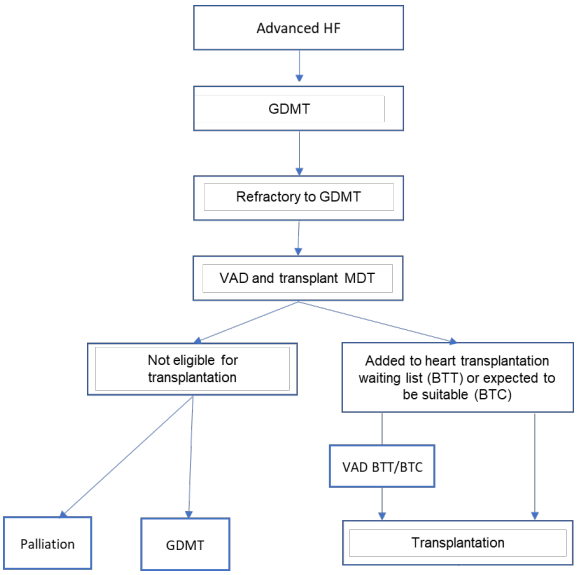


**Figure 3: Current clinical management algorithm**

Source: Adapted from Figure 4, p25 of MSAC application 1749 PICO Set
Abbreviations: BTC, Bridge to candidacy; BTT, Bridge to transplantation; GDMT, Guideline directed medical therapy; HF, Heart failure; VAD, Ventricular assist device

The current practice includes the continuation of GDMT for advanced HF patients who are not eligible for cardiac transplantation, as no other options are available. Currently, BTT and BTC are the two indications

approved in Australia for the insertion of durable VAD under MBS items 38615 and 38618 (Atherton et al., 2018) for advanced HF patients who are waiting for cardiac transplantation or who are expected to be suitable for cardiac transplantation following durable VAD.

Figure 4 illustrates the proposed management algorithm with LVAD as DT for the proposed PICO sets.

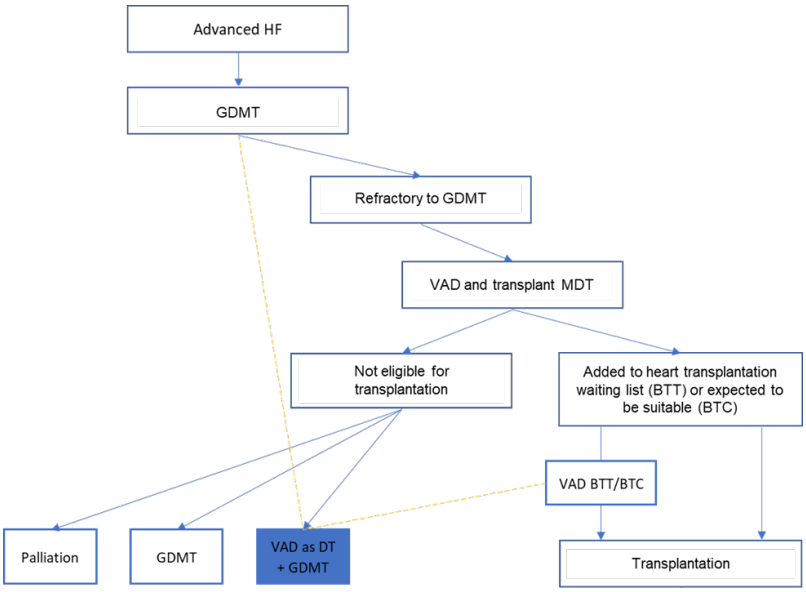


**Figure 4: Proposed clinical management algorithm**

Source: Adapted from Figure 5, p26 of MSAC 1749 application PICO Set
Abbreviations: BTC, Bridge to candidacy; BTT, Bridge to transplantation; GDMT, Guideline directed medical therapy; HF, Heart failure; MDT, Multidisciplinary team; VAD, Ventricular assist device
Notes: *Please see Table 7 for the eligibility criteria
The clinical algorithm was updated to reflect PASC advice that the possibility of patients moving from DT to BTT or from BTT to DT should be denoted in the proposed clinical algorithm.

The application suggested including 'VAD case conference' to the MBS descriptor (Please see the section: Proposal for public funding). The VAD case conference suggested in the application is a process by which a multidisciplinary team (MDT) including cardiothoracic surgeon and specialist or consultant physicians and/or VAD co-ordinator to assess the patient's suitability for VAD.

The application stated that VAD implantation and patient assessment are already well-established for the current MBS items (VAD for BTT or BTC). However, the application did not state whether the suggested 'VAD case conference' is in line with the current practice of assessing patient suitability of VAD in Australian clinical setting.

