Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1749 – Insertion of durable left ventricular assist device for use as destination therapy

Applicant: **Abbott Medical Australia Pty Ltd**

Date of MSAC consideration: **4-5 April 2024**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1.   Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing for the insertion of durable left ventricular assist device (LVAD) for destination therapy (DT) in the management of patients with refractory heart failure (HF) was received from the Abbott Medical Australia Pty Ltd by the Department of Health and Aged Care.

2.   MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC deferred its advice for public funding of insertion of durable LVAD for use as destination therapy for patients with refractory heart failure, despite optimal medical management (OMM), with an INTERMACS profile between 1-4 and who are not eligible for cardiac transplantation. MSAC considered that there was a high unmet clinical need in this group of patients who are on OMM with no other treatment alternatives as determined by a multidisciplinary team. MSAC considered that LVAD had superior effectiveness compared to the comparator (OMM), although considered the magnitude of this effect was uncertain due to limitations in the available evidence. MSAC raised concerns about whether the aftercare costs following LVAD implantation had been adequately captured in the economic and financial analyses, and considered that the resultant incremental cost-effectiveness ratio (ICER) and the financial impact may potentially be underestimated. MSAC deferred its advice and requested consultation be undertaken with Australian healthcare centres to obtain a more contemporary and informed estimate of the aftercare costs following LVAD implantation in Australia; and for the economic and financial analyses to be revised to incorporate the updated additional costs (particularly aftercare costs) associated with the proposed service. MSAC considered that the resubmission could proceed via the direct MSAC assessment pathway.

Consumer summary
This is an application from Abbott Medical Australia Pty Ltd requesting Medicare Benefits Schedule (MBS) listing for inserting a left ventricular assist device (LVAD) for destination therapy in the management of patients with refractory heart failure.

Heart failure is a chronic progressive condition where the ability of the heart to pump blood around the body is impaired. This can be caused by various diseases or conditions such as a heart attack. There are a number of stages of heart failure. Refractory heart failure, also known as end stage or advanced heart failure, is where the patient experiences persistent and |

progressive worsening in their heart function and symptoms despite receiving optimised medical treatment which mainly includes medicines. These patients often require frequent hospitalisation and have poor survival if they don't receive further specialised advanced treatments, such as a heart transplant. However, some patients with refractory heart failure cannot have a heart transplant for various reasons.

An LVAD is a battery-operated mechanical pump that can help pump the patient's blood from the heart to the body. A surgeon would insert the LVAD into the left lower heart chamber, called the left ventricle. Some patients may temporarily receive an LVAD while they are waiting for a heart transplant. However, this application is seeking public funding to insert an LVAD in patients with refractory heart failure who cannot have a heart transplant. For these patients, LVAD would be used as a permanent treatment and is thus called destination therapy.

Based on the available evidence, MSAC considered the use of an LVAD for destination therapy was less safe compared to the current standard of care (optimised medical treatment). This is because the insertion of the LVAD requires an open-heart, high-risk surgery that may cause unwanted events such as stroke, bleeding and infection. It is also possible that once inserted, the LVAD may not function properly and cause problems. Even with the safety concerns, MSAC considered that the LVAD could be beneficial to patients because they do not have any other treatment options, and without it, their condition might worsen more quickly. MSAC considered the device to be more effective than the current standard of care, as it can increase the number of years a patient is alive, reduce the number of hospitalisations and improve a patient's quality of life. MSAC thought the insertion of LVAD was probably good value for money, but MSAC did not have all the information it needed to make an informed decision. Some important costs regarding aftercare may be missing from the application and MSAC wanted more accurate information on the additional costs (especially aftercare costs) that are involved with the insertion and management of the device. MSAC requested that this information be brought directly to MSAC again so that it could assess whether inserting the LVAD is good value for money and also be better able to understand how much this would cost the Australian healthcare system.

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

MSAC deferred its decision on the proposed MBS listing for the insertion of a durable LVAD for destination therapy in the management of patients with refractory heart failure and who are not eligible for a heart transplant. MSAC considered the proposed intervention to be more effective than the current standard of care (optimal medical management) for the target patient population who have no other treatment alternatives. MSAC was not convinced that all the costs associated with the proposed service had been fully accounted for and requested more information, particularly regarding aftercare costs, to evaluate the cost-effectiveness of the proposed service and its total financial impact on the healthcare system.

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

MSAC noted that this application from Abbott Medical Australia Pty Ltd requested MBS listing for the insertion of a durable LVAD for use as DT in the management of patients with refractory HF, despite OMM, who are ineligible for cardiac transplantation.

MSAC noted that the HeartMate3 (HM3), the most recent third-generation magnetically levitated centrifugal-flow LVAD is the only LVAD indicated for DT included on the Australian Register of Therapeutic Goods (ARTG). HM3 is also listed on the Prescribed List of Medical Devices and Human Tissue Products (PL). MSAC further noted that the first and second generation LVADs, HeartMate XVE and HeartMate II respectively, are not listed on the ARTG, and while HeartWare, a

third generation LVAD is listed on the ARTG, it is no longer used in Australia due to safety concerns.

MSAC noted that insertion of ventricular assist devices in patients with refractory HF has already been listed on the MBS (since 1992) for other indications such as bridge to transplant and bridge to transplant candidacy (MBS items 38615 and 38618).

MSAC noted the PICO and the clinical management algorithm. MSAC noted that the proposed population are those with refractory HF despite OMM, with an INTERMACS profile between 1-4 who are not eligible for cardiac transplantation due to frailty or co-morbidities, as determined by a multidisciplinary team. The proposed comparator is OMM. MSAC noted that OMM can include quadruple pharmacological treatments with renin-angiotensin-system inhibitors, beta blockers, mineralocorticoid receptor antagonists and sodium glucose cotransporter 2 (SGLT2) inhibitors; and non-pharmacological interventions such as pacing, angioplasty, hemofiltration and ventilation. MSAC noted from the Applicant Developed Assessment Report (ADAR) that patients with refractory HF on OMM had a 2-year survival rate of 8%. While MSAC raised that this data was non-contemporaneous, MSAC considered the prognosis for this population to be very poor and emphasised that there was a high clinical need for the proposed patient population who are on OMM with no other treatment alternatives, as determined by a multidisciplinary team.

MSAC noted the consumer and organisational input for this application, the majority of which was supportive. Of note, while the feedback stated advantages include prolonging survival and improved patient quality of life, the feedback also noted this intervention comes with a significant aftercare commitment from the patient and carer.

MSAC noted the proposed MBS item descriptor and considered that the multidisciplinary team is critical to the selection of eligible patients who are likely to benefit from the proposed service. MSAC noted that patient selection is to be done by an experienced team that already has the capability to offer LVAD as DT at cardiac specialist centres. MSAC considered restrictions based on frailty unwarranted, as eligible patients would have already been rejected for a heart transplant due to frailty, and frail patients are likely to benefit most from the insertion of an LVAD due to the consequent increase in their cardiac output. MSAC considered that the MBS item for the initial insertion of the LVAD should be restricted to once per lifetime, with a separate MBS item created and designated for re-implantation, if required by the patient. MSAC noted that the proposed MBS fee was $1,677.85 (75% benefit $1,258.40) and considered that this should include all intra-operative imaging required during implantation. MSAC considered it unnecessary to specify that the LVAD should only be inserted into the left ventricle of the heart, as there is minimal evidence (if any) for the insertion of LVAD into the right ventricle for use as DT. MSAC also noted that the Medical Devices and Human Tissue Advisory Committee would need to be informed that no price premium for the HM3 has been requested or considered within the assessment, and that the price relied on for the economic and financial analyses includes the price for any accessories associated with use of the principal device.

MSAC noted that the clinical evidence was based on indirect treatment comparisons derived from three randomised controlled trials (RCTs; MOMENTUM3, Slaughter et al., 2009, REMATCH) and one observational study (ROADMAP). MSAC considered the available clinical evidence to be of high risk of bias resulting in low confidence of the magnitude of benefit, due to several reasons including the absence of any direct comparisons between HM3 and OMM, data from the REMATCH trial being non-contemporary, and differences in study characteristics that affect the transitivity of the indirect treatment comparisons including differences in intent of treatment (i.e. DT), INTERMACS scores, demographics of participants and clinical endpoints. MSAC further noted that there are two ongoing RCTs in the recruitment phase (SweVAD and AMBU-VAD) specifically aimed at directly assessing the efficacy and safety of HM3 compared to OMM.

MSAC considered the ADAR's claim that the device has inferior safety compared to OMM reasonable. However, MSAC considered that the safety analysis was limited by deficiencies in the clinical evidence (as described above) and by the inconsistent/under-reporting of adverse events and hospitalisations in the trials. MSAC noted that according to the ADAR, the suspected HM3 device malfunction rate was 22% at five years post implantation.

Regarding comparative effectiveness, MSAC noted that based on a naïve comparison presented in the ADAR between the LVAD arm of the MOMENTUM3 trial and the OMM arm of the REMATCH trial, the overall survival of HM3 vs OMM was 76.7% vs 8% at two years. MSAC considered that LVAD had superior effectiveness compared to OMM, although considered the magnitude of this effect was uncertain due to limitations in the available evidence, including the absence of any direct evidence comparing HM3 and OMM and the use of OMM data that were not contemporaneous (the REMATCH trial was conducted prior to 2001). Furthermore, MSAC considered that implantation of an HM3 resulted in improved functional status (as assessed by New York Heart Association [NYHA] Functional Classification scores and six-minute walking test [6MWT] scores) and quality of life outcomes (as assessed by EQ-5D VAS), yet reiterated uncertainty surrounding the magnitude of the incremental effects due to the limitations in the available data.

MSAC noted that the economic evaluation was a cost-utility analysis that used a partitioned survival model (PSM) with two health states of alive and dead. MSAC noted that ESC had queried whether the use of a PSM was appropriate. The applicant's pre-MSAC response provided a justification highlighting that the PSM allows more transparent extrapolation of survival curves from the trial data and a state transition model (to model survival via intermediate clinical endpoints) was not required. MSAC considered this justification provided by the applicant appropriate given the severity of the patient population's clinical condition and that transitions via intermediate health states were not required.

MSAC noted that the ADAR's base case ICER based on a 40-year time horizon was $redacted per quality adjusted life year (QALY) gained. MSAC agreed with ESC that a time horizon of 40 years with a baseline age of 65 years is unreasonable as it extends beyond the average life expectancy and considered a time horizon of 10 years more appropriate. MSAC noted the applicant's pre-MSAC response that the ICER increased to $redacted per QALY gained with a time horizon of 10 years (Table 12). MSAC noted that the model time horizon was not a major driver of the ICER.

MSAC noted that the multivariate sensitivity analysis conducted by the assessment group utilised a hazard ratio option in the economic model provided with the ADAR, which increased the ICER to $redacted. MSAC considered the use of the hazard ratio approach inappropriate as this resulted in 54% of LVAD patients dying within one month of the end of the trial, yielding an effective time horizon of 5.1 years (and not 10 years as claimed by the assessment group). MSAC agreed with the applicant's pre-MSAC response that these modified survival curves are not clinically plausible. MSAC therefore considered it unlikely that the true ICER was as high as $redacted per QALY gained. However, MSAC agreed with ESC that the survival curves for each arm presented in the ADAR are uncertain. That is, the modelled survival for LVAD extends beyond the average life expectancy and may overestimate the survival benefit. In addition, MSAC agreed with ESC's concern that the OMM effectiveness data used do not represent current clinical practice (for example, it did not consider use of SGLT2 inhibitors, which may delay the need for LVAD), and this will have favoured LVAD. The applicant's pre-MSAC response highlighted that there is no long-term evidence that use of SGLT2 inhibitors in these patients increases survival. MSAC accepted that there are no long-term data on overall survival with SGLT2 inhibitor treatment, but considered that if contemporary OMM delays the need for an LVAD, then it is clinically plausible to infer that the effectiveness of OMM has improved which would in turn reduce the modelled incremental improvement in overall survival with LVAD.

MSAC noted that the data sources for the baseline utility values were from different populations. MSAC agreed with ESC that utility values should be from the same source. Consequently, MSAC considered that using the utility values from Sato, 2022[1] of 0.64 (OMM all cycles; LVAD first cycle) and 0.79 (all other LVAD cycles) would have been more appropriate.

MSAC noted ESC's concerns that the approaches to including event and deterioration costs were very different in the two arms, making it difficult to reconcile the different approaches used for each arm, thus adding uncertainty in the economic results. The pre-MSAC response provided justification for the different costs, which MSAC accepted. MSAC noted that the ADAR model applied a 1% annual risk of pump thrombosis resulting in replacement from year 2 onwards. However, MSAC agreed with ESC and considered that device replacement for other reasons that might be plausible within the proposed 10 year time horizon should also be considered. MSAC further raised concerns about whether aftercare costs post LVAD implantation had been adequately captured in the economic analysis. This was based on anecdotal information that aftercare costs were possibly up to $redacted per LVAD patient in the first year after implantation. Therefore, MSAC considered that the ICER may potentially be underestimated and requested further information on additional costs of the service (especially aftercare costs) to be sourced from Australian hospitals that provide LVAD insertion for other indications, as well as secondary and tertiary healthcare centres that may be involved in patient post-management, to better inform the economic assessment.

Overall, MSAC considered it more likely that the ICER was around $redacted/QALY, after respecifying the base case (Table 12; that is assuming a time horizon of 10 years; OMM disease-related costs in the first cycle of $0; utility values of 0.64 and 0.79; but not using the alternative hazard ratio approach from the applicant's economic model). However, this may not fully incorporate the aftercare costs and does not include device replacement costs for reasons other than in relation to pump thrombosis.

MSAC noted that insertion of LVAD is currently limited to specialised quaternary centres in Australia and hence capacity constraints would be expected to have a large effect on the likely number of LVAD for DT procedures. Due to the highly specialised nature of the LVAD procedure, MSAC considered it unlikely that these procedures would be performed outside of quaternary hospitals. The ADAR estimated the expected number of LVAD for DT procedures, when accounting for capacity constraints as redacted in year 1, increasing to redacted in year 6. MSAC considered that while these estimates were based on unverifiable expert opinion, they were likely the best estimates currently available. Based on these capacity constraints, the financial impact to the MBS was estimated to be $redacted in year 1 increasing to $redacted in year 6. MSAC noted that in the absence of any capacity constraints the ADAR estimated that redacted LVAD procedures for DT would be performed per year, which increased the financial impact to the MBS to $redacted each year for six years. MSAC highlighted that the largest budget impact would be to private health insurers. With capacity constraints limiting uptake to redacted LVAD for DT procedures annually, the estimated total cost to private health insurers was $redacted million per year. In the absence of capacity constraints, with up to redacted procedures annually, the estimated annual total cost to private health insurers would increase to $redacted. MSAC noted that the ADAR estimated the cost to the private health insurers per LVAD for DT procedure would be $redacted, with the most significant component of this being the cost of the LVAD which is listed on the PL. MSAC considered that the true aftercare costs were unknown and potentially underestimated in the ADAR. MSAC acknowledged that this device would only be used in high-

[1] Sato T, Kobayashi Y, Nagai T, et al. Long-term preservation of functional capacity and quality of life in advanced heart failure patients with bridge to transplant therapy: A report from Japanese nationwide multicenter registry. Int J Cardiol 2022; 356: 66-72. 20220323. DOI: 10.1016/j.ijcard.2022.03.044.

risk patients who are likely to have high healthcare costs regardless of the management approach, but MSAC considered the uncertainty in whether the aftercare costs had been adequately captured to be a significant issue and required further information before MSAC could finalise its decision.

Overall, MSAC considered that there was a high unmet clinical need for LVAD as DT in the proposed patient population and that the available clinical evidence supported the claimed superior effectiveness compared to OMM, but that the magnitude in benefit was uncertain. However, MSAC deferred its advice due to concerns that the economic and financial evaluations may have significantly underestimated the aftercare costs.

MSAC requested the applicant:

- undertake consultation with Australian hospitals that currently provide LVAD for other indications, as well as secondary and tertiary healthcare centres that may be involved in patient post-management, to obtain a more contemporary and informed estimate on the aftercare costs (broken down by payer) and the format of aftercare services (e.g. in-person, telehealth and/or hybrid) following LVAD implantation in Australia
- in addition to presenting after care costs broken down by payer, consultation should be undertaken to describe how private patient funding will be addressed (for aftercare) by the public hospitals (the only sites where this service is currently available), where the majority of the aftercare is provided by nursing and allied health staff (that have no MBS items available)
- re-specify the base case to use a time horizon of 10 years, apply OMM disease related costs in the 1st cycle of $0, apply a utility value of 0.64 for the 1st cycle in both the OMM and the LVAD arms and in subsequent cycles of the OMM arm, and a utility value of 0.79 in the subsequent cycles of the LVAD arm, and further revise this base case to incorporate device replacement costs (other than for pump thrombosis) and aftercare costs informed by the above consultation with Australian hospitals
- update the financial analysis to incorporate the updated additional costs (as above) associated with the proposed service
- provide a proposed MBS item descriptor for the re-implantation of an LVAD for DT.

MSAC considered that the resubmission could proceed via the direct MSAC assessment pathway.

4.   Background

MSAC has not previously considered LVAD for DT. However, LVAD implantation is listed on the MBS for other populations, including use as bridge to transplant (BTT) and bridge to candidacy (BTC) via MBS items 38615 and 38618. These items have been listed on the MBS since 31 October 1992.

5.   Prerequisites to implementation of any funding advice

Over the years, different types of LVADs have been introduced and there are two LVADs (i.e., HeartMate 3 (HM3) and HeartWare) registered in the Australian Register of Therapeutic Goods (ARTG).

HM3 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 ARTG (ARTG 300895) and Prescribed List of Medical Devices and Human Tissue Products (PL). HeartMate XVE (HM XVE) and HeartMate II (HM2) are first generation and second generation LVADs, respectively, that are not included on the ARTG (MSAC 1749 Ratified PICO, pg15).

The indication for the HM3 LVAD as per the ARTG entry (ARTG ID: 300895) is:

- "The HeartMate 3 Left Ventricular Assist System is intended to provide long term hemodynamic support in patients with advanced, refractory left ventricular heart failure. It is intended either for temporary support, such as a bridge to cardiac transplantation (BTT), or as permanent destination therapy (DT). The HeartMate 3 is intended for use inside or outside the hospital".

