Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1523.1 – Transluminal insertion, management and removal of an intravascular microaxial blood pump (Impella®), for patients requiring mechanical circulatory support

Applicant: **Abiomed Australia Pty Ltd (THEMA Consulting)**

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

A reapplication requesting Medicare Benefits Schedule (MBS) listing of transluminal insertion and management of a left intravascular microaxial ventricular assist device (IMVAD) (IMPELLA®) for the management of patients with cardiogenic shock (CS) requiring temporary mechanical circulatory support (MCS) was received from Abiomed Australia Pty Ltd by the Department of Health and Aged Care (the department).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of new MBS items for transluminal insertion and management of a left IMVAD for the management of patients with CS requiring temporary MCS. MSAC considered that the clinical evidence provided low certainty of a small but clinically important difference of the intervention for short term outcomes. However, MSAC considered that there was a clinical need for this intervention in the small, narrowly defined and high-risk population being patients in CS who have not stabilised despite pharmacotherapy. MSAC also considered that the low certainty in comparative effectiveness led to some uncertainty in the incremental cost-effectiveness ratio (ICER), particularly where IMVAD was used in conjunction with veno-arterial extracorporeal membrane oxygenation (VA-ECMO). MSAC acknowledged the Department's concerns regarding possible growth in utilisation with an MBS listing, however, MSAC noted that the estimated utilisation was very low and the financial analysis estimated that an MBS listing for IMVAD may provide a small cost saving to the MBS and a low financial impact to private health insurers (if the IMPELLA IMVAD device is listed on the Prescribed List of Medical Devices and Human Tissue Products).

Consumer summary
This is an application from Abiomed Australia Pty Ltd (THEMA Consulting) requesting Medicare Benefits Schedule (MBS) listings for procedures to insert, manage and remove the IMPELLA device in people who are in cardiogenic shock. Cardiogenic shock (CS) is an urgent and life-threatening condition. It happens when a person's heart cannot pump enough blood around the body. Patients are given medications to help increase their hearts pumping ability but sometimes a patient does not respond and may

Consumer summary
require temporary mechanical support to improve blood flow and deliver oxygen to the body. A current type of temporary mechanical support is veno-arterial extracorporeal membrane oxygenation (VA-ECMO). In VA-ECMO, blood is pumped outside of the body to a heart-lung machine that removes carbon dioxide and sends oxygen-filled blood back to tissues in the body. IMPELLA is another type of temporary mechanical support that aims to help circulate blood from the heart to the body. IMPELLA is an intravascular microaxial ventricular assist device (IMVAD), which is essentially a small pump that is placed inside the left ventricle of the heart, the main pumping chamber of the heart. Once in place, the IMPELLA pumps blood from the heart to the main artery that leaves the heart helping to circulate blood from the heart to the body. It is inserted through an artery in the leg, or directly into the heart through surgery that requires general anaesthetic. It stays in the heart for a short time (hours or days), then it is removed. IMPELLA can also be used at the same time as VA-ECMO, and this procedure is known as ECPELLA™. MSAC noted that the clinical evidence for IMPELLA and ECPELLA was of high risk of bias, which created uncertainty in the conclusions made on this evidence. However, MSAC acknowledged cardiogenic shock is an emergency condition, which makes it difficult to conduct a low risk of bias trial where the safety and effectiveness of intervention is directly compared to the comparator by randomly assigning patients to either the intervention or comparator arm (i.e. a randomised controlled trial). Overall, MSAC considered that in this small population of high-risk patients, the low certainty evidence indicated that IMPELLA and ECPELLA provided a small but important reduction in mortality in the short-term (i.e. 30 days) and likely resulted in reduced mortality in the longer-term (i.e. at 6 and 12 months). MSAC noted uncertainty when considering whether IMPELLA and ECPELLA represented good value for money. However, MSAC considered that there is a clinical need for the intervention for the proposed small number of high-risk patients who are acutely unwell, and funding the intervention may provide a small cost saving to the MBS and a low financial impact to private health insurers. **MSAC's advice to the Commonwealth Minister for Health and Aged Care** MSAC supported the creation of new MBS items for the insertion, removal and management of an IMVAD (IMPELLA or ECPELLA) for the management of patients with cardiogenic shock requiring temporary mechanical support. MSAC considered there is a high clinical need for the intervention for the proposed small number of high-risk patients who are acutely unwell. MSAC considered the evidence supported the comparative effectiveness and cost-effectiveness of IMPELLA and ECPELLA, though there was some uncertainty in these conclusions. Further, MSAC noted that the estimated utilisation was very low and would result in a low total financial impact.

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

MSAC noted that this resubmission sought MBS listing for the transluminal insertion, management and removal of an IMVAD (IMPELLA) for the management of patients with CS requiring MCS.