*PASC suggested that the proposed clinical algorithm by the applicant should be revised to capture the purpose and position of the MDT in the clinical algorithm, whether the intervention is in addition to the GDMT, the possibility of patients moving from DT to BTT or from BTT to DT and palliation as management option.*

*PASC sought clarification from the applicant regarding the purpose and position of the MDT in the clinical algorithm (i.e., whether to assess eligibility for cardiac transplant and/or VAD as DT). The applicant's clinical experts confirmed that in their practice, the MDT first assess the patient's eligibility for heart transplantation. If the patient is not eligible for transplantation, then the assessment is continued to determine eligibility for VAD as DT. The patient's eligibility for transplantation (and subsequent BTT/BTC) or DT depend on several factors such as other comorbidities, age, and psychosocial support.*

The proposed clinical algorithm includes LVAD as DT for advanced HF patients who are not eligible for cardiac transplantation. Approval of LVAD as DT would provide a therapy option for patients not eligible for cardiac transplantation. Some advanced HF patients are not eligible for both cardiac transplantation and LVAD as DT (e.g., unstable psychosocial support). Hence, the GDMT arm remains in the proposed management algorithm.

Of note, the post-operative management and long-term follow-up of LVAD patients include pharmacological management, mainly antithrombotic therapy, blood pressure control and supportive care. GDMT, including ACE inhibitors, BB, MRAs and diuretics, may be continued for some patients as they may reduce morbidity and mortality in patients with LVAD implants (Colvin BM et al., 2021; Kiamanesh et al., 2020). However, evidence for the efficacy of these therapies is limited, particularly after LVAD as DT; hence, future research is required in this area (Colvin BM et al., 2021).

*PASC noted that the applicant's pre-PASC response stated that not all patients will have GDMT in addition to LVAD and suggested it may be appropriate to use LVAD ± GDMT to better reflect this in the proposed management algorithm. As noted by PASC in the Section: Intervention, LVAD as DT might reduce some pharmacological treatments, but most adjunct care will continue. Therefore, PASC considered that the proposed clinical algorithm should reflect LVAD as DT in addition to the GDMT rather than LVAD ± GDMT.*

Of note, there is a possibility that patients may move from DT to BTT (e.g., due to marked improvement in functional class) or from BTT to DT (e.g., due to major VAD complications such as disabling stroke a patient may be no longer suitable for heart transplantation) (Atherton et al., 2018). *PASC queried the possibility of patients moving from DT to BTT or from BTT to DT and suggested to denote these movements in the proposed clinical algorithm. PASC even noted that about 17% of patients who received VAD as DT received transplants over the 5-year follow up in the MOMENTUM 3 trial (Mehra et al., 2022). PASC further queried whether the MDT assessment is performed again to evaluate these possible movements. The applicant's clinical experts indicated that these movements are very rare in actual clinical practice, and it is highly unlikely that the patients are re-evaluated with the MDT once the decision has been made that they are not eligible for heart transplantation. Following the PASC meeting, PASC reiterated that the evidence from the MOMENTUM 3 trial (that 17% of patients received a transplant subsequent to VAD as DT) remained relevant and should be addressed in the assessment report developed for ESC and MSAC consideration. That is, PASC advised that the assessment report (including the clinical algorithm) should address the potential for a patient to move back into active clinical care with view for reassessment for transplant.*

## Proposed economic evaluation

Based on the clinical claim made in the application that LVAD for DT has superior safety and effectiveness compared with GDMT, the appropriate economic evaluation is a cost-effectiveness analysis or a cost-utility analysis.

### *Summary of available evidence for LVAD related to DT for advanced HF and/or HeartMate 3™*

The Assessment Group conducted a rapid literature review to identify available evidence for LVAD as DT for advanced HF patients and/or HeartMate 3™ device. Table 9 provides the summary of available evidence retrieved from the application and the rapid literature search by the Assessment Group. The summary table provided the evidence available for HeartMate 3™ as it is the most recent generation device used in Australian clinical practice. Also, the summary table included the evidence related to LVAD as DT (HeartMate 3™ or older devices as only DT or DT in combination with BTT or BTC) as it is the main indication of interest in the application.

A summary of ongoing studies relevant to HeartMate 3™ and DT is provided in Appendix 1.

**Table 9: Summary of characteristics of studies on VAD**

| Study name | Study design | Population | Intervention | Comparator | No of patients | Effectiveness outcomes reported | Safety outcomes reported |
|---|---|---|---|---|---|---|---|
| Studies related to HeartMate 3™ LVAD | | | | | | | |
| MOMENTUM 3 Final Report *(Mehra et* al., 2019) | RCT | Patients with advanced-stage heart failure (HF) who were deemed to be candidates for LVAD therapy either as a bridge to transplantation (BTT) or as destination therapy (DT)<br>Included patients with INTERMACS profiles 1 to 7 | HeartMate 3™ centrifugal continuous-flow pump group | HeartMate II axial continuous-flow pump group | 1028 (627 DT patients out of total 1028) | Primary composite endpoint- survival at two years free of disabling stroke or reoperation to replace or remove a malfunctioning device<br><br>Secondary endpoints - pump replacement at two years after implantation, actuarial survival, re-hospitalisation, functional status (6MWT and NYHA classification status), and quality of life (EQ-5D-5L; KCCQ) | Rates of major adverse events (stroke, bleeding, right heart failure, and infection) |
| MOMENTUM 3 – Five years follow-up of the MOMENTUM 3 RCT *(Mehra et al., 2022)* | Observational | Patients with advanced-stage HF who were deemed to be candidates for LVAD therapy either as BTT or DT<br>Included patients with INTERMACS profiles 1 to 7 | HeartMate 3™ centrifugal continuous-flow pump group | HeartMate II axial continuous-flow pump group | 1020 | Primary composite endpoint - survival to transplant, recovery, or LVAD support free of debilitating stroke (Modified Rankin Scale score >3) or reoperation to replace the pump five years after the implant<br><br>Secondary endpoints - patient outcomes (transplant, explant/ permanent deactivation, or withdrawal) and survival, functional status (6MWTand NYHA classification status) | Frequency and incidence of serious adverse events (bleeding, major infection, haemolysis, device thrombosis and device malfunction, and neurological dysfunction [including stroke]) |