The HeartWare (ARTG 181875) is no longer listed on the PL or used globally, though it was registered in ARTG. Medtronic ceased the distribution and sale of the HeartWare LVAD 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 LVAD System patients as compared to those who receive other commercially available LVADs[2].

6. Proposal for public funding

A new MBS item for the insertion of LVAD for DT has been proposed with the fee informed by MBS item 38615 (insertion of a left or right ventricular assist device). Although the item descriptor is device agnostic, it is noted that the HM3 is the only LVAD indicated for DT currently included on the ARTG. The proposed item is provided in Table 1 and is consistent with MSAC 1749 Ratified PICO.

Table 1: Proposed MBS item with edits based on ESC advice

Category 3 – Therapeutic Procedures
MBS item xxxx Insertion of a durable left ventricular assist device (LVAD) capable of providing mechanical circulatory support for at least six months, in an LVAD Patient for use as: (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; and (b) other than a service associated with a service to which item 11704, 11705, 11707, 11714, 18260, 33824, 38816, 38828 or 45503 applies. (H) Includes all associated intra-operative imaging. Multiple Operation Rule (Anaes.) (Assist.) Fee: $1,677.85 Benefit: 75% = $1,258.40 (See para TN.8.xx of explanatory notes to this Category)
Explanatory Note TN.8.xx Item xxxx must be performed using open exposure or minimally invasive surgery which excludes percutaneous and transcatheter techniques unless otherwise stated in the item. LVAD Patient An LVAD Patient means a patient who, as a result of an LVAD Case Conference, has been assessed as suitable for LVAD based on the following:

---

[2] Medtronic. Left ventricular assist device (LVAD) for advanced heart failure services and support for HVAD patients. Urgent product update https://www.medtronic.com/us-en/patients/treatments-therapies/ventricular-assist-device.html (2021, accessed 22 June, 2023).

Category 3 – Therapeutic Procedures

(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.
 	
An LVAD Case Conference is a process by which:
(a) there is a team of 4 or more participants, where:
   (i) the first participant is a cardiothoracic surgeon
   (ii) the second participant is an intensive care specialist or consultant physician who does not perform a service described in item xxxx for the patient being assessed; and
   (iii) the third participant is a transplant cardiologist who does not perform a service described in item xxxx for the patient being assessed; and
   (iv) the fourth participant is a transplant coordinator or LVAD coordinator; and
   (v) the first participant will perform the LVAD procedure
(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:
   (i) the patient's risk and technical suitability for a ventricular assist device implantation; and
   (ii) (ii) the patient's cognitive function and frailty; and
(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
(d) the particulars of the assessment and recommendation are recorded in writing.

Source: Table 9, p54 of MSAC 1749 ADAR+ in-line commentary
Abbreviations: DT = Destination therapy; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device; TN = technical notes
Notes: 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 LVAD insertion for DT.

As per MSAC 1749 Ratified PICO confirmation, an explanatory note detailing LVAD case conference to ensure appropriate patient selection and decision for LVAD implantation for DT was proposed in the Applicant Developed Assessment Report (ADAR) (Please see the notes in the proposed MBS descriptor in Table 1). Although MBS items for existing indications (LVAD for BTT/BTC) do not specify a LVAD case conference with multi-disciplinary team (MDT), the ADAR stated that LVAD case conference to assess a patient suitability for LVAD for existing indications is well-established and align with current clinical practice.

The commentary noted that PASC considered the MDT explanatory note for LVAD as DT should be amended to include an intensive care clinician (MSAC 1749 Ratified PICO, pg32). The proposed MDT explanatory note has not been updated to include an intensive care clinician. However, the commentary noted that the LVAD case conference as per the proposed MBS item note does not stipulate the specialty of the physicians, meaning an intensive care clinician can form part of the MDT.

As noted in MSAC 1749 Ratified PICO confirmation, the insertion of LVAD is currently limited to specialised quaternary centres, which may place capacity and capability constraints to deliver the service in Australia. As noted by the applicant in MSAC 1749 Ratified PICO confirmation, continued liaison with local experts will determine the necessity for accreditations of centers and clinicians to ensure appropriate patient care in the expanded patient population intended for treatment with LVAD as DT.

7. Population

The proposed population are patients with advanced HF despite optimum medical management (OMM), with INTERMACS profile 1–4, who are not eligible for cardiac transplantation and in whom LVAD is used as DT (i.e., final therapy).

According to the ADAR's clinical management algorithms, continuation of OMM is the current management option for the proposed population.

The ADAR claimed that reimbursement of LVAD as DT would provide the proposed patient population with an alternative therapy option. The ADAR also noted that some patients with advanced HF are not eligible for either cardiac transplantation nor LVAD as DT (e.g., unstable psychosocial support). Therefore, the OMM remains as an option in the proposed management algorithm along with palliation.

As per the clinical algorithms in MSAC 1749 Ratified PICO confirmation, LVAD as DT is in addition to OMM. This is because, the post-operative management and long-term follow-up of patients implanted with LVAD as DT include pharmacological management, mainly antithrombotic therapy, blood pressure control and supportive care. OMM, including angiotensin-converting enzyme (ACE) inhibitors, beta-blockers (BB), mineralocorticoid receptor antagonists (MRAs) and diuretics, may be continued for some patients as these drugs may reduce morbidity and mortality in patients with LVAD implants[3]. Ongoing management requires check-ups with the patient's HF specialist. The patient is also seen by the broader LVAD team, including the LVAD coordinator, cardiologist, a surgical team, a nutritionist, a physiotherapist, a psychiatrist, and a general practitioner. It is unclear whether the ongoing management costs have been adequately captured in the ADAR.

Consistent with advice from PASC, the clinical algorithms also depict the 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 ventricular assist device complications such as disabling stroke a patient may be no longer suitable for heart transplantation)[4]. Of note, the ADAR provided scenario analysis in the economic evaluation based on proportion of patients who receive heart transplant among the patients implanted with LVAD as DT (i.e., move from DT to BTT).

8. Comparator

The ADAR proposed optimum medical management (OMM) as the comparator to insertion of LVAD as DT. OMM is also referred to as guideline directed medical therapy (GDMT) or optimal medical therapy (OMT). The commentary noted the comparator is consistent with MSAC 1749 ratified PICO confirmation.

The comparator mainly includes pharmacological management and the relevant drugs for the OMM[5] listed under the pharmaceutical benefits scheme (PBS) such as ACE inhibitors.

Non-pharmacological treatments may include ventilation, pacing, angioplasty, extracorporeal membrane oxygenation (ECMO) or hemofiltration. Most patients will receive pharmacological

---

[3] Colvin BM, Coons JC and Beavers CJ. Guideline-Directed Heart Failure Therapy in Patients after Left Ventricular Assist Device Implantation. The VAD Journal 2021; 7: e2021712. DOI: https://doi.org/10.11589/vad/e2021712.

[4] Atherton JJ, Sindone A, De Pasquale CG, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018. Heart Lung Circ 2018; 27: 1123-1208. 2018/08/06. DOI: 10.1016/j.hlc.2018.06.1042.

[5] National Heart Foundation of Australia. Clinical fact sheet - pharmacological management of chronic heart failure with reduced left ventricular ejection fraction (HFrEF). 2018. National Heart Foundation of Australia.

therapy, but these other interventions are likely to be used in addition to pharmacological management for the most severely affected patients as required.

9.   Summary of public consultation input

Consultation input was received from five (5) professional organisations, one (1) consumer organisation and five (5) individuals, all of whom were medical specialists.

The 6 organisations that submitted input were:
- Advanced Heart Failure and Cardiac Transplant Service, Fiona Stanley Hospital, Perth
- Australian and New Zealand Society of Cardiothoracic Surgeons (ANZSCTS)
- Central Adelaide Local Health Network, Royal Adelaide Hospital, Department of Cardiology
- Hearts4heart
- Private Healthcare Australia (PHA)
- Victorian Heart Hospital.

The consultation feedback received was largely supportive of public funding for insertion of durable ventricular assist device (VAD) for use as destination therapy.

Benefits
The feedback indicated the benefits of the intervention include:
- For patients who are not eligible for a heart transplant, LVAD therapy is effective for prolonging life.
- Improved quality of life, with the potential to rehabilitate patients with advanced heart failure to the point of returning to work.
- Equity of care for advanced heart failure patients.
- From a health system perspective, a reduction in heart failure hospitalisations.

Disadvantages
The feedback suggested the following disadvantages:
- Surgical risks of VADs including bleeding, infection and stroke.
- The treatment is invasive and the device requires a substantial commitment by the patient and carer, including battery management, driveline management, responding to alarm codes, compliance with medications (including oral and subcutaneous anticoagulants), post-op rehab and attending regular clinic appointments.
- The ongoing maintenance and tasks associated with the device can limit independence and impose restrictions on daily routines and social interactions, which may have a psychosocial impact.

Other feedback
The feedback highlighted that appropriate patient selection was identified as critical for good outcomes. The feedback considered that clinicians involved in patient selection have experience with this complex patient cohort and can identify with reasonable accuracy, candidates who would benefit the most from this procedure.

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 specialist, physiotherapists, dieticians, pharmacists, psychologists and social workers.

The feedback noted that Advanced Heart Failure and Transplantation programs already have the infrastructure present to support patients with Destination VAD therapy. With an increasing number of patients eligible for Destination VAD, there may be a requirement to increase the highly specialised support services necessary.

10. Characteristics of the evidence base

No randomised controlled trials (RCTs) providing direct head-to-head comparison of HM3 versus OMM were identified. However, direct evidence for HM2 (2nd generation device) versus OMM (ROADMAP) and HM XVE (1st generation device) versus OMM (REMATCH) was identified. Therefore, to enable a comparison between the most current generation (HM3) and OMM, the ADAR presented three indirect treatment comparisons (ITCs) based on four studies: MOMENTUM 3 RCT[6], REMATCH RCT[7], Slaughter (2009)[8] RCT and the ROADMAP[9] observational study (Figure 1).

Two-step Bucher ITC (REMATCH): an ITC of HM3 versus OMM constructed via HM2 and HM XVE (via Slaughter 2009; REMATCH and MOMENTUM 3), reflecting a comparison of OMM with INTERMACS profiles 1–3 (98% of the MOMENTUM 3 population was INTERMACS 1–4; other trials predominantly INTERMACS 1–3).

One-step Bucher ITC (ROADMAP): an ITC of HM3 versus OMM constructed via HM2 (based on MOMENTUM 3 and the ROADMAP observational study). Notably, most of the MOMENTUM 3 participants had INTERMACS profile 1–4 whereas ROADMAP included INTERMACS profiles 4–7. However, the availability of subgroup data from ROADMAP of patients with INTERMACS profile 4 allowed comparison of HM3 vs OMM in patients with the least severe HF within the target MBS population (INTERMACS 4) which have received OMM treatment in the modern setting.

Naïve comparison: a naïve comparison of HM3 (from MOMENTUM 3, 98% of the patients were INTERMACS 1–4) versus OMM (primarily from REMATCH, suggestive of INTERMACS profiles 1–3) was presented for survival to allow for a visual comparison of overall survival (OS) curves of HM3 and OMM in a matched population.
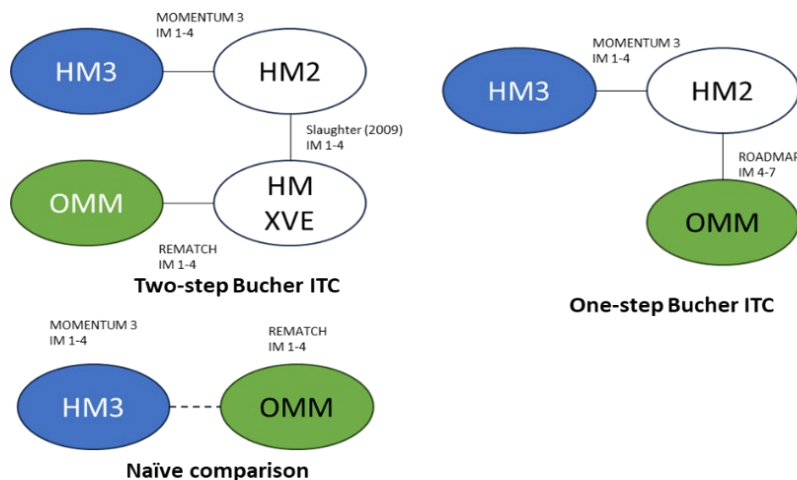
Figure 1: Network diagram of trials included to inform the indirect comparisons of HM3 vs OMM

Source: Figure 5, Pp63-64 of MSAC 1749 ADAR+ in-line commentary

[6] Mehra MR, Uriel N, Naka Y, et al. A Fully Magnetically Levitated Left Ventricular Assist Device - Final Report. N Engl J Med 2019; 380: 1618-1627. 20190317. DOI: 10.1056/NEJMoa1900486.

[7] Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001; 345: 1435-1443. DOI: 10.1056/NEJMoa012175.

[8] Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009; 361: 2241-2251. 20091117. DOI: 10.1056/NEJMoa0909938.

[9] Estep JD, Starling RC, Horstmanshof DA, et al. Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP). The Journal of Heart and Lung Transplantation 2015

MOMENTUM 3 trial was a nonblinded, prospective, multicentre, RCT comparing HM3 LVAD with HM2 LVAD in 1028 patients with advanced HF, including BTT, BTC and DT indications (DT indication represented 61%). MOMENTUM 3 extended, is a multicentre, non-randomised follow-up study that included participants who received HM3 or HM2 in MOMEMTUM 3 and were still receiving LVAD support at two to five years after the implant was conducted. The OS data specific to the DT population is used in the ITC. Of note, safety data specific to DT that was amenable for inclusion in the ITC was not available, hence safety analysis was performed on the entire trial population. The ADAR claimed that the intention to treat (ITT) population from MOMENTUM 3 is considered applicable to the DT population as subgroup analyses of the primary composite outcome of survival free of a debilitating stroke or reoperation to replace the pump by therapy intent showed no statistically significant difference across BTT, BTC, and DT. However, that composite primary outcome of the MOMENTUM 3 trial was different from the outcome used in the ITC (i.e., OS).

REMATCH (HM XVE vs OMM) and Slaughter (2009) (HM2 vs HM XVE) were nonblinded, multicentre, RCT of 129 and 200 patients eligible for LVAD as DT respectively. While REMATCH and Slaughter (2009) did not specify INTERMACS profiles, the ADAR inferred from eligibility and baseline characteristics that patients were predominantly INTERMACS 1–3.

The ROADMAP trial was a prospective, multicentre, non-randomised, controlled observational trial of 200 patients maintained on OMM or received a HM2 LVAD with DT intent (INTERMACS 4–7), considered of moderate bias in the context of being a non-randomised study. Given OMM patients were less ill (i.e., having higher INTERMACS scores), any comparison of survival and safety from ROADMAP could be biased against LVAD (which has a flow on effect biasing the ITC of HM3 vs OMM against HM3).

A summary of the key features of the trials of LVAD used to provide clinical evidence is reported in Table 2.

Table 2: Key features of the included evidence comparing LVAD with OMM

References	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
MOMENTUM 3 NCT02224755	1028	RCT, MC, OL	Low	Advanced HF candidates for LVAD as BTT (22.8%), BTC (16.2%) or DT (61.0%), symptomatic (NYHA class III/IV); INTERMACS 1-7 (97.6% INTERMACS 1-4)	Primary: composite of survival free of a debilitating stroke or reoperation to replace the pump Powered secondary: pump replacement Other secondary: survival, device malfunctions, rehospitalisations, functional status, QoL, AEs	Yes
MOMENTUM 3 Extended FU NCT03982979	1020	Observational, MC, non-randomised	NA	Participants who received HM3 or HM2 in MOMEMTUM 3 and were still receiving LVAD support at the 2-year FU.	Composite endpoint: survival to transplant, recovery, or LVAD support free of debilitating stroke or reoperation to replace the pump 5 years post implant Others: patient outcomes (transplant, explant/permanent deactivation, or withdrawal), survival, AEs, functional status	
Slaughter (2009) NCT00121485 [a]	200	RCT, MC, OL	Low	Patients with advanced HF who were ineligible for heart transplantation and whose HF was refractory to OMM.	Primary: composite of survival free of a debilitating stroke or reoperation to replace the pump Powered secondary: survival, pump replacement, device malfunctions, rehospitalisations, functional status, QoL, AEs	No
ROADMAP NCT01452802	200	Prospective, MC, non-randomised, controlled, observational study	Moderate	Advanced HF not dependent on IV inotropes, candidates for LVAD as DT, symptomatic (NYHA class III/IV); INTERMACS 4–7	Primary: Composite of survival and improvement ≥75 m in 6MWD at 12 months Secondary: survival, functional status, QoL, AEs	Yes
REMATCH	129	RCT, MC, OL	Low	End-stage HF, contraindicated to heart transplantation, candidates for LVAD as DT, symptomatic (NYHA class IV); peak VO2 <12 ml/kg/min or IV inotrope dependent (i.e., ~INTERMACS 2-3 equivalent a)	Primary: death from any cause Secondary: hospitalisation, functional status, QoL, AEs	Yes

Source: Table 12, Pp 67-68 of MSAC 1749 ADAR+ in-line commentary

Abbreviations: AEs = adverse events; BTT = bridge to transplant; BTC = bridge to candidacy; DT = destination therapy; FU = follow-up; HF = heart failure; HM2 = HeartMate 2; HM3 = HeartMate 3; INTERMACS profiles = The Interagency Registry for Mechanically Assisted Circulatory Support; IV = intravenous; LVAD = left ventricular assist device; MC = multicenter; NA = not applicable; NCT = National Clinical Trial; NYHA = New York Heart Association; OL = open label; OMM = optimal medical management; QoL = quality of life; RCT = randomised controlled trial; VO2 = volume of oxygen; 6MWD = six-minute walk distance

Notes: a INTERMACS profiles were not an eligibility criterion in the trial, however 'IV inotrope dependent' indicates patients with INTERMACS profiles 1-3.

The risk of bias assessment of the MOMENTUM 3, Slaughter (2009) and REMATCH RCTs was based on the National Heart, Lung, and Blood (NHLBI) Study Quality Assessment Tools for RCTs, and the commentary considered that all three studies were of low risk of bias. The assessment of the ROADMAP comparative study was based on the NHLBI Study Quality Assessment Tools for Observational Cohort and Cross-Sectional Studies, and the commentary considered that the study was associated with a moderate risk of bias.