| Study name | Study design | Population | Intervention | Comparator | No of patients | Effectiveness outcomes reported | Safety outcomes reported |
|---|---|---|---|---|---|---|---|
| CE Mark Clinical trial *(Netuka et al., 2021; Zimpfer et al., 2016)* | Single arm, non-randomised | Adult advanced-stage heart failure patients who are indicated for:<br>1. BTT or DT<br>2. Ejection fraction ≤25%<br>3. Cardiac index <2.2 l/min/m2 while not on inotropes or inotrope-dependent status<br>4. Who were either on optimal medical management for 45 out of 60 days or listed for cardiac transplantation<br>Included patients with INTERMACS profiles 2-6 | HeartMate 3™ | NA | 50 | Operative data, pump performance, survival, and changes in quality of life and NYHA class after 30 days of LVAD. | Adverse event rates occurring within the first 30 days after implant (bleeding, thrombosis, haemolysis, stroke, device-related infection, and pump replacement or failure) |

| Study name | Study design | Population | Intervention | Comparator | No of patients | Effectiveness outcomes reported | Safety outcomes reported |
|---|---|---|---|---|---|---|---|
| Studies related to LVAD as DT | | | | | | | |
| ROADMAP (*Estep et al.,* 2015; *Rogers et al., 2015)* | Non-randomised observational | Patients with advanced HF with:<br>1. NYHA class IIIB or IV functional limitations<br>2. Left ventricular ejection fraction ≤25%<br>3. Not currently listed for any organ transplant, including cardiac transplantation, with no plan for listing in the next 12<br>4. Treatment with OMM<br>5. 6MWT <300 m<br>6. At least one previous unscheduled hospitalisation for HF in the last 12 months<br>7. The LVAD cohort consisted of those who elected to undergo LVAD implantation. The OMM cohort consisted of subjects who met study entrance criteria, including the DT indications for LVAD but elected to remain on OMM<br>Included patients with INTERMACS profiles 4 to 7 *(INTERMACS 1-3 patients were not included in the patient group)* | HeartMate II LVAD as DT | OMM | 200 | Primary composite endpoint - survival and improvement in 6MWT distance from the baseline of ≥75 m at 12 months<br><br>Secondary endpoints - actuarial survival (LVAD patients free of an urgent heart transplant or explant, and OMM patients free of LVAD implantation or urgent heart transplant; survival free of stroke; quality of life (EQ-5D-5L); depression using Patient Health Questionnaire; functional status using 6MWT distance and NYHA classification | Adverse events, hospitalisations, days alive and not hospitalised |

| Study name | Study design | Population | Intervention | Comparator | No of patients | Effectiveness outcomes reported | Safety outcomes reported |
|---|---|---|---|---|---|---|---|
| REMATCH<br>*(Rose et al.*, 2001) | RCT | Adult patients with chronic end-stage HF and contraindications to transplantation with:<br>1. NYHA class III/ IV functional limitations<br>2. Left ventricular ejection fraction ≤25%<br>3. A peak oxygen consumption of no more than 14 ml per kilogram of body weight per minute or a continued need for intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion | HeartMate vented electric device LVAD as DT | OMM | 129 | Primary endpoint- death from any cause<br><br>Secondary endpoints - number of days of hospitalisation; quality of life (Minnesota Living with Heart Failure questionnaire and SF-36); functional status (NYHA classification); symptoms of depression (Beck Depression Inventory) | Incidence of serious adverse events (adverse events caused death or permanent disability) |
| INTrEPID Trial<br>*(Rogers et al., 2007*) | Non-randomised trial | Adults with inotrope-dependent stage D HF and who are not eligible for heart transplantation:<br>1. NYHA functional class IV symptoms for ≥3 months,<br>2. Ejection fraction ≤25% for six months<br>3. Fail two attempts at weaning from inotropic support separated by at least seven days<br>4. Patients in the OMT group met all study criteria but did not receive an LVAD because they chose not to undergo LVAD implantation or there were inadequate identifiable financial resources to cover the cost of device implantation and follow-up | Novacor LVAD | OMT | 55 | Primary endpoint- all-cause mortality<br><br>Secondary endpoint - functional capacity (NYHA function class) and health-related quality of life (Minnesota Living with Heart Failure Questionnaire and SF-36) | Adverse events |

| Study name | Study design | Population | Intervention | Comparator | No of patients | Effectiveness outcomes reported | Safety outcomes reported |
|---|---|---|---|---|---|---|---|
| ENDURANCE (*Rogers* et al., 2017) | RCT | Patients with advanced HF with:<br>1. NYHA functional class IIIB or IV limitations<br>2. Left ventricular ejection fraction ≤25%<br>3. Ineligible for transplantation at the time of enrolment<br>Included patients with INTERMACS profiles 1 to 7 | HeartWare centrifugal-flow pump | Heart-Mate II axial flow pump | 297 | Primary endpoint- 2-year survival free from disabling stroke (modified Rankin scale score of ≥4 assessed 24 weeks after the stroke)<br><br>Secondary endpoint – overall survival, changes in quality of life and health status (KCCQ and the EQ-5D VAS) and functional status (NYHA functional class and 6MWT) | *Incidence of major adverse events (classified according to the INTERMACS definitions)* |

*When there is a series of publications relevant to the same trial, the data relevant to the study protocol and/or major analysis were included.