The commentary noted there were significant differences across the four trials in terms of the intended use of LVAD and INTERMACS profiles. The MOMENTUM 3 trial included indications other than DT, 61% of MOMENTUM 3 patients were included in the effectiveness analysis based on indication for DT, the other three studies only included patients based on indication for DT. The REMATCH study did not report INTERMACS profiles; however, the whole cohort were classified as NYHA Class IV and assumed to be INTERMACS 1-3. In the Slaughter (2009) study, INTERMACS profiles were not an eligibility criterion in the trial. Patients on inotrope therapy within 30 days were excluded from the ROADMAP study. Therefore, only a subgroup of the ROADMAP trial population (36.1% of HM2 arm and 61.2% of the OMM arm), that were INTERMACS 4 patients, were relevant for this application.

The definitions of the clinical outcomes varied across the four included studies. For example, in the MOMENTUM 3 trial, the primary endpoint was a composite of survival free of a debilitating stroke or reoperation to replace the pump. Debilitating stroke was defined as a stroke with Modified Ranking Score (MRS) ≥3 assessed at 60 days after the event in accordance with adjudication from the MOMENTUM 3 Clinical Events Committee. The primary outcome in the ROADMAP study was a composite of survival and improvement ≥75 m in 6-minutes walking test (6MWT) at 12 months. In the REMATCH trial, the primary end point was death from any cause. Secondary endpoints in the studies included OS, days of hospitalisation and adverse events, functional status as assessed by New York Heart Association (NYHA) class, and quality of life (QoL) as assessed by the 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36).

The selected socio demographic and clinical baseline characteristics of the included studies are provided in Table 3.

Table 3: Baseline characteristics in MOMENTUM 3, Slaughter (2009), REMATCH and ROADMAP

	MOMENTUM 3		Slaughter (2009)		REMATCH		ROADMAP	
	HM2	HM3	HM2	HM XVE	HM XVE	OMM	HM2	OMM
N (whole cohort)	**512**	**516**	**134**	**66**	**68**	**61**	**97**	**103**
N (population and indication of interest)[a]								
DT	310/512 (60.5%)	317/516 (61.4%)	134/134 (100.0%)	66/66 (100.0%)	68/68 (100.0%)	61/61 (100.0%)	97/97 (100.0%)	103/103 (100.0%)
INTERMACS 1-4 patients indicated for DT	INTERMACS 1-3 259/304 (85.2%) INTERMACS 4-7 45/304 (14.8%)[b]	INTERMACS 1-3 265/316 (83.8%) INTERMACS 4-7 51/316 (16.1%)[b]	INTERMACS profiles not reported.	INTERMACS profiles not reported.	INTERMACS profiles not reported. Suggestive of INTERMACS 1-3.	INTERMACS profiles not reported. Suggestive of INTERMACS 1-3.	INTERMACS 4 35/97 (36.1%)	INTERMACS 4 63/103 (61.2%)
Baseline demographics								
Age, years								
Mean (SD)	60 (12.0)	59 (12.0)	62 (12)	62 (12)	66 (9.1)	68 (8.2)	NR	NR
Median (range)	63 (21-84)	62 (18-83)	64 (26-79)	65 (29-81)	NR	NR	64 (55-70) [a]	66 (54-74) [a]
Mean (SD)	28.8 (6.2)	29.2 (6.3)	28.2 (5.5)	28.2 (5.6)	NR	NR	NR	NR
Median (range)	27.9 (14.9-53.1)	28.5 (12.8-54.0)	NR	NR	NR	NR	29 (25-33) [a]	28 (23-37) [a]
Males	419/512 (81.8%)	411/516 (79.7%)	108/134 (80.6%)	61/66 (92.4%)	53/68 (77.9%)	50/61 (82.0%)	75/97 (77.3%)	71/103 (68.9%)
Females	93/512 (18.2%)	105/516 (20.3%)	26/134 (19.4%)	5/66 (7.6%)	15/68 (22.1%)	11/61 (18.0%)	22/97 (22.7%)	32/103 (31.1%)
Ischaemic aetiology, n/N (%)	240/512 (46.9%)	216/516 (41.9%)	88/134 (65.7%)	45/66 (68.2%)	53/68 (77.9%)	42/61 (68.9%)	58/97 (59.8%)	51/103 (49.5%)
Non-Hispanic	485/512 (94.7%)	486/516 (94.2%)	NR	NR	NR	NR	NR	NR
Hispanic,	27/512 (5.3%)	29/516 (5.6%)	NR	NR	NR	NR	NR	NR
Subject refused to provide	0/512 (0.0%)	1/516 (0.2%)	NR	NR	NR	NR	NR	NR
White	367/512 (71.7%)	342/516 (66.3%)	101/134 (75.4%)	48/66 (72.7%)	NR	NR	72/97 (74.2%)	60/103 (58.3%)
Black or African American	120/512 (23.4%)	145/516 (28.1%)	24/134 (17.9%)	16/66 (24.2%)	NR	NR	21/97 (21.6%)	35/103 (34.0%)
Asian	3/512 (0.6%)	8/516 (1.6%)	NR	NR	NR	NR	0/97 (0.0%)	0/103 (0.0%)
Native Hawaiian or other Pacific Islander	4/512 (0.8%)	0/516 (0.0%)	NR	NR	NR	NR	0/97 (0.0%)	0/103 (0.0%)
Other	18/512 (3.5%)	21/516 (4.1%)	9/134 (6.7%)	2/66 (3.0%)	NR	NR	4/97 (4.1%)	8/103 (7.8%)
Intended use, INTERMACS Profile and NYHA Class								

	MOMENTUM 3		Slaughter (2009)		REMATCH		ROADMAP	
	HM2	HM3	HM2	HM XVE	HM XVE	OMM	HM2	OMM
Intended use, n/N (%)								
BTT	121/512 (23.6%)	113/516 (21.9%)	0/134 (0.0%)	0/66 (0.0%)	0/68 (0.0%)	0/61 (0.0%)	0/97 (0.0%)	0/103 (0.0%)
Possibly BTT: likely be eligible	45/512 (8.8%)	45/516 (8.7%)	0/134 (0.0%)	0/66 (0.0%)	0/68 (0.0%)	0/61 (0.0%)	0/97 (0.0%)	0/103 (0.0%)
Possibly BTT: moderate likelihood	33/512 (6.4%)	32/516 (6.2%)	0/134 (0.0%)	0/66 (0.0%)	0/68 (0.0%)	0/61 (0.0%)	0/97 (0.0%)	0/103 (0.0%)
Possibly BTT: unlikely to be eligible	3/512 (0.6%)	9/516 (1.7%)	0/134 (0.0%)	0/66 (0.0%)	0/68 (0.0%)	0/61 (0.0%)	0/97 (0.0%)	0/103 (0.0%)
DT	310/512 (60.5%)	317/516 (61.4%)	134/134 (100.0%)	66/66 (100.0%)	68/68 (100.0%)	61/61 (100.0%)	97/97 (100.0%)	103/103 (100.0%)
INTERMACS Profile, n/N (%)								
1	18/512 (3.5%)	11/516 (2.1%)	NR	NR	NR	NR	0/97 (0.0%)	0/103 (0.0%)
2	146/512 (28.5%)	156/516 (30.2%)	NR	NR	NR	NR	0/97 (0.0%)	0/103 (0.0%)
3	251/512 (49.0%)	272/516 (52.7%)	NR	NR	NR	NR	0/97 (0.0%)	0/103 (0.0%)
4	82/512 (16.0%)	67/516 (13.0%)	NR	NR	NR	NR	35/97 (36.1%)	63/103 (61.2%)
5	6/512 (1.2%)	5/516 (1.0%)	NR	NR	NR	NR	21/97 (21.6%)	29/103 (28.2%)
6	4/512 (0.8%)	3/516 (0.6%)	NR	NR	NR	NR	35/97 (17.8%)	10/103 (9.7%)
7			NR	NR	NR	NR	0/197 (0.0%)	2/103 (1.9%)
Not provided	5/512 (1.0%)	2/516 (0.4%)	NR	NR	NR	NR	0/97 (0.0%)	0/103 (0.0%)
NYHA Class, n/N (%)								
Class IIIA	0/512 (0.0%)	0/516 (0.0%)	27/134 (20.1%)	11/66 (16.7%)	0/68 (0.0%)	0/61 (0.0%)	0/97 (0.0%)	0/103 (0.0%)
Class IIIB	20/512 (3.9%)	36/516 (7.0%)	4/134 (3.0%)	1/66 (1.5%)	0/68 (0.0%)	0/61 (0.0%)	47/97 (48.5%)	77/103 (74.8%)
Class IV	490/512 (95.7%)	477/516 (92.4%)	95/134 (70.9%)	43/66 (65.2%)	68/68 (100.0%)	61/61 (100.0%)	50/97 (51.5%)	26/103 (25.2%)
Baseline 6MWD, m								
Mean (SD)	128 (155.0)	136 (160.0)	NR	NR	NR	NR	NR	NR
Median (range)	NR	NR	NR	NR	NR	NR	182 (122-259)[c]	219 (157-269)[c]

Source: Table 88, Pp296-300 of MSAC 1749 ADAR+ in-line commentary

Abbreviations: 6MWD = 6-minute walk distance; BMI = body mass index; BTT = bridge to therapy; DT = destination therapy; HM = HeartMate; HM XVE = HeartMate vented electric left ventricular assist device; INTERMACS = The Interagency Registry for Mechanically Assisted Circulatory Support; LV = left ventricular; NR = not reported; NYHA = New York Heart Association; OMM = optimal medical management; SD = standard deviation.

Notes: [a] Population and indication of interest (i.e., patients received LVAD as DT and INTERMACS profile 1-4)

[b] 84% of DT patients implanted with HM3 had INTERMACS 1-3 and 16.1% had INTERMACS 4-7. Amongst the INTERMACS 4-7, the majority were INTERMACS 4. Therefore, ADAR approximate the whole DT population to INTERMACS 1-4 during the analysis. [c] Result is median (IQR).

Certain patient characteristics vary across the included studies. For example, the study population in REMATCH study is older (mean age 66 years in the HM XVE arm and 68 years in the OMM arm) compared to the other studies (mean age ranged from 59 years to 66 years). ROADMAP study included higher percentage of females in both arms compared to other studies. The Slaughter (2009) study, HM XVE arm included 7.6% female patients whereas MOMENTUM 3, REMATCH and HM2 arm of the Slaughter (2009) studies included around 20% females. Patients with NYHA stage IV was highest in REMATCH (100%) compared with MOMENTUM 3 (ranged between 92-95%) and Slaughter, 2009 (ranged between 65%-71%).

Only MOMENTUM 3 reported the breakdown of cardiovascular history by specific diagnoses and the other 3 trials had minimal record. Patients with history of defibrillator was recorded in MOMENTUM 3, Slaughter (2009) and ROADMAP, where latter had the lowest proportion (69.1% HM2 and 64.1% OMM in ROADMAP) and Slaughter (2009) had the most proportion (82.8% HM2 and 78.8% HM XVE).

The OMM in the comparator arm of the REMATCH RCT refers to the management of patients with end-stage HF based on guidelines developed by the medical committee, with the aim of minimising HF symptoms and optimising organ perfusion. Notably, REMATCH was reported in 2001 and therefore the contemporary management of advanced HF is different to the OMM in the REMATCH study[3]. Based on the recent 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guideline for the management of HF, GDMT (i.e., OMM) for HF with reduced ejection fraction (HFrEF) consists of new medication classes including sodium-glucose cotransporter-2 inhibitors (SGLT2i) which provide further survival benefit compared to old treatment regimens.[10,11]

The baseline medications were not consistent across all 4 trials. The prescription of ACE inhibitors was more common in ROADMAP (68.0% HM2 and 76.7% OMM) but minimal in MOMENTUM 3 (23.2% HM2 and 22.9% HM3) and Slaughter (2009) (32.1% HM2 and 33.3% HM XVE). Similar trend was observed for beta-blockers, where about half of the patients in MOMENTUM 3 and Slaughter (2009) were prescribed a beta-blocker compared with 86.6% in the HM2 group in ROADMAP. While above differences in study characteristics can affect the transitivity of the ITC, it is difficult to assess the impact of these variations on the ITC results.

11. Comparative safety

The main safety outcomes presented in the ADAR were all cause adverse events (all cause AEs) and serious adverse events (SAEs). These safety outcomes are presented as single or composite outcome measures based on following ITC.

- Two-step Bucher ITC: Common SAEs in the As-Treated population at two years (MOMENTUM 3/Slaughter (2009)/REMATCH) were compared, noting that Slaughter (2009) reported AEs without specifying if these were serious or not.
- One-step Bucher ITC: Common AEs in the As-treated population at two years (MOMENTUM 3 and ROADMAP)
- Naïve ITC: SAEs in MOMENTUM 3 and REMATCH at two years

[10] McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2022; 24: 4-131. DOI: 10.1002/ejhf.2333.

[11] Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022; 145: e895-e1032. 20220401. DOI: 10.1161/CIR.0000000000001063.

The analyses were performed on the events per patient year (EPPYs) with resultant relative risk estimates and associated confidence intervals.

However, the ADAR interpreted the comparative safety based on the two-step Bucher ITC of HM3 vs OMM (via HM2 and HM XVE). The evidence profile for the safety ITC of HM3 vs OMM in DT is presented in Table 4.

Table 4: Evidence profile table for the safety ITC of HM3 vs OMM in DT

Outcome -	No. of studies & design	HM3 vs HM XVE (via HM2) [95%CI]	OMM vs HM XVE [95%CI]	IEE: HM3 vs OMM RR [95%CI]	Quality	Importance
Two-step Bucher ITC (REMATCH)						
Bleeding, 2 years	ITC of RCT K=3; N=1349	0.428 [0.283, 0.647]	0.11 [0.03, 0.43]	4.051 [0.929, 17.676] (p=0.0627)	⊕⊕⊕⊙ MODERATE [a]	A higher rate of bleeding was experienced by HM3 patients based on 2 years data from MOMENTUM 3 vs OMM.
Bleeding, 5 years data from MOMENTUM 3	ITC of RCT K=3; N=1349	0.388 [0.258, 0.583]	0.11 [0.03, 0.43]	3.67 [0.84, 15.60]; (p=0.083)	⊕⊕⊙⊙ LOW [a,b]	A higher rate of bleeding was experienced by HM3 patients based on 5 years data from MOMENTUM 3 vs OMM.
Stroke, 2 years	ITC of RCT K=3; N=1349	0.248 [0.102, 0.6]	0.27 [0.03, 1.23]	0.905 [0.115, 7.104] (p=0.9247)	⊕⊕⊕⊙ MODERATE [a]	A lower rate of stroke was experienced by HM3 patients based on 2 years data from MOMENTUM 3 vs OMM.
Stroke, 5 years data from MOMENTUM 3	ITC of RCT K=3; N=1349	0.217 [0.09, 0.522]	0.27 [0.03, 1.23]	0.793 [0.101, 6.204] (p=0.8254)	⊕⊕⊙⊙ LOW [a,b]	A lower rate of stroke was experienced by HM3 patients based on 5 years data from MOMENTUM 3 vs OMM.
Sepsis, 2 years	ITC of RCT K=3; N=1349	0.347 [0.196, 0.614]	0.49 [0.24, 1.01]	0.703 [0.282, 1.756] (p=0.4541)	⊕⊕⊕⊙ MODERATE [a]	A lower rate of sepsis was experienced by HM3 patients based on 2 years data from MOMENTUM 3 vs OMM.
Sepsis, 5 years data from MOMENTUM 3	ITC of RCT K=3; N=1349	0.337 [0.192, 0.591]	0.49 [0.24, 1.01]	0.684 [0.275, 1.697] (p=0.4121)	⊕⊕⊙⊙ LOW [a,b]	A lower rate of sepsis was experienced by HM3 patients based on 5 years data from MOMENTUM 3 vs OMM.

Source: Table 48, p181 of MSAC 1749 ADAR+ in-line commentary

Abbreviations: CI = confidence interval; DT = destination therapy; EPPY = events per patient year; HM2 = HeartMate 2; HM3 = HeartMate 3; HM XVE = vented electric left ventricular assist device; HR = hazard ratio; IEE = indirect estimate of effect; ITC = indirect treatment comparison; OMM = optimal medical management; RCT = randomised controlled trial; RR = relative risk.

Notes:

⊕⊕⊕⊕ **High quality:** Very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊙ **Moderate quality:** Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕⊙⊙ **Low quality:** Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⊕⊙⊙⊙ Very low quality: Very little confidence in the effect estimates: The true effect is likely to be substantially different from the estimate of effect.

[a]The starting grade for the two-step Bucher ITC is HIGH, on the basis of including three RCTs with low risk of bias and based on a well matched population; rated down to MODERATE due to the two-step indirect nature of the comparison.

[b]The Extended follow-up study was further rated down because the survival analysis censored subjects at Year 2 who were at sites that declined participation, transferred, were unable to be reached, or who were unable to participate for other reasons. Missing outcome data from the extended-phase study were filled in with additional data (occurrence of death, transplant, device explant, including dates of these outcomes, within 5 years after implant) from the sponsor's device tracking database as permissible by state regulations.

The two-step Bucher ITC showed that the rate of bleeding was numerically higher with HM3 vs OMM (Table 4). The ADAR claimed that the magnitude of the RR from the comparison of HM XVE vs OMM from REMATCH (RR = 9.47) compared with the estimate derived from the indirect comparison of HM3 vs OMM (RR = 4.05) highlights that HM3 showed a device improvement compared to HM XVE in relation to bleeding. This could be possible, but the magnitude of improvement is hard to assess given the differences in the characteristics of the studies as outlined above. The observed rates for the stroke (24-month endpoint) in the two-step ITC was 0.90 (95% CI: 0.11, 7.10) and in the one-step 0.58 (95% CI: not estimated). Sepsis at the 24-month endpoint for the two-step ITC was 0.70 (95% CI: 0.28, 1.76), numerically in favour of HM3.

In the Momentum 3 RCT adverse events were not reported based on the intend use for HM3 and HM2 arms separately. Therefore, the data from MOMENTUM 3 RCT for common SAEs were related to the entire cohort not only DT patients relevant for this application.