6MWT, six-minute walk test; BTT, bridge-to-transplant; DT, destination therapy; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; HF, heart failure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVAD, left ventricular assist device; NYHA, New York Heart Association; OMM, optimal medical management, RCT, randomised controlled trial; SF-36,36-Item Short Form Survey; VAS, Visual Analogue Scale.

*PASC queried whether evidence from LVADs other than the HeartMate 3™ would be beneficial to assess the comparative safety and effectiveness of LVAD as DT in the assessment report even though those older generation LVADs are currently not used in Australian clinical practice. PASC was interested in understanding if there were significant differences in the efficacy and safety that would warrant excluding evidence for other VADS. The applicant's clinical expert indicated that there are large differences in earlier devices compared to the new generation HeartMate 3™. The applicant also claimed there were problems and issues identified with the earlier VAD devices particularly the HeartWare VAD. Furthermore, comparative evidence related to HeartMate 3™ and any other new generation VAD are not available to date. PASC accepted the applicant's rationale for the assessment to be limited to evidence relevant to the HeartMate 3™ LVAD.*

Evidence is available for the cost-effectiveness of HeartMate 3™ compared to medical therapy using a model-based economic evaluation from a UK perspective (Lim et al., 2022). The model inputs were from the literature, mainly from the MOMENTUM 3 trial for the device arm and the REMATCH and ROADMAP trials for the medical therapy. This study was an indirect comparison as the common comparator of these studies was the HeartMate II device. The main outcome measure used is the quality-adjusted life-year (QALY), and the cost-effectiveness was assessed in terms of cost per QALY gained (Lim et al., 2022).

Furthermore, several systematic reviews and cost-effectiveness analyses have been published related to the older generation LVADs, such as HeartMate VE LVAD and HeartMate II as DT for advanced HF patients (Chew et al., 2017; Neyt et al., 2014).

*PASC raised concerns over the high device cost (discussed in detail in the section: Proposal for public funding) and significant continuous support including specialist nurses require by the LVAD patients (discussed in detail in the section: Intervention). PASC considered that these costs should be captured in the economic evaluation, in addition to the cost of the procedure to insert.*

## Proposal for public funding

Insertion of VAD for BTT, BTC and BTR but not DT is currently funded under MBS items 38615 and 38618. This application proposed amendment to MBS items 38615 and 38616 (and the associated explanatory note TN.8.67) to include VAD for DT in patients who are ineligible for cardiac transplantation.

The applicant proposed amendments are available in MSAC 1749 Application PICO Set, Table 7 on page 17 of 32. The applicant proposed amendments included using 'durable VAD' instead of 'left or right VAD' and the definition 'capable of providing mechanical circulatory support for at least six months' to ensure that items 38615 and 38618 are purely used for long-term use of VAD. However, these amendments would have affected the existing indications in MBS item 38615 and 38618, particularly with criteria (b) and (c) with existing MBS item codes for temporary circulatory support. The application also suggested considering a separate MBS item for the indication of DT alone if the amendment of the existing MBS items 38615 and 38618 would create issues related to the existing indications. Noting the applicant was open to new MBS item for VAD for DT and as these proposed amendments to MBS items 38615 and 38618 would impact existing indications for BTT, BTC and BTR in MBS items 38615 and 38618, the department proposed creation of new MBS items for insertion of VAD for DT (Table 10).