Overall, the commentary considered the safety analysis was limited by the indirect nature of the comparison and the lack of safety data. The differences in the characteristics of the trials such as the intent of treatment (i.e., DT), INTERMACS scores, follow-up duration, and differences in the demographics of participants affect the transitivity of the studies in the ITC. Furthermore, underreporting of worsening HF and rehospitalisation outcomes in the MOMENTUM 3 and REMATCH trials did not allow for ITCs of HM3 versus OMM.

12.   Comparative effectiveness

The ADAR presented the effectiveness evidence based on following indirect comparisons.

- Two-step Bucher ITC: OS in the As-Treated DT population at two and five years (MOMENTUM 3/Slaughter (2009)/REMATCH)
- One-step Bucher ITC: OS in the As-Treated DT population at two years (MOMENTUM 3 and ROADMAP)
- Naïve ITC: OS in the As-Treated DT population in MOMENTUM 3 and ROADMAP, and OS in the ITT population in REMATCH, at two years, functional status as assessed by NYHA Classification and 6-minute walk distance (6MWD) in MOMENTUM 3 and ROADMAP and QoL as assessed by EQ-5D visual analogue score (VAS) in MOMENTUM 3 and ROADMAP.

Overall survival

Table 5 reports the evidence profile for the effectiveness ITC of HM3 vs OMM in DT based on OS. Figure 2 presents an overlay of the OS curves for patients eligible for LVAD as DT in the MOMENTUM 3 (98% of the patients were INTERMACS 1–4), ROADMAP (INTERMACS 4) and REMATCH trials (suggestive of INTERMACS 1–3).

Table 5: Evidence profile table for the effectiveness ITC of HM3 vs OMM

Outcome	No. of studies and study design	HM3 vs HM XVE (via HM2) HR [95%CI]	OMM vs HM XVE HR [95%CI]	IEE: HM3 vs OMM HR [95%CI]	Quality	Importance
Two-step Bucher ITC (REMATCH)						
OS, 2 years	ITC of RCTs K=3; N=953	0.47 [0.27, 0.83]	1.92 [1.28, 2.94]	0.24 [0.12, 0.49]; p=0.0001	⊕⊕⊕⊙ MODERATE [b]	The OS was statistically significantly greater for HM3 vs OMM over 2 years in a well matched population. However, the OMM in REMATCH was not contemporary.
OS, 5 years	ITC of RCTs K=3; N=953	0.38 [0.22, 0.64]	1.92 [1.28, 2.94]	0.20 [0.10, 0.38]; p<0.00001	⊕⊕⊙⊙ LOW [b, d]	The OS was statistically significantly greater for HM3 vs OMM over 5 years; in a well-matched population. However, the OMM in REMATCH was not contemporary.
One-step Bucher ITC (ROADMAP)						
Outcome	No. of studies and study design	HM3 vs HM2	OMM vs HM2	IEE: HM3 vs OMM	Quality	Importance
OS, 2 years	ITC of RCT and non-RCT; K=2; N=1228	0.87 [0.63, 1.20]	2.30 [1.50, 3.70]	0.38 (0.22, 0.66); p=0.0006	⊕⊕⊙⊙ LOW [a]	The OS was statistically significantly greater for HM3 vs OMM over 2 years; however, the ITC is biased against HM3 given ROADMAP participants were less ill than MOMENTUM 3.
OS, 2 years: IM 4	ITC of RCT and non-RCT; K=2; N=722	0.87 [0.63, 1.20]	3 [1.6, 5.5]	0.29 [0.15, 0.58]; p=0.0005	⊕⊕⊙⊙ LOW [a]	The OS was statistically significantly greater for HM3 vs OMM in IM 4 patients over 2 years; with the analysis better matched in severity.
OS, 5 years	ITC of RCT and non-RCT; K=2; N=1228	0.7 [0.55, 0.9]	2.3 [1.5, 3.7]	0.35 [0.15, 0.84]; p=0.0181	⊕⊙⊙⊙ VERY LOW [a, d]	The OS was statistically significantly greater for HM3 vs OMM over 5 years; however, the ITC is biased against HM3 given ROADMAP participants were less ill than MOMENTUM 3.
OS, 5 years: IM 4	ITC of RCT and non-RCT; K=2; N=722	0.7 [0.55, 0.9]	3 [1.6, 5.5]	0.233 [0.12, 0.454]; p<0.0001	⊕⊙⊙⊙ VERY LOW [a, d]	The OS was statistically significantly greater for HM3 vs OMM in IM 4 patients over 5 years; with the analysis better matched in severity.
Naïve ITC (REMATCH)						
Outcome	No. of studies and study design	HM3	OMM	IEE: HM3 vs OMM	Quality	Importance

| OS, 2 years (naïve ITC) | RCTs K=2; N=753 | KM estimate = 76.7% | KM estimate = 8% | RD = 68.7% NNT = 2 | ⊕⊙⊙⊙ VERY LOW[c] | A higher proportion of HM3 vs OMM patients survived at 2 years. For every two patients treated with HM3 one additional patient would survive. |

Source: Table 47, Pp174-175 of MSAC 1749 ADAR+ in-line commentary

Abbreviations: CI=confidence interval; HM2=HeartMate 2; HM3=HeartMate 3; HM XVE=vented electric left ventricular assist device; HR, hazard ratio; IM=INTERMACS; ITC=indirect treatment comparison; KM=Kaplan Meier; OMM=optimal medical management; OS=overall survival; RCT= randomised controlled trial; RD=risk difference; RR=relative risk.

Notes:

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⊕⊙⊙⊙ Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

a The starting grade for the one-step Bucher ITC is MODERATE (instead of HIGH), on the basis of including one RCT and one well conducted observational study (in which plausible confounders increase our confidence in the estimated effect; see Appendix D). The one-step Bucher ITC is rated down one level for indirectness due to differences in populations and due to the indirect nature of the comparison.

b The starting grade for the two-step Bucher ITC is HIGH, on the basis of including three RCTs with low risk of bias and based on a well matched population; rated down to MODERATE due to the two-step indirect nature of the comparison.

c Based on a naïve ITC using individual arms from separate well conducted studies.

d The Extended FU study was further rated down because the survival analysis censored subjects at Year 2 who were at sites that declined participation, transferred, were unable to be reached, or who were unable to participate for other reasons. Missing out come data from the extended-phase study were filled in with additional data (occurrence of death, transplant, device explant, including dates of these outcomes, within 5 years after implant) from the sponsor's device tracking database as permissible by state regulations.

Source: ITC HM3 vs OMM.xlsx (Attachment 2.3).
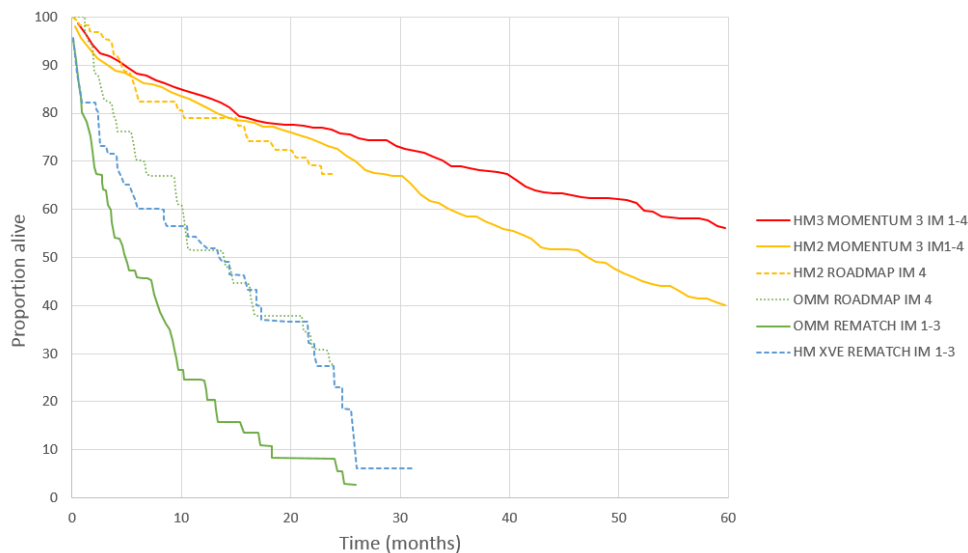
Figure 2: Overlay of OS curves informing the naïve ITC in the DT populations with INTERMACS 1-4 (MOMENTUM 3, ROADMAP and REMATCH)

Source: Figure 47, p162 of MSAC 1749 ADAR+ in-line commentary
Abbreviations: HM2 = HeartMate 2; HM3 = HeartMate 3; HM XVE = HeartMate vented electric left ventricular assist device; IM= INTERMACS; OMM = optimal medical management.
Note: red indicates HM3, yellow indicates HM2, blue indicates HM XVE, green indicates OMM.

The ADAR presented effectiveness analysis based on OS of all four trials (Table 5). However, the commentary noted that there were differences in the definition of OS across the included trials. The ADAR used all-cause mortality and event free survival interchangeably for the OS. In the MOMENTUM 3 trial, REMATCH trial and Slaughter (2009) trial, OS data was based on the actuarial survival, which was defined as all-cause mortality in as-treated population. In contrast, the OS data from ROADMAP was based on event-free survival of as-treated population, defined as patients received LVAD as DT free of urgent heart transplant or explant, and OMM patients free of LVAD or urgent heart transplant.

Further, the ADAR claimed that the naïve comparison (Figure 2) was consistent with the results from the Bucher ITCs as patients who received HM3 had the highest OS whereas patients receiving HM2 in the MOMENTUM 3 and ROADMAP trials had similar OS. The ADAR also claimed, due to a sicker patient population and older device, patients in both the HM XVE (blue line) and OMM (green lines) arm had poorer survival when compared to the MOMENTUM 3 and ROADMAP trials. The KM estimates from the survival curves show that 76.7% of HM3 patients eligible for LVAD as DT were alive at 24 months compared with 8% in the OMM arm from REMATCH, reflecting a magnitude of effect of 68.7% in favour of HM3. By 25 months, almost 100% of OMM patients in REMATCH were dead. The ADAR claimed that the naïve comparisons, therefore, support conclusions from two-step and one-step ITCs whereby the incremental benefit in term of OS in favour of LVAD is increasing relative to OMM with newer generation devices and lower baseline INTERMACS profiles. The commentary considered that this is reasonable to assume regarding the new LVAD generations, however, this comparison ignores the improvement in survival associated with newer agents used in OMM in general. The OMM management in this population is not contemporary and OS may not reflect current practice.

Of note, although the ADAR presented ITCs, the naïve comparison of Momentum 3 HM3 and Rematch OMM KM curves (Figure 2) informed the OS between treatment and control arms in the economic model.

Secondary effectiveness outcomes

Functional status

Insufficient data was available to perform anchored ITCs for functional status. Table 6 provides the naïve indirect comparisons of functional status as assessed by NYHA classification and 6MWD.

Table 6: Naïve indirect comparison of functional status as assessed by NYHA classification and 6MWD

Comparison	Timepoint	MOMENTUM 3 HM3 vs HM2	ROADMAP HM2 vs OMM
NYHA classification[a], %	Baseline (pre-implant)	I: **0%** vs 0% II: **0%** vs 0% III: **7%** vs 4% IV: **93%** vs 96%	I: 0% vs **0%** II: 0% vs **0%** III: 46% vs **77%** IV: 54% vs **22%**
	Post (12 months)	I: **33%** vs 31% II: **48%** vs 50% III: **17%** vs 17% IV: **2%** vs 2%	I: 25% vs **0%** II: 52% vs **29%** III: 21% vs **60%** IV: 2% vs **11%**
	Post (24 months)	I: **28%** vs 24% II: **51%** vs 52% III: **16%** vs 20% IV: **4%** vs 3%	I: 23% vs **11%** II: 46% vs **26%** III: 29% vs **59%** IV: 2% vs **4%**
6MWD, baseline (pre-implant)		91 (0, 950) vs 54 (0, 847)	187 (NR) vs 214 (NR)
Metres walked, median (range)	Post (12 months)	335 (0, 1275) vs 353 (0, 1035)	263 ($p < 0.001$) vs 249 ($p = 0.325$)[b]
	Post (24 months)	335 (0, 1236) vs 350 (0, 3429)	337 m ($p < 0.05$) vs 249 (remain same)[b]

Source: Table 27, p128; Table 45, p172 of MSAC 1749 ADAR+ in-line commentary
Abbreviations: 6MWD = 6-minute walk distance; HM2 = HeartMate 2; HM3 = HeartMate 3; NA = not available; NR = not reported; NYHA = New York Heart Association; OMM = optimal medical management
Notes: [a] NYHA classification: Class I = no limitation of physical activity; Class II = slight limitations of normal physical activity, comfortable at rest; Class III = marked limitation of physical activity, no symptoms at rest; Class IV = symptoms of heart failure at rest or on any physical activity
[b] p-value was reported for the difference from the baseline

In the REMATCH trial, NYHA classification was reported as median NYHA class in each arm, and the 6MWD was not an endpoint in the trial. Therefore, no comparison can be made with respect to the REMATCH trial. Overall, there was a shift in distribution for NYHA classification. For HM3 patients (in MOMENTUM 3), the majority of patients shifted from class III/IV to class I/II at one- and two years post implant (i.e., 0% of patients had class I/II, whereas approximately 80% of patients had class I/II over two years). For OMM patients in (in ROADMAP), less patients were in class I/II (approximately 35% over two years) at one and two years follow-up when compared to patients receiving HM3.

In terms of 6MWD, greater improvements were seen in patients with HM3 compared to OMM (244 m vs 35 m at one year). Of note, the difference in the baseline of the MOMENTUM 3 and REMATCH studies may be a potential reason for the lower change from baseline in OMM patients compared to the HM3 e.g., the improvement was higher in HM3 group because the baseline was 91m, compared to the baseline of 214m in OMM group.

QoL

Insufficient data was available to perform anchored ITCs for functional status. The only commonly assessed, comparable QoL outcome in MOMENTUM 3 and ROADMAP was EQ-5D VAS at one- and two-year follow-up. However, given differences in reporting, a Bucher ITC could not be constructed. Therefore, a naïve indirect comparison of QoL as assessed by EQ-5D VAS was presented (Table 7). Similar results were seen at one and two-year follow-up in patients receiving LVADs (both HM3 and HM2) in MOMENTUM 3 and ROADMAP (~27 point improvement). Patients receiving OMM had poorer improvement in EQ-5D VAS (~9 point improvement). The REMATCH trial did not report any EQ-5D VAS result; therefore, no comparison can be made with this trial.

Table 7: Naïve indirect comparison of QoL as assessed by EQ-5D VAS

Comparison		MOMENTUM 3	ROADMAP
		HM3 vs HM2	HM2 vs OMM
Baseline (pre-implant)		**50** vs 48	NR
Change from baseline in EQ-5D VAS	Post (12 months)	**26** vs 26	29 vs **10**
	Post (24 months)	**26** vs 27	27 vs **8**

Source: Table 46, p173 of the MSAC 1749 ADAR+ in-line commentary
Abbreviations: HM2 = HeartMate 2; HM3 = HeartMate 3; NR = not reported; OMM = optimal medical management; QoL = quality of life; VAS = visual analogue scale.

Of note, EQ-5D VAS is a self-rated overall assessment of their health and provides complementary information on patients' views about their own health. However, it is subjective (the EQ-VAS labels mean different things to different people; hence, commentary considered it may affect the comparison of scores)[12].

The ADAR claimed that the results of the Bucher ITCs and naïve comparison supports the superior efficacy of HM3 relative to OMM in INTERMACS 1–4 patients with respect to OS. The commentary considered this claim reasonable, however, it also considered the magnitude of effectiveness uncertain given the indirect nature of the comparison and transitivity issues arising from the differences in the characteristics of the studies included in the ITCs. Furthermore, OMM used in the REMATCH trial is different to the contemporary OMM recommended in current guidelines (e.g., SGLT2i), which has been shown to improve survival in patients with advanced HF [9].

There are applicability issues between the studies included in the ITCs and the Australian population. None of the included studies were conducted in the Australian setting. Study participants were predominantly male, with a mean age between 59 and 68 years for four studies included in the analysis. The prevalence of HF is estimated to be 1–2% in Australia, with a higher prevalence observed in older people and the Indigenous population[13].The Australian HF data were mainly based on self-reported National Health Survey 2017-2018 data. Hence evidence is limited for the proportion of patients with advanced HF from the overall HF population in Australia[14]. Overall, the hospitalisation rates for HF or cardiomyopathy were 1.5 times higher for males compared to females in Australia after adjusting for differences in the age structure of the populations and the age-specific hospitalisation rates were higher among males than females in

[12] Feng Y, Parkin D and Devlin NJ. Assessing the performance of the EQ-VAS in the NHS PROMs programme. *Quality of Life Research* 2014; 23: 977-989. DOI: 10.1007/s11136-013-0537-z.

[13] Sahle BW, Owen AJ, Mutowo MP, et al. Prevalence of heart failure in Australia: a systematic review. BMC Cardiovasc Disord 2016; 16: 32. 20160206. DOI: 10.1186/s12872-016-0208-4.

[14] Australian Institute of Health and Welfare. Heart, stroke and vascular disease-Australian facts, https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/hsvd-facts/contents/heart-stroke-and-vascular-disease-subtypes/heart-failure-and-cardiomyopathy.

all age groups[7]. The Australian Institute of Health and Welfare (AIHW) has not reported demographic data on patients with HF specifically. In patients with cardiovascular disease, it is reported that 15.7% are between the aged of 18 and 54. Further, 44% of cardiovascular disease patients in Australia are female. Therefore, demographic composition of the included studies is slightly different from the Australian setting.

Clinical claim

The commentary considered the ADAR's clinical claim of superior effectiveness and inferior safety of LVAD, HeartMate 3 (HM3) compared with OMM reasonable. However, the commentary considered the magnitude of clinical effectiveness uncertain due to the following reasons:

- The clinical claim was based on three ITCs: 1) two-step Bucher ITC using four trials; REMATCH (HeartMate XVE (HMHXE) vs OMM), Slaughter (HeartMate2 (HM2) vs HMXVE) and MOMENTUM 3 (HM3 vs HM2), 2) one-step Bucher ITC using ROADMAP observational study (HM2 vs OMM) and MOMENTUM 3 (HM3 vs HM2), and 3) unanchored (naïve) comparison between MOMENTUM 3 trial and REMATCH trial (HM3 vs OMM). Overall, the commentary noted following issues in the ITCs:

  #### Two-step Bucher

  o Differences in trial characteristics affected the transitivity of the trials in the ITC.
  - NYHA class- REMATCH trial included 100% NYHA class IV patients whereas > 90% in MOMENTUM 3 and >75% of Slaughter 2009 were NYHA class IV patients. This is bias towards the LVAD arm.
  - INTERMACS profiles- The MOMENTUM 3 trial included patients with INTERMACS profile 1-7 and ROADMAP study included patients with INTERMACS profile 4-7. Both Slaughter, 2009 and REMATCH trials were not based on INTERMACS profiles, but indicative of INTERMACS profiles 1-3.
  - Patients in the REMATCH RCT were noticeably older with mean age of 66-year-old in HM XVE group and 68-year-old in OMM group. On the other hand, patients from MOMENTUM 3 and Slaughter (2009) were slightly younger with mean age of 59 to 62-year-old, with similar median age to ROADMAP.
  - Contemporary management of advanced HF is different to the OMM used in the REMATCH study, which was conducted before 2001. The use of REMATCH data may have underestimated OMM effectiveness.
  o The 2 step ITC involves more indirect comparisons introducing more uncertainty.

  #### One-step Bucher

  o Differences in trial characteristics affected the transitivity of the trials in the ITC.
  - INTERMACS profiles- The MOMENTUM 3 trial included patients with INTERMACS profile 1-7 and ROADMAP study included patients with INTERMACS profile 4-7 (Of note, the ADAR presented subgroup analysis of patients with INTERMACS profile 4 in ROADMAP study.
  - ROADMAP study included higher percentage of females (%) in both arms compared to other studies.
  - The prescription of ACE inhibitors was more common in ROADMAP (68.0% HM2 and 76.7% OMM) but minimal in MOMENTUM 3 (23.2% HM2 and 22.9% HM3).
  o ROADMAP study is an observational study, therefore associated with high risk of bias.

  #### Naïve comparison

  o Differences in trial characteristics affected the transitivity of the trials in the ITC.
  - NYHA class- REMATCH trial included 100% NYHA class IV patients whereas > 90% in MOMENTUM 3 were NYHA class IV patients. This is bias towards the LVAD arm.

- INTERMACS profiles- The MOMENTUM 3 trial included patients with INTERMACS profile 1-7 and REMATCH trials were not based on INTERMACS profiles, but indicative of INTERMACS profiles 1-3.
    - Patients in the REMATCH RCT were noticeably older with mean age of 66-year-old in HM XVE group and 68-year-old in OMM group.
    - Contemporary management of advanced HF is different to the OMM used in the REMATCH study, which was conducted before 2001. The use of REMATCH data may have underestimated OMM effectiveness.
  - The naïve comparison provided very low-quality evidence and as such there is low certainty in the magnitude of difference reported.

- The comparative effectiveness evidence provided only related to OS. The other secondary effectiveness measures (e.g., functional status and QoL) only based on naïve comparison.

- Underreporting of AEs, particularly in REMATCH, and inconsistent reporting of outcomes across trials limits comparisons of safety outcomes across all three indirect comparisons.

13. Economic evaluation

The ADAR presented a cost-utility analysis (CUA) comparing HM3 with OMM in patients with advanced HF with INTERMACS 1-4 classification who are ineligible for heart transplantation. The CUA was based on the clinical claim of superior effectiveness and inferior safety of HM3 LVAD + OMM compared to OMM. This is in line with the ratified PICO.

The ADAR presented a trial-based analysis and a modelled CUA over a 40-year (i.e., lifetime) time horizon.

Summary of economic evaluation

Table 8 provides a summary of economic evaluation presented in the ADAR.

Table 8: Summary of the economic evaluation

Component	Description
Perspective	Australian Health care system perspective
Population	Patients with advanced HF despite OMM, with INTERMACS profile 1–4, who are not eligible for cardiac transplantation and in whom LVAD is used as DT (i.e., final therapy)
Comparator	OMM – also referred to as GDMT or OMT
Type(s) of analysis	Cost-utility analysis
Outcomes	Life years QALYs Healthcare resource costs
Time horizon	Lifetime horizon (baseline age is 65) vs. Trial reporting 5-year outcomes (MOMENTUM 3).
Computational method	Partitioned survival analysis
Generation of the base case	Modelled EE: Trial based effectiveness outcomes based on naïve comparison are derived from subgroup analyses of MOMENTUM 3 (5-year OS data from the MOMENTUM 3 study for a DT subgroup excluding patients receiving heart transplant for the LVAD arm; INTERMACS 1-7)[a] and REMATCH (patients receiving LVAD as DT; INTERMACS suggestive of 1-3 for the OMM arm) in accordance with the target MBS population (in relation to the patients receiving LVAD as DT) in the submission

Component	Description
	Trial based OS curves are extrapolated over a lifetime horizon.
	Healthcare resource use and utility weights derived from the literature are applied to generate total costs and QALYs in each treatment arm.
Health states	Alive and Dead
Cycle length	1 month
Transition probabilities	No specific transition probabilities are modelled.
	Health state allocation over time determined by OS curves from MOMENTUM 3 (LVAD arm) and REMATCH (OMM arm)
Discount rate	5% for both costs and outcomes
Software	Excel

Source: Table 49, p185 of the of the MSAC 1749 ADAR+ in-line commentary
Abbreviations: DT = destination therapy; EE = Economic evaluation; GDMT = Guideline directed medical therapy; HF = heart failure; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device; MBS = Medicare benefit schedule; OMM = Optimum medical management; OMT = optimal medical therapy; OS = overall survival; QALY = quality adjusted life year
Notes: ªDT subgroup of MOMENTUM 3 included INTERMACS 1-3 83.8% and INTERNMACS 4-7 16.1% in HM3 arm and INTERMACS 1-3 85.2% and INTERNMACS 4-7 14.8% in HM2 arm. No separate data available for the INTERMACS 1-4, the target population in this application.
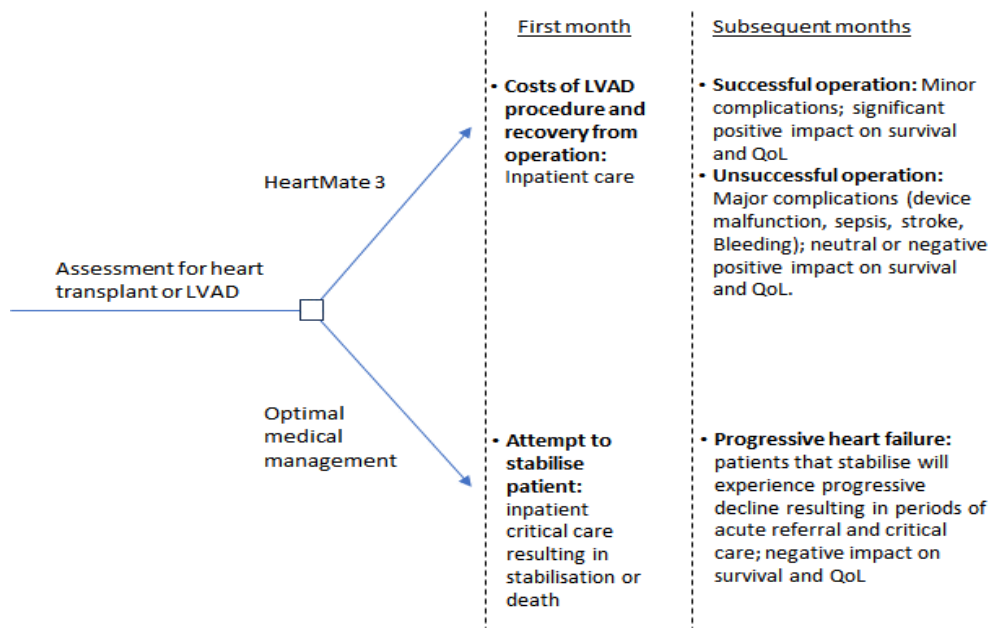
The commentary considered the population, comparator, outcomes and the type of economic analysis appropriate and in line with MSAC 1749 Ratified PICO Confirmation. The commentary also considered the perspective and discount rate appropriate. The commentary identified issues in the model and the model input parameters, which are discussed in detail in relevant sections below.

Model structure

The ADAR presented an economic evaluation using a partitioned survival model with two health states: alive and dead, to estimate the incremental QALYs and health costs of LVAD compared to OMM. Distribution of the modelled cohort between health states was based on extrapolation of OS curves. Patients in the alive health state are at risk of disease and device related events specific to the clinical context of patients eligible for LVAD as DT or OMM across the entire lifespan, including:

- Pre-implant stage,
- The period following implant in LVAD patients and continued attempts to stabilise OMM patients, and finally
- The long-term disease trajectories for OMM and LVAD patients which survive including the circumstances of death.

Figure 3 provides a conceptual schematic of the ADAR's economic evaluation.

First month | Subsequent months

Assessment for heart transplant or LVAD

HeartMate 3
- **Costs of LVAD procedure and recovery from operation:** Inpatient care
- **Successful operation:** Minor complications; significant positive impact on survival and QoL
- **Unsuccessful operation:** Major complications (device malfunction, sepsis, stroke, Bleeding); neutral or negative positive impact on survival and QoL.

Optimal medical management
- **Attempt to stabilise patient:** inpatient critical care resulting in stabilisation or death
- **Progressive heart failure:** patients that stabilise will experience progressive decline resulting in periods of acute referral and critical care; negative impact on survival and QoL

Figure 3: Conceptual schematic of the ADAR's economic evaluation

Source: Figure 50, p184 of the MSAC 1749 ADAR+ in-line commentary
Abbreviations: LVAD = left ventricular assist device; QoL = quality of life.

The ADAR proposed model structure is different from the typical partitioned models as it did not include, for example, an event free survival health state. It is also different from previously published models (e.g., Schueler, 2021[15]) which used a Markov model to capture various health states associated with the management of patients with advanced HF and management complications (e.g., stroke and hospitalisation).

The ADAR used trial-based OS curves to determine the proportion of patients in the alive and dead health states over the modelled time horizon. As there were no head-to-head trials of HM3 versus OMM available, the OS curves in the model are informed by separate studies. The model used the OS curves from MOMENTUM 3 trial for HM3 for the intervention arm and the OMM from REMATCH for the comparator arm. This naïve comparison ignored the ITC conducted in the ADAR.

The OS curves applied in the LVAD arm derived from the MOMENTUM 3 trial extrapolated beyond the trial period (5-year follow-up) via fitting of parametric models to KM data. However, as 100% of the cohort of the REMATCH trial died by approximately 25 months, the ADAR did not extrapolate the comparator arm beyond 2 years. This may bias the results against OMM given that medicines used in the REMATCH trial are not contemporary and therefore the OS curves used likely underestimate the OS in the OMM arm of the model.

## Model input parameters

Time Horizon

The ADAR justified the use of lifetime horizon in its base case analysis given the evidence that LVAD significantly improves life expectancy and ongoing QoL in patients with advanced HF indicated for LVAD as DT. The baseline age is 65 and the ADAR applies a lifetime horizon and extrapolated the OS curve from the MOMENTUM 3 over 40 years. However, the commentary considered a 10-year time horizon may be more appropriate given that the starting age of the

---

[15] Schueler S, Silvestry SC, Cotts WG, et al. Cost-effectiveness of left ventricular assist devices as destination therapy in the United Kingdom. ESC Heart Failure 2021; 8: 3049-3057. DOI: https://doi.org/10.1002/ehf2.13401.

model was 65 years. Although the other economic evaluations of LVAD have used lifetime horizon, those studies used shorter time horizon as lifetime e.g., Lim, 2022 had used 5 years and Scheuler 2021 had used 10 years as time horizon. Based on the recent INTERMACS registry data, median survival with LVAD DT is 5 years[16]. Considering model start age is 65 years, as well as the average life expectancy at birth (81.2 years for males and 85.3 years for females in 2018-20) in Australia, the commentary did not consider extrapolation over 40 years to be appropriate.

Model transition probabilities, variables and extrapolation

Transition probabilities are not explicitly modelled but are implicit in OS curves that make up the model structure. OS curves applied in the OMM arm are derived from REMATCH trial up to two years as 100% of the cohort are dead by approximately 25 months. OS curve applied in the LVAD and derived from the MOMENTUM 3 trial was extrapolated beyond the trial period (5-year follow-up) via fitting of parametric models to KM data. Per cycle death rates in each model arm are based on competing risk between trial based OS KM curves, parametrically extrapolated over a lifetime horizon, and age-related population death rates (Australian lifetables). The ADAR estimated survival models for the several distributions including exponential, Weibull, Log-normal and Generalised gamma. Figure 4 provides the parametric OS models for the LVAD arm.
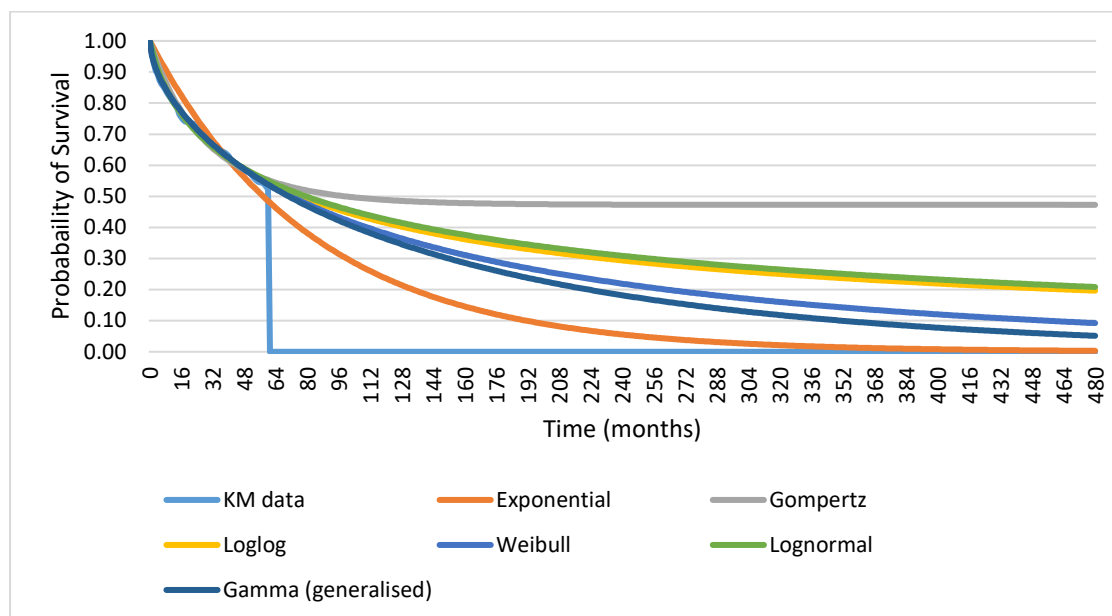
Figure 4: Parametric OS models for the LVAD arm

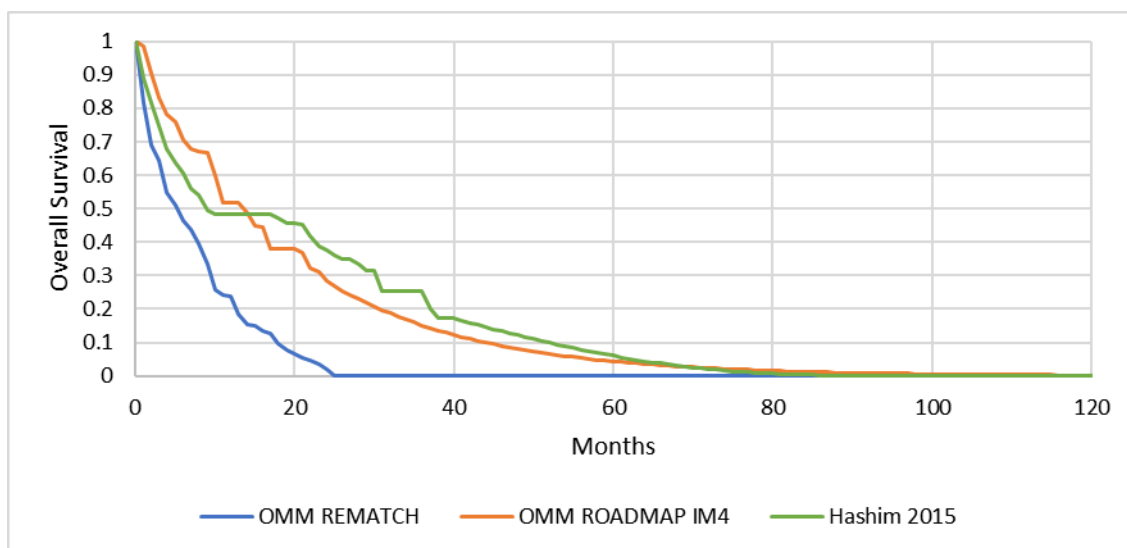Source: Figure 57, p199 of the MSAC 1749 ADAR+ in-line commentary
Abbreviations: KM, Kaplan-Meier; OS, overall survival; LVAD = left ventricular assist device

The generalised gamma distribution was used in the ADAR's base-case analysis as it has the lowest Akaike information criteria/ Bayesian information criteria statistics, and therefore was statistically the best fitting model. The commentary considered; however, that this distribution, as shown in Figure 4, resulted in the unrealistic survival probability of 10% at the age of 105 (40 years after the baseline age of 65). Visually, the exponential distribution appears to model survival more realistically and converges with the OMM curve.

[16] Yuzefpolskaya M, Schroeder SE, Houston BA, et al. The Society of Thoracic Surgeons Intermacs 2022 Annual Report: Focus on the 2018 Heart Transplant Allocation System. Ann Thorac Surg 2023; 115: 311-327. 20221201. DOI: 10.1016/j.athoracsur.2022.11.023.

The ADAR used separate parametric extrapolation in the control arm and treatment arm rather than applying the hazard ratio for the OS estimated in the ITC to the parametrically extrapolated arm in the base case analysis. The extrapolation of OS data only for the LVAD arm over a long-time horizon overestimate the survival benefit associated LVAD arm.