**Table 10: Department proposed new MBS items for insertion of LVAD for DT**

| **Category 3 – Therapeutic Procedures** |
|---|
| **MBS item xxxx**<br>Insertion of a left ventricular assist device (VAD) in the left side of the heart only, capable of providing mechanical circulatory support for at least six months, in a VAD Patient for use as:<br>(a) destination therapy in the management of a patient with refractory heart failure, despite optimal medical management including device use where appropriate, *with INTERMACS profile 1–4*, who is not eligible for cardiac transplantation.<br>other than a service associated with a service to which:<br>(b) item 11704, 11705, 11707, 11714, 18260, 33824, 38816, 38828 or 45503 applies.<br><br>Applicable once in a six month period<br>(H)<br>Multiple Operation Rule<br><br>(Anaes.) (Assist.)<br><br>Fee: $1,619.15 Benefit: 75% = $1,214.70<br><br>(See para TN.8.xx of explanatory notes to this Category) |
| **Explanatory Note TN.8.xx**<br>Item xxxx must be performed using open exposure or minimally invasive surgery which excludes percutaneous and transcatheter techniques unless otherwise stated in the item.<br>**VAD Patient**<br>A VAD Patient means a patient who, as a result of a VAD Case Conference, has been assessed as suitable for left VAD based on the following:<br>a) destination therapy in the management of a patient with advanced heart failure, despite optimal medical management including device use where appropriate, *with INTERMACS profile 1–4*, who is not eligible for cardiac transplantation.<br>A VAD Case Conference is a process by which:<br>(a) there is a team of 3 or more participants, where:<br>(i) the first participant is a cardiothoracic surgeon<br>(ii) the second participant is a specialist or consultant physician who does not perform a service described in item xxxx for the patient being assessed; and<br>(iii) the third participant is a specialist or consultant physician or VAD coordinator or intensive care clinician who does not perform a service described in item xxxx for the patient being assessed; and<br>(iv) the first participant will perform the VAD procedure<br>(b) the team assesses a patient's risk and technical suitability to receive the service described in item xxxx, taking into account matters such as:<br>(i) the patient's risk and technical suitability for a ventricular assist device implantation; and<br>(ii) the patient's cognitive function and frailty; and<br>(c) the result of the assessment is that the team makes a recommendation about whether or not the patient is suitable to receive the service described in item xxxx; and<br>(d) the particulars of the assessment and recommendation are recorded in writing. |

Source: Proposed by the department based on applicant proposed amendments to MBS items 38615 and 38618 and to reflect PASC advice that the proposed MBS item should be limited to single left VAD insertion for DT.

MBS items for 38615 and 38618 are for single left or right VAD insertion and biventricular left and right VAD insertion, respectively and are therefore similar in all indications and clauses except the fee. Similarly, two new proposed MBS items for VAD for DT were instead proposed for single left or right VAD insertion (proposed item xxxx) and biventricular left and right VAD insertion (proposed item yyyy – no longer shown per PASC advice below). Although the item descriptors are device agnostic, it is noted that the HeartMate 3™ is the only VAD indicated for DT currently included on the ARTG and is described as a Left Ventricular Assist System in the ARTG Summary 300895.

*PASC noted the application was seeking MBS listing for both single left or right VAD insertion for DT and biventricular left and right VAD insertion for DT, similar to the existing MBS items for VAD for BTT, BTC and BTR. However, PASC noted that the HeartMate 3™ device is listed on the ARTG as a left VAD and that the majority of the evidence for VAD as DT will come from the MOMENTUM 3 trial in which the HeartMate 3™ device was used. The applicant's clinical experts stated that managing patients with biventricular VAD (BiVAD) devices is challenging. As such, BiVAD use under the existing MBS item (in a different indication than DT) is only performed in select patients with high clinical need and ability to anatomically accommodate BiVAD insertion. The applicant's clinical experts considered that there is a clinical need but that the use of BiVAD as DT would be very rare. For the purpose of the assessment, PASC advised that the proposed MBS listing (and therefore the intervention description in the PICO) should be limited to single left VAD insertion for DT only given the only VAD for DT on the ARTG is the HeartMate 3™ device and the ARTG specifies the HeartMate 3™ as a left VAD (i.e., proposed item xxxx should specify insertion of LVAD as DT only and proposed item yyyy for biventricular VAD insertion for DT should be removed). Following the PASC meeting, PASC noted that MBS claims data for the existing VAD MBS items indicated that over the last 5 years, ~40% of VAD procedures were claimed under the BiVAD MBS item 38618. As such, PASC noted that BiVAD use may not be as rare as claimed by the applicant's clinical experts and reiterated that VAD as DT should be limited to single left VAD insertion for the reasons already stated.*

*PASC queried whether the proposed MBS item for LVAD as DT should specify an upper age limit. The applicant's clinical experts acknowledged that while age would be a consideration when an MDT considers a patient's eligibility for LVAD as DT, it would not be a sole determinant as other factors such as comorbidities and other psychosocial factors impact a patient's suitability for VAD as DT. Setting an age limit may be arbitrary and may exclude an otherwise suitable patient from being able to receive VAD as DT. PASC queried whether the proposed MBS item descriptor or explanatory note should include other exclusion criteria but considered this was not necessary as patients' eligibility for LVAD as DT would be assessed by the MDT, which would take into consideration absolute and relative exclusion criteria.*

Consistent with the application, the proposed population in the two proposed MBS items for insertion of VAD for DT, specify patients with advanced heart failure who are ineligible for cardiac transplantation with an INTERMACS profile of 1–4 (please see criteria (a) in xxxx proposed items in Table 10). However, adding restrictions based on the INTERMACS profiles for the decision on DT would filter advanced HF patients who may be eligible for LVAD as DT (Please see the section: Population for more details). Furthermore, MBS items 38615 and 38618 do not include any classification systems to denote eligibility.

*As noted in the 'Population' section of the PICO, PASC considered that the proposed population description (and therefore the MBS items) should specify "with INTERMACS profile 1-4" as shown in Table 10.*

*PASC noted the Department sought PASC advice on whether the proposed MBS item for LVAD for DT should use 'advanced HF' (as per the proposed items in Table 10*) *instead of 'refractory HF'. PASC considered that consistent terminology should be used and the proposed new MBS item for VAD as DT should be consistent with the existing MBS items for VAD.* Therefore, the wording 'refractory HF' is used in the proposed MBS descriptor in Table 10.