The OS curve used for OMM from the REMATCH could underestimate OS of the comparator given that the REMATCH is an old study and that contemporary treatment options could provide longer OS. Of note, there are recent modifications to the drug types included in the OMM as well. Based on the recent 2022 AHA/ACC/HFSA Guideline for the management of HF, OMM for HF with reduced ejection fraction (HFrEF) now includes new medication classes such as SGLT2i, which may provide additional survival benefits. More recent OMM studies showed more survival benefit than the OS reported in REMATCH study. For example, Hashim, 2015[17] study reported median survival of 9.0 months (interquartile range, 3.1–37.1 months), actuarial 1-year survival of 47.6%, and 2-year survival of 38.4%. Figure 5 provides the OS curves for OMM treated patients from REMATCH, INTERMACS 4 subgroup of ROADMAP and Hashim 2015.

Figure 5: OS curves for OMM treated patients from REMATCH, INTERMACS 4 subgroup of ROADMAP and Hashim 2015

Source: Figure 55, p195 of the MSAC 1749 ADAR+ in-line commentary
Abbreviations: IM4 = INTERMACS 4; OMM: optimum medical management; OS = overall survival
Note: Kaplan-Meier curve fitting was applied to assess long-term survival of OMM patients beyond the follow up period reported in studies

The ADAR argued that the increase in OS reported in the Hashim study could be due to the fact that the patient population (patients receiving inotropes at home setting) in Hashim 2015 study would be more comparable with INTERMACS profile 4 and therefore, less sick than the REMATCH population. However, the commentary noted the population in Hashim 2015 study were more likely to be categorised as INTERMACS 1-3 since the revised INTERMACS 3 profile include patients with inotropic infusions at home (Frequent Flyer Modifier "FF")[18].

---

[17] Hashim T, Sanam K, Revilla-Martinez M, et al. Clinical Characteristics and Outcomes of Intravenous Inotropic Therapy in Advanced Heart Failure. Circ Heart Fail 2015; 8: 880-886. 20150715. DOI: 10.1161/CIRCHEARTFAILURE.114.001778.

[18] Stevenson LW, Miller LW, Desvigne-Nickens P, et al. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). Circulation 2004; 110: 975-981. 20040816. DOI: 10.1161/01.CIR.0000139862.48167.23.

Health outcomes

Health state utilities

The ADAR sourced health state utility values for the first cycle in both the LVAD and OMM arms based on the Prichard study. MOMENTUM 3 RCT included patients with NYHA Class III with dyspnoea upon mild physical activity or NYHA Class IV. Hence, it was argued that it is more appropriate to use mean EQ-5D index scores among patient with NYHA class III or IV for LVAD and OMM arm from the Prichard, 2021[19] study, a health utility study among patients with advanced HF at Australian setting.

For the subsequent cycles, the ADAR assumed a constant health state utility for OMM patients of 0.44. However, the health state utility for the subsequent cycles for the LVAD arm was based on Sato, 2022 study[20], a Japanese study that used Japanese population norms for calculation of utility values among BTT patients. In Sato et al., the EQ-5D index score was 0.64 (IQR 0.47–0.79) at baseline, which significantly improved to 0.79 (IQR: 0.69–1.00) at 3 months. The difference between the EQ-5D index score at first cycle and subsequent cycles from second month (0.35) used in the ADAR was higher than the difference between the EQ-5D index score at baseline and 3 months (0.15) in Sato, 2022 study as well in the other studies in literature (e.g., Suzuki et al, 2022[21] reported 0.18 improvement of EQ-5D index values (0.59 before LVAD to 0.77 after LVAD) among LVAD patients. Hence, the use of Prichard study baseline utility in the first cycle and the Sato study utility value for subsequent cycles, together with a constant over extrapolated time (no QALY gain for OMM arm for subsequent cycle or extrapolated time) overestimates QALYs gained for the LVAD arm. Furthermore, the ADAR did not include disease or device related disutility for either arm, which is not appropriate.

Health care resource use and costs

The ADAR accounted for the clinical context of patients eligible for LVAD as DT treated with LVAD or OMM across the entire disease course including pre-implant stage, period following implant in LVAD patients and continued attempts to stabilise OMM patients and long-term disease trajectories. These stages of disease and treatment are captured predominately in the costing in the economic evaluation.

The ADAR included cost data from the Prichard, 2020 study,[22] a micro costing study of before and after LVAD implant among Australian patients. This study was based on 2014 prices; hence these costs were inflated to 2023 values using AIHW values before application in the economic model. Of note, Prichard study was based on BTT patients rather than the patients eligible for LVAD as DT. However, Prichard 2020 is the only available study from the Australian setting.

The commentary noted that while the economic model accounted for the cost of replacing the device battery every 3 years and captured device replacement costs due to 'Pump thrombosis resulting in reoperation', the ADAR did not account for device replacement costs due to device

[19] Prichard RA, Zhao FL, McDonagh J, et al. Discrepancies between proxy estimates and patient reported, health related, quality of life: minding the gap between patient and clinician perceptions in heart failure. Qual Life Res 2021; 30: 1049-1059. 20210102. DOI: 10.1007/s11136-020-02722-z.

[20] Sato T, Kobayashi Y, Nagai T, et al. Long-term preservation of functional capacity and quality of life in advanced heart failure patients with bridge to transplant therapy: A report from Japanese nationwide multicenter registry. Int J Cardiol 2022; 356: 66-72. 20220323. DOI: 10.1016/j.ijcard.2022.03.044.

[21] Suzuki, F., Sato, H., Akiyama, M., Akiba, M., Adachi, O., Harada, T., ... & Kohzuki, M. (2022). Changes in the Quality of Life of Patients with Left Ventricular Assist Device and their Caregivers in Japan: Retrospective Observational Study. The Tohoku Journal of Experimental Medicine, 257(1), 45-55.

[22] Prichard R, Kershaw L, Goodall S, et al. Costs Before and After Left Ventricular Assist Device Implant and Preceding Heart Transplant: A Cohort Study. Heart Lung Circ 2020; 29: 1338-1346. 20190829. DOI: 10.1016/j.hlc.2019.08.008.

malfunction over the 40-year modelled time horizon. It is unclear if this is appropriate given that in the MOMENTUM 3 study, 12 (2.3%) HM3 devices were replaced within 2 years post-implant, 6 due to driveline damage and other LVAD issues, 3 due to suspected device thrombosis or elevated lactate dehydrogenase, 1 due to infection, 1 due to right heart failure and 1 due to mitral valve bioprosthesis malfunction.

The commentary considered the approach followed by the ADAR overestimates the cost associated with the OMM arm for the following reasons:

- The cost for the pre-implant stage is applied to both arms of the model. This is not appropriate as patients in the LVAD arm may require more preparation for LVAD and consume more health care resources compared to the OMM patients.
- The ADAR applied an upfront critical care cost to the OMM arm only. This cost should be applied equally to both arms since all patients need to be stabilised before subsequent management.
- The ADAR included one-off cost applied when a patient transitions to death to account for additional costs of patient deterioration before death in the OMM arm only. However, patients in the LVAD arm also should include additional costs of patient deterioration before death as they also require additional management when they deteriorate before death.

Results of the economic evaluation

Stepped presentation of results

The ADAR presented a trial-based analysis for five years and then extrapolated to 40-year time horizon to obtain the base case results. At 5-year follow-up, based on the MOMENTUM 3 trial, the incremental cost per additional life year is $redacted (Step 1), and the incremental cost per life gained after extrapolation is $redacted (Step 2). The incremental cost per QALY gained reduced to $redacted at 40 years (Step 3). Therefore, the base case incremental cost per QALY of LVAD versus OMM was $redacted. The results of the stepped trial-based analysis for the LVAD versus OMM comparison is presented in Table 9.

Table 9: Results of the stepped economic analysis

Step	LVAD	OMM	Increment	ICER
Step 1 –Trial-based costs and outcomes (Time horizon: 5 years)				
Costs	$redacted	$85,833	$redacted	
Life years	3.127	0.586	2.542	$redacted
Step 2 – Time horizon extrapolated to 40 years				
Costs	$redacted	$85,833	$redacted	
Life years	6.258	0.586	5.672	$redacted
Step 3 – Outcomes transformed into QALYs				
Costs	$redacted	$85,833	$redacted	
QALY	4.929	0.258	4.671	$redacted

Source: Section 3.xlsx Workbook of the MSAC 1749 ADAR
Abbreviations: ICER = incremental cost-effectiveness ratio; LVAD = left ventricular assist device; OMM = optimal medical management.; QALY = quality-adjusted life year.
Note: Multiple outcomes may be informative for MSAC decision making-within each step.

The commentary considered the results of the economic evaluation uncertain for the following reasons:

- The simple model structure was based on the difference between OS curves for HM3 from the MOMENTUM 3 trial and for OMM from the REMATCH trial, which may not capture other health outcomes (e.g., event free survival, functional status)
- The comparison of the two OS curves was naive and did not utilise the relative effectiveness measure (e.g., Hazard ratio) estimated from the ITC.
- The time horizon of 40 years for this population of patients with advanced HF (mean age 65) is too long and favours LVAD.
- The model applied the same utility score (0.44) across LVAD and OMM in the first cycle, however, that score was maintained in the subsequent cycles in the OMM arm whereas a higher score of 0.79 was assumed for LVAD in the subsequent cycles that was maintained through the extrapolated period of 40 years.
- The model overestimated the cost of the comparator by applying only to the OMM arm an upfront critical care cost of $34,218 (i.e., in the first model cycle) and an additional one-off cost when a patient transitions to death.

Uncertainty analysis: Model inputs and assumptions

The ADAR performed sensitivity analyses exploring the impact of all model inputs. The sensitivity analysis with the largest impact on cost-effectiveness (CE) was reducing the time horizon to 5 years (trial-based period), which resulted in an ICER of $redacted per QALY. The LVAD device cost and the subsequent health state utility values for the LVAD arm are the other key drivers of the economic model. Using the 0.59 utility value for the subsequent cycle in the LVAD arm (to be in line with the 0.15 improvement from the baseline 0.44 as in the literature) increased the ICER to $redacted/QALY. Table 10 summarises the key drivers of the model.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: $redacted/QALY gained
Time horizon	Treatment effect continued beyond the 5-year trial period for up to 40 years	High, favours LVAD Using a time horizon of 5 years increased the ICER to $redacted/QALY gained.
Comparative effectiveness	Naively comparing survival curves of LVAD from MOMENTUM 3 and OMM from REMATCH instead of using the hazard ratio for OS estimated in the ITC	High, favours LVAD Application of the hazard ratio increased the ICER to $redacted/QALY gained.
Utilities	High values for model health states compared to the baseline taken for LVAD arm from literature and no disutility for AEs	High, favours LVAD + OMM Use of health state utility 0.59 for LVAD subsequent cycles increased the ICER to $redacted/QALY gained.
LVAD device cost	High device cost was included in the model as the device is highly expensive.	High, favours OMM Using a device cost of $58,460.00 decreased the ICER to $redacted/QALY gained.
KM curve fitting - LVAD arm, parametric model	Generalised Gamma in base case	Moderate, favours LVAD + OMM Using exponential distribution increased the ICER to $redacted/QALY gained.

Abbreviations: AE = adverse event; OMM = Optimum medical management; OS = overall survival; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LVAD = left ventricular assist device, KM = Kaplan Meier; QALY = quality-adjusted life year.

The results of key univariate sensitivity analyses provided in the ADAR and conducted by commentary are summarised in Table 11.

The multivariate sensitivity analysis performed by the commentary showed that assuming a time horizon of 10-year, health state utility - LVAD subsequent cycles 0.59, applying the "HR" method of extrapolation (as provided in the economic model) and OMM disease related costs in the 1st cycle of $0, would increase the ICER from $redacted/QALY (base case) to $redacted/QALY.

Table 11: Sensitivity analyses

Parameter	Base Case	Sensitivity	Incremental Cost	Incremental QALY	ICER	% change from base case ICER
Base Case			$redacted	4.671	$redacted	0%
Discount rate	5%	0.0%	$redacted	7.100	$redacted	-26%
		3.5%	$redacted	5.221	$redacted	-8%
Time horizon	Lifetime	5	$redacted	2.198	$redacted	86%
		10	$redacted	3.391	$redacted	29%
		20	$redacted	4.390	$redacted	5%
Device costs	**$redacted**	**$redacted**	$redacted	4.671	$redacted	-30%
		$redacted	$redacted	4.671	$redacted	28%
Procedural and recovery costs in LVAD arm	$75,009.85	$37,504.92	$redacted	4.671	$redacted	-17%
		$112,514.77	$redacted	4.671	$redacted	18%
OMM disease related costs 1st cycle	$34,218.02	$17,109.01	$redacted	4.671	$redacted	6%
		$51,327.02	$redacted	4.671	$redacted	-4%
OMM disease related costs subsequent cycle (baseline)	$4,862.80	$2,431.40	$redacted	4.671	$redacted	8%
		$7,294.20	$redacted	4.671	$redacted	-8%
Health state utility - LVAD subsequent cycles	0.79	0.59	$redacted	3.444	$redacted	36%
		0.99	$redacted	5.899	$redacted	-21%
KM curve fitting - LVAD arm, parametric model	Generalised Gamma	Exponential	$redacted	3.865	$redacted	16%
		Gompertz	$redacted	5.532	$redacted	-12%
		Log-Log	$redacted	5.115	$redacted	-7%
		Weibull (next best fit)	$redacted	4.837	$redacted	-3%
		Log-normal	$redacted	5.176	$redacted	-7%
Sensitivity analysis performed by the commentary						
Univariate analysis						
Applying the "HR" as method of extrapolating in the economic model			$redacted	2.559	$redacted	85%
OMM disease related costs 1st cycle	$34,218.02	$0	$redacted	5.672	$redacted	8%
Multivariate analysis						
Assuming a time horizon of 10 years, health state utility - LVAD subsequent cycles 0.59, applying ITC hazard ratio and OMM disease related costs in 1st cycle $0			$redacted	1.591	$redacted	160%

Source: Table 76, Pp251-253 of MSAC 1749 ADAR+ in-line commentary
Abbreviations: HR= Hazard ratio; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; KM = Kaplan Meier; LVAD = left ventricular assist device; OMM = optimal medical management; QALY = quality adjusted life year.

Table 12 presents additional sensitivity analyses provided by the applicant in their pre-MSAC response and the MSAC's re-specification of the base case.

Table 12: Re-specification of base case

Parameter	Incremental cost	Incremental QALY	ICER
ADAR base case (time horizon 40 years)	$redacted	4.671	$redacted
ADAR base case (time horizon 10 years)	$redacted	3.391	$redacted
Applicant pre-MSAC response multivariate analysis (assuming a time horizon of 10 years and OMM disease related costs in 1st cycle $0)	$redacted	3.391	$redacted
Applicant pre-MSAC response multivariate analysis (assuming a time horizon of 10 years, OMM disease related costs in 1st cycle $0, health state utility – LVAD subsequent cycles 0.59)	$redacted	2.472	$redacted
MSAC re-specification of base case[a] (assuming a time horizon of 10 years, OMM disease related costs in 1st cycle $0, health state utility – 0.64, LVAD subsequent cycles 0.79)	$redacted	3.268	$redacted

Abbreviations: ADAR = applicant developed assessment report; ICER = incremental cost-effectiveness ratio; LVAD = left ventricular assist device; MSAC = medical services advisory committee; OMM = optimal medical management; QALY = quality adjusted life year.
[a] Note that this base case does not fully incorporate the aftercare costs and does not include device replacement costs for any reason other than in relation to pump thrombosis.

Scenario analysis

The ADAR also presented two scenario analyses: 1) Heart transplant in a proportion of patients post LVAD as DT using MOMENTUM 3 and REMATCH trials, and 2) Comparison using LVAD arm data from MOMENTUM 3 versus OMM arm data from ROADMAP.

1. Heart transplant in a proportion of patients post LVAD as DT

As noted in the clinical algorithms, a proportion of patients may become eligible for heart transplant following LVAD. In MOMENTUM 3, 17.0% of patients initially classified as DT and implanted with an LVAD proceeded to receive a heart transplant. Therefore, the ADAR presented a scenario analysis to explore the impact on the ICER of including subsequent heart transplant in LVAD patients.

The model structure and inputs of the heart transplant scenario analysis were similar to the base case analysis, with the following two changes:

- Change in the OS curve for the LVAD arm to account for survival in patients who eventually receive a heart transplant. In MOMENTUM 3, the only OS data available for DT patients was KM curves which excluded patients who received heart transplant (base case analysis), or KM curves which censored patients at the time of receiving a heart transplant. For the scenario analysis, the ADAR used the OS curves that censored patients at the time of receiving a heart transplant. The ADAR justified this approach by arguing that survival in patients successfully living with LVAD as DT would be comparable to patients who received a heart transplant. The ADAR claimed that this assumption was supported by survival data from INTERMACS registry, where the 5-year survival rates were 49.4% and 42.4% in BTC and DT patients, respectively. The commentary considered this claim uncertain given the difference in the 5-year survival presented above.

- Application of additional costs associated with heart transplant (rates of transplant were based on the MOMENTUM 3 trial and the cost of heart transplant was based on the AR-DRG code F23Z).

Table 13 summarise the results of this scenario analysis, indicating that allowing for a proportion of patients to receive heart transplant following LVAD as DT has a modest impact on the base case ICER (increase from $redacted to $redacted).

Table 13: Results for the transplant scenario analysis

Category	Variable	LVAD	OMM	Incremental
Outcomes	Life years	6.618	0.586	6.033
	QALYS	5.214	0.258	4.956
Costs	**Total Costs**	$redacted	$85,833	$redacted
	Pre-Implant procedural costs	$21,997	$21,997	$0
	LVAD procedural costs	$redacted	$0	$redacted
	Device Costs	$redacted	$0	$redacted
	Implant and post implant procedural costs	$75,010	$0	$75,010
	Ongoing management	$11,375	$941	$10,434
	Device related event costs	$redacted	$0	$redacted
	Disease related event costs	$39,359	$62,895	-$23,535
	Transplant Costs	$44,508	$0	$44,508
IC/LY				$redacted
IC/QALY				$redacted

Source: Table 72, p238 of MSAC 1749 ADAR+ in-line commentary
Abbreviations: IC=incremental cost; LY=life years; LVAD = left ventricular assist device; OMM = optimal medical management; QALY = quality adjusted life year.

2. Comparison using LVAD arm data from MOMENTUM 3 versus OMM arm data from ROADMAP

The ADAR presented a scenario analysis that used LVAD arm data from MOMENTUM 3 and OMM arm data from ROADMAP (instead of REMATCH as per the base case). Subgroup analysis data for DT patients with INTERMACS 4 were not available from MOMENTUM 3 RCT. Therefore, the base case inputs for the LVAD arm remain unchanged in this scenario analysis, and OS data for LVAD arm was based on entire DT population (INTERMACS 1-7) of MOMENTUM 3 RCT (of which 83.8% were patients with INTERMACS 1-3) as in base case analysis.

The model structure and inputs of the heart transplant scenario analysis were similar to the base case analysis, with the following two changes:

- The OS data for the OMM arm was derived from the subgroup analysis of INTERMACS 4 patients in the ROADMAP trial.
- Removal of the critical care cost in the first cycle of the OMM arm and instead assuming pre-admission costs are applicable to INTERMACS 4 patients from the first cycle given that these patients do not require inpatient IV inotropic therapy. Pre-transplant costs were also removed in the OMM arm.

The ADAR again selected the generalised gamma model for the OS data applied in the scenario analysis, considering both AIC/BIC statistics and visual fit to the observed KM data. Table 14 summarise the results of this scenario analysis. The results of this scenario analysis indicate that applying model inputs (survival and costs) for an INTERMACS 4 population in the OMM results in

comparable ICER relative to the base case ($redacted versus $redacted base case) (Table 14).The ADAR stated this occurred because while OMM patients from ROADMAP had superior survival compared to OMM patients from REMATCH (refer back to Figure 5), in the model the patients are living for a longer period of time at a low QoL and accruing significant costs of care over this period. That is, in this scenario analysis using OMM arm data from the ROADMAP study:

- The OS curve for OMM was extrapolated out to 10 years before OS reached 0% compared to ~2 years in the base case analysis (using OMM data from the REMATCH study).
- The disease related event costs in the OMM arm was $102,356 compared to $62,895 in the base case analysis (using OMM data from the REMATCH study).

The ADAR claimed that this scenario analysis would be informative to MSAC, suggesting that LVAD was cost-effective in this scenario too. However, the commentary noted that the uncertainties identified in the base case analysis, such as model structure, time horizon extrapolation of OS and other model input parameters, are also applicable to the scenario analyses, in particular, relying on two OS curves from a naïve comparison.

Table 14: Results for the scenario analysis using OMM data from ROADMAP (instead of REMATCH)

Category	Variable	LVAD	OMM	Incremental
Outcomes	Life years	6.258	1.478	4.779
	QALYS	4.929	0.650	4.279
	Health State QALYs	4.929	0.650	4.279
Costs	**Total Costs**	$redacted	$104,925	$redacted
	Pre-Implant procedural costs	$21,997	$0	$21,997
	LVAD procedural costs	$redacted	$85	$redacted
	Device Costs	$redacted	$0	$redacted
	Implant and post implant procedural costs	$75,010	$0	$75,010
	Ongoing management	$10,751	$2,485	$8,266
	Device related event costs	$redacted	$0	$redacted
	Disease related event costs	$37,608	$102,356	-$64,748
	Transplant Costs	$0	$0	$0
IC/LY				$redacted
IC/QALY				$redacted

Source: Table 75, p243 of MSAC 1749 ADAR+ in-line commentary
Abbreviations: IC=incremental cost; LY=life years; LVAD = left ventricular assist device; OMM = optimal medical management; QALY = quality adjusted life year.

14. Financial/budgetary impacts

The ADAR estimated the potential financial impact for the proposed MBS listing of LVAD as DT using two approaches: 1) Expected number of LVAD procedures when accounting for capacity constraints in the Australian healthcare system, 2) Expected number of LVAD procedures without capacity constraints in the Australian healthcare system. The ADAR presented this approach as sensitivity analysis.

1) Expected number of LVAD procedures when accounting for capacity constraints in the Australian healthcare system

This was based on the estimated capacity of the Australian healthcare system to deliver LVAD as DT. The rational for this approach was that the LVAD procedures can be performed only in specialised quaternary centres, hence, the capacity constraints would have a large effect on expected number of LVAD procedures.

Estimated extent of use and financial implications

Table 15 describes the expected number of LVAD procedures when accounting for current and projected capacity constraints in the Australian healthcare system.

Table 15: Expected number of LVAD procedures when accounting for capacity constraints in the Australian healthcare system

	2024	2025	2026	2027	2028	2029	Source
Number of quaternary centres in Australia able to conduct LVAD procedures	4	4	4	4	4	4	Based on input from advisory board
Number of additional procedures able to be conducted per year per quaternary centre	redacted	redacted	redacted	redacted	redacted	redacted	Based on input from advisory board
Expected number of DT procedures when accounting for capacity constraints	redacted	redacted	redacted	redacted	redacted	redacted	Calculated
Additional increase in capacity over time	redacted	redacted	redacted	redacted	redacted	redacted	Assumption
Expected number of DT procedures when accounting for capacity constraints over time	redacted	redacted	redacted	redacted	redacted	redacted	Calculated

Source: Table 82, p266 of the MSAC 1749 ADAR+ in-line commentary
Abbreviations: DT = Destination therapy; LVAD = left ventricular assist device.

Table 16 summarises the parameter values applied in the financial estimates.

Table 16: Data sources and parameter values applied in the financial estimates

Relevant payer	Cost components	Value
MBS	LVAD procedure	$2,846.06 (cost per procedure)
	Incremental costs of ongoing management in LVAD patients versus OMM patients	$3,290.91
	Total	$6,136.96
PBS	Incremental costs of ongoing management in LVAD patients versus OMM patients	$2,085.52
Private health funds	Device and Total LVAD system cost[a]	$redacted
	Implant procedure and post-recovery costs (less cost of device[a])	$72,163.79
	Battery replacement	$4,592.00
	Total	$redacted

Source: Table 81, p265 of the MSAC 1749 ADAR+ in-line commentary
Abbreviations: LVAD = left ventricular assist device; OMM=Optimum medical management; MBS = Medicare benefit schedule; PBS = Pharmaceutical benefit schedule
Notes: [a] This cost includes the LVAD device cost and the 'consumables' component itemised in Prichard.

The financial implications to the MBS resulting from the proposed listing of LVAD are summarised in Table 17. The estimated total cost of LVAD as DT to MBS is $redacted and to private health insurers is $redacted in year 6 after listing.

Table 17: Financial implications for the government health budget of LVAD as DT

Parameter	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Year 4 (2027)	Year 5 (2028)	Year 6 (2029)
Number of LVAD procedures reimbursed on the MBS for DT	redacted	redacted	redacted	redacted	redacted	redacted
Total cost to the MBS	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total cost to the PBS	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total cost to private health funds	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

Source: Table 83, p267 of MSAC 1749 ADAR+ in-line commentary Abbreviations: DT = Destination therapy; LVAD = left ventricular assist device; MBS = Medicare benefit schedule; PBS = Pharmaceutical benefit schedule

2) Expected number of LVAD procedures without capacity constraints in the Australian healthcare system.

The expected number of LVAD procedures without capacity constraints was inferred from the current MBS utilisation of LVAD as BTT/BTC between 2010 and 2022. The rationale for this approach was that the LVAD is already in use and included in MBS data as BTT/BTC in the patients with advanced HF in Australia. The ADAR assumed that all these procedures were LVAD rather than RVAD procedures for simplicity and given the low rates of RVAD implantation in the INTERMACS registry. The rates of LVAD for BTT and BTC indications have remained relatively constant over the past 12 years with a moving average of 15 in the last 4 years. Thus, it was estimated that there are on average 15 patients receive an LVAD as BTT or BTC in Australia each year. The ADAR assumed a redacted expected ratio of DT procedures relative to BTT and BTC procedures if there were no capacity constraints based on utilisation by device strategy in the INTERMACS registry (i.e., redacted% DT, redacted% BTT/BTC during 2017-2021).

Table 18 describes the expected number of LVAD procedures without accounting for capacity constraints in the Australian healthcare system. The ADAR did not apply gradual uptake as the sensitivity analysis is intended to reflect an upper estimate of utilisation. Of note, Table 16 cost applied in the financial estimates are similar to the cost applied to calculate the financial estimates based on capacity constraints approach (Table 16).

Table 18: Expected number of LVAD procedures without accounting for capacity constraints in the Australian healthcare system

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Source
	2024	2025	2026	2027	2028	2029	
Projected utilisation of LVAD or RVAD procedures funded on the MBS for BTT and BTC patients	15	15	15	15	15	15	Inferred from current MBS utilisation data for BTT/BTC
Projected utilisation of LVAD procedures funded on the MBS for BTT and BTC patients	15	15	15	15	15	15	Assumption that majority of procedures involve LVAD
Expected ratio of DT procedures relative to BTT and BTC procedures if there were no capacity constraints	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Expected number of DT procedures if there were no capacity constraints	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	Calculated

Source: Table 84, p268 of the MSAC 1749 ADAR+ in-line commentary
Abbreviations: BTT=bridge to transplant; BTC=bridge to candidacy; DT = Destination therapy; MBS = Medicare benefit schedule; LVAD = left ventricular assist device; RVAD = right ventricular assist device.

The financial implications to the MBS resulting from the proposed listing of LVAD are summarised in Table 19. The estimated total cost of LVAD as DT to MBS is $**redacted** and to private health insurers is $**redacted** in year 6 after listing. The cost to private health insurers was estimated to be approximately $**redacted** per LVAD for DT procedure. This cost incorporated the costs for:

- the LVAD device and system ($**redacted**)
- battery replacements ($4,592)
- hospital procedure/post recovery costs ($72,163).

Table 19: Financial implications for the government health budget of LVAD as DT

Parameter	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Year 4 (2027)	Year 5 (2028)	Year 6 (2029)
Number of LVAD procedures reimbursed on the MBS for DT	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Total cost to the MBS	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Total cost to the PBS	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Total cost to private health funds	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**

Source: Table 85, p268 of MSAC 1749 ADAR+ in-line commentary
Abbreviations: DT = Destination therapy; LVAD = left ventricular assist device. MBS = Medicare benefit schedule; PBS = Pharmaceutical benefit schedule

The commentary considered that the financial estimates were appropriate. The insertion of ventricular assist devices is currently limited to specialised quaternary centres, which may place capability constraints to deliver the service in Australia. Therefore, the commentary considered the financial analysis based on capacity constraints was more appropriate. However, the number of additional procedures able to be conducted per year per quaternary centre was uncertain as it was based on expert opinion and therefore cannot be verified.

The ADAR also provided sensitivity analysis of financial estimates based on expected number of procedures inferred from relative number of patients receiving LVAD as BTT or BTC using MBS utilisation data (i.e., **redacted** expected ratio of DT procedures relative to BTT and BTC procedures based on utilisation by device strategy in the INTERMACS registry during 2017-2021). However, the commentary noted that, the uptake/utilisation of LVAD for BTT/BTC vs DT may be different due to the differences in the population and treatment options available. Furthermore, the 2022 annual report from the INTERMACS registry reported that the proportion of patients that received LVAD for DT had increased to 81.1%[23] (versus the **redacted**% reported in the ADAR). Hence, overall, the commentary considered the finance estimates were uncertain.

15. Other relevant information

As other relevant information, the ADAR presented patient experience and 'Rule of Rescue' circumstances.

With regard to the patient perspective, the ADAR quoted the findings from Silbert et al (2023) study. In the retrospective analysis of LVAD recipients in the Western Australian LVAD programme, 4% of patients received LVAD as DT, spending almost all of their days (97%) with an LVAD as an outpatient. The ADAR reported that the two longest surviving patients with LVAD as DT worldwide (11.3 and 10.5 years) are amongst this group. In terms of what LVAD as DT means for patients, for their lives and the things they enjoy, Silbert et al (2023) noted:

"DT patients have lived remotely in WA and enjoyed interstate and international travel. They have been able to continue many of their previous activities, such as competitive lawn bowls, animal conservation work, gardening, winemaking and running their businesses".

The ADAR claimed from this that LVAD as DT doesn't just improve survival without improving QoL – patients can live longer and enjoy what is important to them.

The ADAR also highlighted that benefits of LVAD as DT are also described in patient experiences provided in the response to PICO consultation from hearts4heart, the national charity which provides support, education and advocacy for Australians living with heart disease.

<u>'Rule of Rescue' circumstances</u>

The ADAR claimed that the survival of most severely ill patients with HF who are ineligible for heart transplant is very poor if the only option is OMM. The ADAR proposed that the use of an LVAD as DT meets the four factors that all apply in 'rule of rescue' circumstances (Table 20).

---

[23] Yuzefpolskaya M et al. (2023) The Society of Thoracic Surgeons Intermacs 2022 Annual Report: Focus on the 2018 Heart Transplant Allocation System. *The Annals of Thoracic Surgery*. 115(2):311-327

Table 20: Rule of rescue circumstances

Rule of Rescue Factor	ADAR Comment
No alternative treatment available in Australia	Yes There is no effective alternative treatment.
Medical condition is severe, progressive, and expected to lead to premature death	Yes Without DT, the prognosis for patients is very poor
Medical condition applies only to a small group of patients	Yes LVAD therapy is highly specialised, and are currently performed in 4 quaternary centres, which results in a very small number of procedures that are possible each year
Proposed technology provides a clinical improvement sufficient to qualify as a rescue from the medical condition	Yes Evident from the survival and QoL benefits presented in the ADAR

Source: p270 of MSAC 1749 ADAR+ in-line commentary
Abbreviations: Abbreviations: DT = Destination therapy; HM3 = HeartMate 3; LVAD = left ventricular assist device; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; OMM = optimal medical management; NNT = number needed to treat; QoL = quality of life

The commentary considered the rules of rescue appropriate for patients eligible for LVAD as DT as it is the only option for patients who are ineligible for transplantation, the condition is severe, progressive, and expected to lead to premature death. However, the commentary considered the medical condition applies only to a small group of patients denotes rare disease rather than the limitations due to capacity constraints. Hence, it is not applicable in this population.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration
Clinical issues: • The intervention is proposed for use in a small and seriously ill patient population. • The HeartMate 3 (HM3) is the only left ventricular assist device (LVAD) included on the Australian Register of Therapeutic Goods for use as destination therapy (DT). There are no randomised controlled trials (RCTs) directly comparing the HM3 against the nominated comparator optimal medical management (OMM). • There are RCTs comparing earlier generation LVADs and OMM within the proposed population. Therefore, the comparative evidence for the intervention is based on indirect treatment comparisons (ITC) and naïve comparison of HM3 versus OMM. **Economic issues:** • The use of a partitioned survival model instead of a state transition model was not adequately justified. ESC considered that a state transition model (e.g. Markov model), similar to published cost-effectiveness studies on this intervention, would have been appropriate. • The lifetime time horizon of 40 years, with a baseline age of 65 years, extends beyond the average life expectancy (**redacted**) and is therefore unreasonable. A time horizon of 10 years is more appropriate. • The base case model was informed by the results of the naïve comparison (very low-quality evidence) of the HM3 arm from the MOMENTUM 3 versus the OMM arm from the REMATCH

study. Although a scenario analysis using a hazard ratio approach to extrapolate survival also has some limitations, this analysis highlighted uncertainty in the model and ICER.

- The REMATCH study was conducted prior to 2001, as such OMM in the REMATCH study differs from contemporary OMM treatment options for advanced heart failure (HF), which may underestimate the OMM effectiveness. More recent studies (ROADMAP and Hashim 2015) demonstrate a better overall survival in OMM compared to that of the REMATCH study. Although the ADAR claimed the ROADMAP patients were 'less sick', ESC considered this issue had not been adequately explored through sensitivity or scenario analyses.

- The data sources for the baseline utility values were not well justified. There is a discrepancy in the populations used to inform the utility values for the OMM arm and the baseline in the HM3 arm. The utility value of the OMM arm was informed by an Australian study (Prichard 2021) with NYHA class 3 or 4 patients while the utility value of the subsequent cycles of the LVAD arm was based on a Japanese study (Sato 2022) with bridge to transplant patients.

- A multivariate analysis by the commentary that attempted to correct model input issues (e.g. assume 10 year time horizon, adjust health state utility score for LVAD, device cost $redacted, apply trial-based hazard ratios and $0 OMM disease-related costs in first cycle) resulted in an ICER of $redacted. Although this analysis highlights the base case model and ICER is highly uncertain, this multivariate analysis is also subject to uncertainty and still uses the unjustified partitioned survival model.

- The approaches to including event and deterioration costs are very different in the two arms. It is difficult to reconcile the different approaches used for each arm, and this adds to the level of uncertainty in the economic results.

Financial issues:
- The estimated usage, based on unverifiable expert opinion is uncertain and may be underestimated. While the estimated total cost to the MBS is modest ($redacted to $redacted per year), it would have a large budget impact on private health insurers. That is, the total cost to private health funds is approximately $redacted million per year for reimbursing redacted LVAD for DT services per year.

- The most significant component of the cost is the cost of the device which for private patients including those in public hospitals, will be borne by the private health insurers.

Other relevant information:
- Heart failure treated with OMM is associated with significant frailty in some patients, so excluding people from an alternative treatment based on frailty may not be appropriate. However, it may be worthwhile asking the applicant and advisory groups whether there should be restrictions based on frailty index and/or comorbidities (e.g. kidney failure on dialysis). It may also be beneficial to clarify whether the intervention may be used in a paediatric population in the future as devices become smaller.

- An additional item may be required to cover replacement of the device. The proposed service could then be restricted to once per lifetime.

- There is a requirement for access to specialist care, including for ongoing specialist follow-up. In Australia, this specialist care is currently only offered at one paediatric and four adult quaternary hospitals, which introduces access issues.

ESC discussion

ESC noted that this application from Abbott Medical Australia Pty Ltd requested Medicare Benefits Schedule (MBS) listing for the insertion of a durable left-ventricular assist device (LVAD) for use as destination therapy (DT) for patients with refractory heart failure (HF), despite optimal medical management (OMM), who are ineligible for cardiac transplantation. ESC noted that

refractory HF is defined as the presence of persistent or progressive symptoms alongside ventricular dysfunction despite OMM. ESC noted that the prognosis for patients with this condition is poor, with observed 2-year survival rates of 8%[24].

ESC noted that ventricular assist device implantation is listed on the MBS for other populations, including as a bridge to transplant (BTT) and bridge to (transplant) candidacy (BTC) since 1992 (MBS items 38615 and 38618).