The application also suggested adding notes related to the 'VAD case conference' to the explanatory note TN.8.67. The application stated that this suggestion was based on consultation with four leading experts in managing patients with advanced HF and VAD implantation / cardiac transplantation. These notes were suggested to ensure appropriate patient selection for VAD implantation for DT and the decision of the VAD implantation to be determined via a VAD Case Conference (Please see the notes in the proposed MBS descriptor). These notes are currently not needed for the existing indications of MBS items 38615 and 38618.

However, the application stated that the clinician suggested these notes as expanding LVAD eligibility to those with DT warrants a decision be made by a multidisciplinary team.

Of note, the application did not provide the details of the four clinical experts who suggested the addition of VAD case conference to explanatory note and it is not clear whether it is in line with the current practice at Australian clinical setting for the treatment decision on VAD.

Furthermore, patients with INTERMACS profile 1 'crash and burn' require definitive intervention within hours, and INTERMACS profile 1-4 is the suggested population for DT in this application. Hence, adding these notes to the existing MBS items may require further consultations with the clinical experts. As the department has proposed creating new MBS items for VAD for DT, similarly a new explanatory note with guidance on VAD case conference specific to the proposed MBS items for VAD for DT has been suggested.

*PASC queried whether the MDT should include an intensive care clinician as suggested in the consultation feedback. The applicant's clinical experts agreed and stated that in their practice, intensive care clinicians are currently included in the MDT for assessing a patent's eligibility for transplantation and VAD. PASC considered the MDT explanatory note for VAD as DT should be amended to include an intensive care clinician.*

*PASC queried whether the MDT would include a patient or a patient representative. The applicant's clinical expert advised that MDT does not include the patient or a patient representative, but the patient is involved in the decision (i.e., would be an elective procedure) and all VAD and transplantation treatments are performed after obtaining informed consent.*

Of note, there is a possibility that patients may move from DT to BTT (e.g., due to marked improvement in functional class) or from BTT to DT (e.g., due to major VAD complications such as disabling stroke) (Atherton et al., 2018). Hence, international literature has discussions on whether to continue this nomenclature to denote LVAD implantation indications (Fukunaga & Rao, 2018).

As the application is relevant for the amendment of existing MBS items to include a new indication, no change is proposed to the fee for the existing MBS items. The application anticipated that the out-of-pocket costs to patients would be similar as per current VAD use on the MBS and estimated as a minimum amount of $404.89, reflecting 25% of the MBS fee for item 38615 (noting that for most patients, the out-of-pocket costs would likely exceed this).

The HeartMate 3™ Implant kit costs $95,000 (PL benefit for the device), and the applicants confirmed that the hospitals (or private health insurers if a private patient has private health insurance) would bear the device cost. Also, the application estimated the total overall cost per patient to be $243,942.56 including pre-implant, device, and procedural/recovery costs. This estimation was based on the patient-level micro-costing study for LVAD procedures in Australia (Prichard et al., 2020). Table 11 summarises the estimated total cost and cost breakdown per LVAD procedure.

**Table 11: estimated total cost per LVAD procedure.**

| | Median costs, AUD 2014 (Prichard et al., 2020) | Median costs inflated[a] to AUD 2023 | Total cost per implant | Reference/Calculation |
|---|---|---|---|---|
| Pre-implant cost: assessment and preparation of a patient for the LVAD procedure | $2,050 per diem | $2,444.14 per diem | $21,997.30 | (Prichard et al., 2020): Median pre-implant per diem cost inflated to 2023 prices cost × 9 days |
| Device Cost (2023) | | | $95,000 | 2023 PL benefit |
| Implant procedure and post- recovery costs (less cost of device) | $106,474.00 per implant | $126,945.26 per implant | $126,945.26 | (Prichard et al., 2020): Median cost (less 2014 device cost: ($209,474 - $103,000)) inflated to 2023 prices |
| Total cost | | | $243,942.56 | Sum of pre-implant, device and procedural/recovery costs |

Source: Table 1, p3 of the Attachment cost breakdown: MSAC application 1749 PICO Set
Abbreviations: LVAD, Left Ventricular assist device; PL, Prescribed List
Notes: [a]2014 to 2023 inflation index (Australian Institute of Health and Welfare, 2022)

### *Private health insurance*

The most recent generation LVAD, HeartMate 3™ implant kit and all associated devices (e.g., System controller, battery charger) are currently included on the Prescribed List of Medical Devices and Human Tissue products (PL) - formerly the Prostheses List - under subcategory 09.11 Implant Ventricular Assist System. The current benefit amount for 09.11.01 HeartMate 3™ Implant Kit is $95000.

## Summary of public consultation input

*PASC noted and welcomed consultation input from 5 organisations and 3 individuals, all of whom were health professionals. The 5 organisations that submitted input were:*

- Hearts4heart
- Private Healthcare Australia (PHA)
- Advanced Heart Failure and Cardiac Transplant Service, Fiona Stanley Hospital, Perth
- Central Adelaide Local Health Network, Royal Adelaide Hospital, Department of Cardiology
- Australian and New Zealand Society of Cardiothoracic Surgeons (ANZSCTS).