ESC noted that the LVAD in this application, HeartMate 3 (HM3), is a fully magnetic levitation centrifugal pump that provides mechanical circulatory support (MCS) by assuming some or all the workload of the ventricle. Insertion is an open procedure performed by a cardiothoracic surgeon. As per current clinical management in Australia, patients eligible for LVAD would be implanted in one of four adult quaternary hospitals or one paediatric hospital.

ESC noted and welcomed consultation input from 4 professional organisations, 1 consumer organisation and 3 individuals, all of whom were medical specialists. ESC noted from consumer feedback that the device not only prolongs life, but also improves the quality of life. Other consultation feedback identified access issues, especially for people not living close to one of the few sites performing the service, and that patients and general practitioners are required to self-advocate to hospitals for this kind of therapy. Feedback also identified the need for multidisciplinary team (MDT) care, and ESC noted that it was important that patients had flexible options for accessing MDT care so that they could get the support and rehabilitation they required. ESC also noted the importance of ensuring that the eligibility criteria did not exclude patients based on assumptions that they are unable to do or understand the aftercare required. Finally, feedback from one organisation suggested that an MBS listing for LVAD as DT could lead to cost shifting to private health insurers, which could have negative implications for people paying private health premiums. ESC considered that there were other benefits that were difficult to capture, such as the value of small increases in functional capacity when OMM is applied with enough resources. ESC also considered that many patients may not want an external cardiac device as a first-line option and would likely prefer to try OMM first. ESC considered that it may be beneficial to seek qualitative data from people with severe HF.

ESC noted that the proposed item descriptor is device agnostic, although HM3 is the only LVAD for DT listed on the Australian Register of Therapeutic Goods (ARTG). ESC advised that the use of the acronym "VAD" (short for ventricular assist device) should be avoided as this acronym can also mean "voluntary assisted dying" in clinical practice. ESC noted that PASC had considered that the MDT explanatory note should be amended to include an intensive care clinician. ESC noted that the MDT as described in the proposed explanatory note does not stipulate the specialty of the second and third participating specialist or consultant physicians, meaning that an intensive care clinician can already form part of the MDT. ESC considered that one of the participating specialists or consultants should be specified in the case conference explanatory note as a transplant physician given their significant involvement in determinations of transplant eligibility (i.e. confirming that the patient under consideration for LVAD is not transplant eligible) and in transplant aftercare. Additionally, ESC considered that the case conference in the explanatory note should specify the inclusion of a fourth participant who should be the transplant coordinator. ESC noted that the proposed MBS item fee was $1,677.85 (75% benefit 1,258.40). ESC advised that the fee should cover all imaging required during implantation, so the descriptor should specify "all associated intra-operative imaging". However, this should not include workup

---

[24] Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001; 345: 1435-1443. DOI: 10.1056/NEJMoa012175.

imaging to determine suitability and approaches for the procedure nor any post-operative imaging required to monitor for any complications.

ESC advised that there should not be a 6-month claiming restriction even though the proposed item states 'capable of providing mechanical circulatory support for at least six months'. Rather, ESC considered that the MBS item should be restricted to once per lifetime, with a separate MBS item designated for re-implantation, if required by the patient. ESC considered whether there should be a restriction based on age or frailty index. ESC noted that OMM is intolerable for many patients, causing them to become frail very quickly, so it may not be appropriate to exclude people from alternative treatment based on frailty. It was also noted that small gains in functional capacity can translate to large improvements in quality of life. However, ESC considered that there should be further consultation with the applicant and advisory groups regarding whether there should be restrictions based on frailty index and/or comorbidities. ESC also queried whether this intervention may be used in a paediatric population in the future as devices get smaller, and noted this may be something MSAC would like clarification on.

ESC noted that patients with advanced HF are classified according to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles, which classifies patients requiring advanced therapies such as long-term MCS devices into one of seven profiles (with profile 1 being the most severe). ESC noted the proposed population is patients with advanced HF despite OMM with INTERMACS profiles 1–4 (i.e. who are considerably to critically unwell) and ineligible for cardiac transplant. ESC noted that the comparator for the intervention is OMM.

ESC noted that in the proposed clinical management algorithm advanced HF patients will first be treated with OMM. ESC noted that most patients will receive pharmacological management as part of OMM. ESC noted that the consensus statement on the pharmacological management of HF patients in Australia (based on 2018 NHFA/CSANZ[25]guidelines) recommend "quadruple therapy" (including renin-angiotensin-system inhibitors, beta-blockers, mineralocorticoid receptor antagonists and sodium glucose cotransporter 2 inhibitors) as first-line treatment in patients with HF with reduced ejection fraction. Non-pharmacological treatments (such as ventilation, pacing, angioplasty, extracorporeal membrane oxygenation and haemofiltration) are likely to be used in addition to pharmacological management for most severely affected patients. ESC noted that patients who are refractory to OMM will be assessed through a case conference for cardiac transplant and LVAD eligibility. ESC considered the eligibility for LVAD to be on a case-by-case basis and noted that clinical guidelines from Australia (2018 NHFA/CSANZ[26]), the United States (2022 AHA/ACC/HFSA[27]) and Europe (2021 ESC HF[28]) provide eligibility criteria or recommendations for consideration, and broadly apply to a relatively small number of patients with an INTERMACS profile between 1-4 or display other high risk characteristics.

ESC noted that post-operative management and long-term follow-up of LVAD patients includes pharmacological management (mainly antithrombotic therapy: warfarin, aspirin), blood pressure

---

[25] NHFA CSANZ Heart Failure Guidelines Working Group, National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018. Heart Lung Circ. 2018 Oct;27(10):1123-1208. doi: 10.1016/j.hlc.2018.06.1042. PMID: 30077227.

[26] NHFA CSANZ Heart Failure Guidelines Working Group, National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018. Heart Lung Circ. 2018 Oct;27(10):1123-1208. doi: 10.1016/j.hlc.2018.06.1042. PMID: 30077227.

[27] Heidenreiche, P. et al., ACC/AHA/HFSA Guideline for the Management of Heart Failure, Journal of Cardiac Failure 2022 28(5): e1-e167. https://doi.org/10.1016/j.cardfail.2022.02.010.

[28] McDonagh T et. Al., ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368. Erratum in: Eur Heart J. 2021 Oct 14;: PMID: 34447992.

control, supportive care, clinical assessment of patient wellbeing (e.g. check of vital signs, mental status, level of consciousness) and technical assessment of the LVAD device (e.g. pump function, pump speed, flow). OMM, including ACE inhibitors, beta blockers, mineralocorticoid receptor antagonists and diuretics, may be continued for some patients.

ESC noted that PASC had advised that the assessment report (including the clinical algorithm) should address the potential for a patient in DT to move back into active clinical care with a view for reassessment for transplant. ESC noted that the proposed clinical algorithm depicted that patients could move from DT to BTT. ESC agreed that DT patients should be provided the option to be re-assessed for cardiac transplant eligibility, but considered transfer from DT to BTT rare once patients are determined to be transplant ineligible.

ESC noted that the clinical evidence presented in the ADAR comprised data from three randomised controlled trials (RCTs) and one observational study:

- MOMENTUM 3 (2019, RCT compared HM3 versus 2nd generation HeartMate II [HM2], n=1028)
- Slaughter et al. (2009) (RCT, compared HM2 versus 1st generation HM XVE, n=200)
- REMATCH (2001, RCT, compared HM XVE versus OMM, n=129)
- ROADMAP (2015, observational study, compared HM2 versus OMM, n=200).

ESC noted that there were no head-to-head trials identified comparing HM3 and OMM. A literature search identified two ongoing trials (AMBUVAD and SweVAD) that are yet to be published. ESC noted the ADAR therefore presented indirect treatment comparisons (ITCs):

- 2-step ITC comparing HM3 vs HM2 vs HM XVE vs OMM (using Momentum 3, Slaughter et al. 2009 and REMATCH)
- 1-step ITC comparing HM3 vs HM2 vs OMM (using Momentum 3 and ROADMAP)
- Naïve comparison of HM3 arm from MOMENTUM 3 versus OMM arm from REMATCH.

ESC raised several issues with the clinical evidence and ITCs:

- The ADAR claimed patients in the ROADMAP study were less sick (INTERMACS profiles 4-7), so ADAR asserted that the 1-step ITC (using ROADMAP OMM) was biased against HM3.
- The MOMENTUM 3 trial included a mixed population of DT, BTT and BTC patients, of which 61% were DT patients, and included patients with INTERMACS profiles 1–7, although the majority (97%) were profiles 1–4, which was consistent with the proposed population.
- Contemporary management of advance HF is different to the OMM used in the REMATCH study, which may underestimate contemporary OMM effectiveness.
- Some outcomes could not be compared due to differences in reporting across the trials.

ESC noted that, when compared to the second-generation device (HM2), HM3 had a statistically significantly shorter median duration of rehospitalisation (18 days HM2 versus 13 days HM3) for the overall population. The rate of rehospitalisation was also statistically significant in favour of HM3 over HM2. For days out of hospital and duration of rehospitalisation, recipients of HM3 had an additional 24 days out of hospital over a 2-year period compared with recipients of HM2, and a 12% reduction in rehospitalisation rates over that period.

For device malfunctions, ESC noted that, of the 329 suspected malfunctions of HM3 at 2 years post-implantation, 23 were associated with adverse clinical effects. These included apical cuff malfunctions resulting in bleeding or the inability to secure haemostasis during the procedure; suspected malfunctions with the system controller, modular cable and mobile power unit

resulting in dizziness, dyspnoea, syncope and chest pain; assembly malfunctions resulting in outflow graft twist occlusion; and suspected device thrombosis or outflow obstruction. In all cases, the action taken by the sites included pump replacement, outflow graft revision, heart transplant or other surgery. ESC also noted that, at 2 years post-implantation, there was a higher percentage of patients with confirmed HM3 malfunctions than HM2 malfunctions (31% versus 24%, respectively). The numbers were more similar 5 years post-implantation (6% for HM3 versus 10% for HM2), but the overall patient numbers were much smaller. For patients continuing with OMM, ESC considered that the available pharmacological and non-pharmacological interventions would be associated with adverse events.

Regarding comparative effectiveness, ESC noted that the ADAR reported that all ITCs demonstrated statistically significant superior overall survival (OS) with HM3 versus OMM over 2 years. From the naïve comparison (very low-quality evidence), the ADAR reported OS for HM3 as 76.7% versus 8% for OMM and claimed that based on this magnitude of effect of 68.7% in favour of HM3 that the treatment of two patients with HM3 would therefore save one patient life relative to OMM. ESC noted that limited data were available to permit formal comparison of functional and quality of life (QoL) endpoints, but qualitative comparisons indicate improvements in functional class, the six-minute walking test (6MWT) and the EQ-5D questionnaire.

ESC noted that the economic evaluation was a cost-utility analysis that used a partitioned survival model with two basic health states – alive and dead – with allocation to the states determined by naïve comparisons of OS curves and extrapolations from the MOMENTUM 3 trial (LVAD arm) and REMATCH trial (OMM arm). The model used a lifetime time horizon of 40 years (baseline age of 65 years).

ESC considered that use of a partitioned survival model, which is typically used to model cancer treatments and can include interim states of progression free survival, was not justified. ESC also questioned why other health states (such as event-free survival) were not included in the model. ESC noted that guidelines and previous studies[29] suggest the choice of either a partitioned survival model or state transition model can have substantial impacts on results, particularly for extrapolation. ESC considered that a Markov model similar to published economic evaluations for this intervention, would be appropriate.

Aside from ESC concerns that model type was inappropriate, ESC also noted a number of concerns with the inputs for the model. ESC noted that instead of using the hazard ratios from the indirect treatment comparison, the ADAR's model was informed by the naïve comparison of OS data from the OMM arm of the REMATCH trial versus OS data from the HM3 arm of the MOMENTUM 3 trial. ESC noted the uncertainties from this naïve comparison impacted the economic evaluation (e.g. very-low quality data, OMM in REMATCH is not contemporary). ESC noted that, based on the REMATCH data, OMM survival stopped at 25 months in the model (i.e. all patients were deceased by that time). ESC noted that more recent studies (such as ROADMAP and Hashim et al. 2015) have longer survival for OMM. The ADAR claimed that the improved survival for OMM in more recent studies was due to the populations being healthier at baseline. However, the commentary had considered that the populations were similar and the improvement could be due to regime improvements. ESC considered that both scenarios were likely, and the impact of this had not been adequately explored in the sensitivity analyses.

ESC considered that the choice of a 40-year lifetime time horizon (from a baseline age of 65 years) was questionable given only 5-year outcome data is available from the MOMENTUM 3 trial. Further, the time horizon and extrapolations used redacted well beyond the average life

---

[29] Woods BS et al. Partitioned survival and state transition models for healthcare decision making in oncology: where are we now? *Value in Health* 2020. 23(12):1613–21.

expectancy, which ESC considered was inappropriate. ESC noted that other recent economic evaluations used time horizons of 5–10 years, which ESC considered more reasonable. Although, the 40-year model did include some device replacement costs (e.g. for battery replacement and device replacement due to thrombosis), the model did not factor in any other device replacement (i.e. assumed if no adverse events the device would last/perform for 40 years), which ESC did not consider reasonable.

ESC noted that there were differences in utility scores between the LVAD (0.79) and OMM (0.44) arms for subsequent model cycles that were not well justified. That is, the utility value of the OMM arm was informed by an Australian study (Prichard 2021) with NYHA class 3 or 4 patients while the utility value of the subsequent cycles of the LVAD arm was based on a Japanese study (Sato 2022) with BTT patients. ESC noted that this may have resulted in a higher utility improvement in favour of the intervention. ESC considered that better-matched data sources should be used. However, ESC acknowledged that sensitivity analyses exploring this uncertainty indicated that this did not have a large impact on the ICER. ESC also noted that there was no deterioration in QoL for the HM3 arm over time from 0.79 (that is, age and adverse events had no impact on health-related QoL), which was not addressed in the ADAR.

ESC noted that, in the base case, both incremental costs ($redacted) and incremental gains (5.672 life years gained, 4.671 quality-adjusted life years [QALYs] gained) were high, resulting in an incremental cost-effectiveness ratio (ICER) of $redacted per QALY gained. ESC noted that the time horizon was a key driver of the model – using a trial-based time horizon of 5 years increased the ICER by 86%, to $redacted/QALY. Changing the parametric model used to extrapolate the Kaplan–Meier (KM) curves beyond the trial period for the LVAD arm had a smaller effect on the ICER.

ESC noted that the commentary performed a sensitivity analysis that applied the ADAR's alternative hazard ratio approach for extrapolation in the economic model, which increased the ICER by 85% from the base case, to $redacted/QALY. ESC acknowledged the applicant's pre-ESC response which highlighted that the ADAR had explored this alternative analysis but found it resulted in 50% of the LVAD cohort dying within 1 month following the end of the KM period. ESC agreed that the hazard ratio approach as presented did not appear to be more reliable than the base case. ESC also noted that there was insufficient information to understand how the hazard ratio approach had been undertaken (e.g. the source of the hazard ratio was unclear, etc) but that it highlighted the uncertainty in the robustness of the model and base case ICER.

ESC noted that the commentary stated that additional costs associated with initial critical care stabilisation, and deterioration and death, were only included in the OMM arm. However, ESC noted that these costs were applied to both arms, but that they were managed very differently and were from different data sources; ESC acknowledged that it was difficult to reconcile and compare the different approaches used for each arm. ESC noted that when the initial stabilisation costs were removed for OMM in a sensitivity analysis, the analysis indicated this change had a small impact on the ICER.

ESC noted that a multivariate analysis, assuming a time horizon of 10 years, a health state utility score for LVAD of 0.59 for subsequent cycles, a device cost of $redacted, and applying trial-based hazard ratios and OMM disease-related costs of $0 for the first cycle resulted in an ICER of $redacted – a 160% increase from the base case ICER. ESC noted the robustness of this multivariate analysis is uncertain due to the issue with the hazard ratios approach (discussed earlier). However, ESC considered that the multivariate analysis highlighted that the base case model and ICER are highly uncertain. ESC also noted that these changes did not address the key underlying issue, that is the unjustified use of a partitioned survival model instead of a state transition model.

In addition to addressing the issues raised, ESC noted that the applicant could consider sourcing real world Australian data to help address some of the uncertainties where there are evidence limitations, such as to provide real-world data on the characteristics of patients who are receiving LVAD therapies in comparison to OMM therapy, the age distribution of patients, etc.

ESC noted that for the financial impact analysis, the ADAR stated that the utilisation of LVAD for DT would be constrained by capacity of the Australian healthcare system. The ADAR estimated the expected number of LVAD for DT procedures, when accounting for capacity constraints over time, was **redacted** in year 1 increasing to **redacted** in year 6. ESC noted these figures were based on assumptions (informed by expert opinion that were not able to be verified), so were uncertain. ESC considered that the number of procedures could be underestimated, especially if the expertise was redistributed outside of the quaternary hospitals, including through a mentoring program of smaller centres.

This uncertainty carried through to the financial estimates, where the financial impact to the MBS was estimated to be $**redacted** in year 1 increasing to $**redacted** in year 6. The estimated financial impact without capacity constraints – where it was estimated that **redacted** LVAD procedures for DT would be performed each year – increased the estimated total cost to the MBS to $**redacted** each year. ESC highlighted that the largest budget impact would be to private health insurers. Assuming capacity will constrain uptake to **redacted** LVAD for DT services per year, the total cost to private health insurers was estimated to be approximately $**redacted** per year. Increasing the number of services to **redacted** per year, increased the estimated annual total cost to private health insurers to $**redacted**. This cost is driven by the high cost of the LVAD which is listed on the Prescribed List of Medical Devices and Human Tissue Products (PL). The ADAR estimated that would cost private health insurers $**redacted** per LVAD for DT (accounting for LVAD device + system costs $**redacted**, battery replacement cost $4,592 and hospital procedure/post recovery costs $72,163).

17. Applicant comments on MSAC's Public Summary Document

The Applicant agrees with MSAC's assessment that there is a high unmet clinical need for LVAD as DT and that the clinical evidence supports its superior effectiveness compared to OMM. The Applicant will address MSAC's requests in a forthcoming resubmission, to ensure timely access of LVAD as DT.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website