With the exception of Private Healthcare Australia (PHA) who were not supportive, the consultation feedback received was all supportive of public funding for insertion of durable ventricular assist device (VAD) for use as destination therapy. The consultation feedback raised a number of concerns, predominately in relation to the need to care for the device and lifestyle changes required and the flow on cost including the device cost if this application is listed on the MBS.

**Clinical need and public health significance**

The main benefits of public funding received in the consultation feedback included increased survival time, improved quality of life, and the potential to rehabilitate to the point of returning to work for patients with advanced heart failure. Royal Adelaide Hospital Department of Cardiology state that left VAD (LVAD) can change the options for patients whose ineligibility for cardiac transplantation requires a waiting time (such as treatment of a malignancy) and can render them to become transplant eligible in future.

The main disadvantages of public funding received in the consultation feedback included the surgical risks of VADs including bleeding, infection, stroke, the need to care for the device (driveline and battery management), responding to alarms, and the psychosocial impact and lifestyle adjustments needed by the patient and their carer. Private Healthcare Australia (PHA) state that there is potential for substantial out of pocket expenses to the patient. PHA stated that the requested MBS service fee is less than 1/75 of the cost of this procedure that would add over $100,000+ in direct cost to Private Health Insurers.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included comprehensive care by a multidisciplinary team including intensive care specialists, psychosocial support, dietician, exercise physiology and physiotherapy.

**Indication(s) for the proposed medical service and clinical claim**

The consultation feedback ranged from strongly disagreeing to strongly agreeing with the proposed population. Hearts4heart stated that the one year mortality is between 25% and 63% even with guideline directed medical therapy in the advanced heart failure population. Six consultation feedback surveys highlighted the importance of selecting suitable patients within the eligible population due to the ongoing self-care required for patients with a VAD.

The consultation feedback ranged from strongly disagreeing to strongly agreeing with the proposed comparators of guideline-directed medical therapy/optimal medical care, with three surveys noting that this includes palliative care.

The consultation feedback ranged from strongly disagreeing to strongly agreeing with the clinical claim. Almost all of the consultation feedback noted that there is good evidence to support the clinical claim, with two individuals noting that mechanical circulatory support (MCS) which includes VAD is standard therapy internationally.

PHA strongly disagree with the proposed population, comparator, and clinical claim, stating that they support the existing service descriptor, and do not support the expansion sought in this application which would result in low value care being funded.

**Cost information for the proposed medical service**

The consultation feedback ranged from strongly disagreeing to strongly agreeing with the proposed service descriptor. One individual advocated to include intensive care specialists in the VAD case conference team to assist in optimising perioperative management and mitigating potential risks.

The consultation feedback ranged from strongly disagreeing to strongly agreeing with the proposed service fee, with one individual noting it is in line with the current fee for MBS item code 38615. PHA strongly disagree with the proposed service fee, stating that private health insurers will be responsible for the device cost of $98,000 with no ability to debate funding due to the Private Health Insurance Act. PHA stated that no health authority globally have found destination therapy with VAD to be cost effective.

**Additional comments**

Two respondents highlighted that VADs are currently only implanted in the public sector due to association with transplant. One respondent considered new centres should be credentialled.

The Advanced Heart Failure and Cardiac Transplant Service at the Fiona Stanley Hospital in Perth and ANZSCTS stated that destination therapy implants should occur at transplant centres in Australia with the experience and multi-disciplinary resourcing to achieve good outcomes.

**Consumer Feedback**

Hearts4heart provided two consumer stories from patients who have had LVAD as destination therapy. The stories highlighted positive patient experiences including the return to daily activities of driving, gardening, and working, and longer life expectancy allowing more time with close family.

*PASC noted the feedback from PHA that raised multiple concerns particularly the high cost of the HeartMate 3™ device. The applicant did note the concerns raised by PHA and claimed that the evidence supports that this high-cost device is highly valuable in appropriately selected patients. The applicant did not agree with the level of concern raised by PHA and indicated that assessment of the financial impact will help provide perspective on the implications to the Australian Healthcare system including the Prescribed List.*

## Next steps

*PASC noted the applicant has elected to progress its application as an ADAR (Applicant Developed Assessment Report).*

## Applicant comment on the ratified PICO Confirmation

We welcome the PASC comments regarding access to DT for children and patients living in rural and remote parts of Australia. As stated by the clinical experts, access arrangements are in place should these groups require DT, with ongoing support systems in place for patients in rural and remote areas. Hence, equity of access to DT will be possible should the new service be implemented on the MBS.

We are aware that the MSAC prefer direct evidence of a proposed service vs current care, ideally in the form of a randomised controlled trial (RCT). We note two RCTs which would provide direct evidence relevant to this application – the AMBUVAD and SweVAD studies. Given the available evidence for HeartMate 3 in DT patients, it is reasonable to claim that there is no clinical equipoise regarding the effectiveness of HeartMate 3 vs. medical therapy in patients ineligible for cardiac transplantation.

The SweVAD study started in June 2016 – if MOMENTUM 3 data was available at this time (published in 2019), such a study may not have gained ethics approval. We are also aware that there have been challenges recruiting for this RCT - indicating the difficulties in conducting RCTs in this patient population. The AMBUVAD study started in 2021 – it is somewhat concerning that this study had ethics approval. We are aware that the SweVAD study has had challenges enrolling patients, which is reflective of the difficulties of recruiting patients who may prefer a VAD based on available data or who may prefer medical management due to concerns about VAD implantation and living with a VAD.

Considering that durable VAD therapy is effectively an ‘end-of-life’ treatment option that addresses an unmet need – and that the number of patients who would be treated is small – we are of the view that waiting for results of these RCTs would be unethical – as it would potentially delay access to patients who would benefit from durable VAD therapy (and these trials may never be completed).

The HeartMate 3 LVAD is the only LVAD currently available in Australia.

We note the PASC comment:

*Following the PASC meeting, PASC noted that MBS claims data for the existing VAD MBS items indicated that over the last 5 years, ~40% of VAD procedures were claimed under the BiVAD MBS item 38618. As such, PASC noted that BiVAD use may not be as rare as claimed by the applicant's clinical experts and reiterated that VAD as DT should be limited to single left VAD insertion for the reasons already stated.*

To suggest that BiVAD use in DT may not be as rare as claimed by the clinical experts is flawed logic - BiVAD use in BTT/BTC cannot be extrapolated to DT – the patient population/indication is different.

Although clinicians may use treatment with BiVAD as a temporary measure, in the case of DT both devices would remain with the patient for life – which requires more careful consideration of BiVAD use in DT). It has been demonstrated that in a DT population, only 4.1% had a right ventricular assist system (RVAS) due to right heart failure RHF (Goldstein 2020, supplement eFigure 6).

We welcome the feedback that was received during the public consultation and note:

*With the exception of Private Healthcare Australia (PHA) who were not supportive, the consultation feedback received was all supportive of public funding for insertion of durable ventricular assist device (VAD) for use as destination therapy.*

While we note PHAs concerns regarding the high cost of the device, there appears to be a misunderstanding: the current capacity for DT provisions means the number of patients treated per year will be very small. The health system capacity to perform VAD insertions for DT is very small. While individual VAD devices are high cost, the total costs to private health insurers will be lower than higher volume procedures e.g. knee replacements procedures.

PHAs comments that LVAD therapy is not supported by Health Technology Assessment is not accurate. Most HTAs predate the recent MOMENTUM 3 study. OHTAC support the use of LVAD for DT:

Ontario Health Technology Advisory Committee recommends that continuous-flow left ventricular assist devices (LVAD) be publicly funded as permanent therapy (also known as destination therapy) in patients with end-stage heart failure who are ineligible for heart transplantation.[1][2]

Addendum_ Ontario Clinical Guidelines - VAD for Destination Therapy 2017.pdf (giftoflife.on.ca)

We thank the PASC for their comments and look forward to progressing the application as an ADAR.

[1] http://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment/Reviews-And-Recommendations/Left-Ventricular-Assist-Devices-for-Destination-Therapy

[2] https://www.giftoflife.on.ca/resources/pdf/transplant/Addendum_ Ontario Clinical Guidelines - VAD for Destination Therapy 2017.pdf

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## Appendix 1:

**Table 12: Summary of ongoing studies relevant to the HeartMate 3™**

| Study | Study design type | Short description of research | Study ID | Status |
|---|---|---|---|---|
| LVAD Versus GDMT in Ambulatory Advanced Heart Failure Patients (AMBU-VAD) | RCT | BTT, BTC or DT patients will be randomised to HM3 or OMM, and assessed 12 months post implantation.<br>Expected sample = 92 | NCT04768322 | Status: recruiting<br>Expected completion: February 2027 |
| Swedish Evaluation of Left Ventricular Assist Device as Permanent Treatment in End-stage Heart Failure (SweVAD) | RCT | The primary objective is to compare survival between HM3 as DT and OMM in a Swedish end stage HF population ineligible for cardiac transplantation.<br>Expected sample = 80 | NCT02592499 | Status: recruiting<br>Expected completion: December 2025 |
| Prospective Multi-Center Randomized Study for Evaluating the EVAHEART®2 Left Ventricular Assist System (COMPETENCE) | RCT | The objective of the study is to evaluate the safety and effectiveness of the EVA2 by demonstrating non-inferiority to HM3 when used for the treatment of refractory advanced heart failure.<br>Expected sample = 399 | NCT01187368 | Status: recruiting<br>Expected completion: March 2024 |
| Evaluation of the Jarvik 2000 Left Ventricular Assist System With Post-Auricular Connector--Destination Therapy Study | RCT | The MC study will be prospective, dual-armed, non-blinded (open-label) and randomised, comparing a treatment group receiving the Jarvik 2000 LVAD with post-auricular connector to HM2 for DT.<br>Expected sample = 350 | NCT01627821 | Status: recruiting<br>Expected completion: December 2023 |

Source: Table 'Identify yet-to-be-published research that may have results available in the near future' of MSAC 1749 application PICO Set
Abbreviations: BTC, bridge to candidacy; BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device; MC, multicentre; OMM, optimal medical management; RCT, randomised controlled trial.
Notes: Included studies relevant for the HeartMate 3™ or DT and the study ID is based on the clinical trials.gov