MSAC recalled that it had previously considered and not supported public funding for IMVAD (application 1523) for any of the three populations proposed in 2019. At that time, MSAC considered that:

- the evidence for comparative safety and effectiveness was too uncertain relative to standard care in all three populations, which had flow-on effects to the economic analyses

- the financial estimates were also highly uncertain and likely underestimated for all three populations
- additional data from randomised controlled trials (RCTs) would be required to give greater certainty regarding comparative safety, effectiveness and cost-effectiveness.

MSAC noted this resubmission had narrowed the proposed population to patients with CS with no evidence of significant anoxic neurological injury which included a subpopulation who are on veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and who require unloading of the left ventricle (LV). MSAC noted that for patients with CS with no evidence of significant anoxic neurological injury, the resubmission compared the use of IMPELLA against VA-ECMO. For patients with CS who are on VA-ECMO and who require LV unloading, the resubmission compared the use of IMPELLA in conjunction with VA-ECMO (referred to as ECPELLA) against VA-ECMO ± surgical venting (SV).

MSAC noted the consultation feedback received, including the letters of support from the Australian and New Zealand Intensive Care Society (ANZICS), Cardiac Society of Australia and New Zealand (CSANZ) and Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS). MSAC noted these societies represent the physicians who are involved in the multi-disciplinary team decision to use MCS devices, their implantation, and the ongoing management of CS patients. These professional societies all supported listing of IMPELLA and/or ECPELLA on the MBS.

MSAC noted that the first line of treatment for patients with CS is pharmacotherapy and where a patient does not stabilise, they are initiated on temporary MCS. Currently, patients with CS who require temporary MCS are initiated on VA-ECMO. Despite the availability of VA-ECMO, MSAC agreed with consultation feedback that there remained a high clinical need for clinicians to be able to employ an alternative intervention, such as the IMPELLA, in this small, narrowly defined and high-risk population who are critically unwell with low cardiac output. MSAC noted that the ability to use IMPELLA in combination with VA-ECMO (referred to as ECPELLA) when patients who are on VA-ECMO require unloading of the left ventricle, providing an alternative to other means of LV unloading. MSAC noted supportive evidence indicated that approximately 25% of VA-ECMO patients may require ECPELLA for left ventricle decompression.

MSAC noted that no RCT data existed to inform an analysis of IMPELLA compared with VA-ECMO, or ECPELLA compared with VA-ECMO in patients with CS. RCTs are difficult to recruit to, and complete, in this population, given the urgent nature of CS management. MSAC noted that the clinical evidence for the intervention relied on non-randomised studies where the key evidence base that informed the comparative assessment consisted of non-randomised studies that used propensity score matching or other adjustment methods. Other unmatched/unadjusted non-randomised studies were provided as supportive evidence only. MSAC noted that selection bias and residual confounding may still exist in the matched/adjusted studies and that the certainty of the evidence was low to very low (for outcomes at 12 months) but accepted that the evidence presented was the most informative evidence currently available.

Regarding comparative safety, MSAC noted that the evidence suggested that IMPELLA resulted in a reduction in bleeding requiring transfusion compared with VA-ECMO, although the quality of the evidence is low. However, MSAC noted that ECPELLA, when compared to VA-ECMO ± SV, can lead to increased bleeding requiring transfusion (due to insertion of two devices), with associated haemolysis and possible renal consequences. Therefore, MSAC agreed with ESC that ECPELLA had inferior comparative safety compared with VA-ECMO ± SV. MSAC also noted the Therapeutic

Goods Administration (TGA)[1] and the United States Food and Drug Administration[2] had issued recall notifications to correct the product instructions for use to include precautions that operators should take when inserting the device to reduce the risk of perforating the wall of the left ventricle in the heart.

Regarding comparative effectiveness, MSAC noted that the evidence suggested that IMPELLA resulted in a reduction in in-hospital and 30-day mortality compared with VA-ECMO, although the certainty of evidence is low. IMPELLA may reduce 6-month and 12-month mortality (odds ratio [OR] 0.71 and 0.72, respectively), but the evidence is very uncertain due to the high risk of bias and lack of statistical significance for these reductions (imprecision). Similarly, the evidence suggested that ECPELLA resulted in a reduction in in-hospital and 30-day mortality compared with VA-ECMO ± SV, although the certainty of evidence was low. One study also suggested that ECPELLA resulted in a statistically significant reduction in 12-month mortality. MSAC also noted that in patients treated for CS, existing evidence[3] suggests that if patients do survive the acute CS phase (including secondary shocks), these patients tend to experience longer-term survival profiles similar to people who have not had CS. Therefore, noting the improved survival in the acute phase, MSAC accepted that the reported reduction in longer-term mortality was likely, despite the lack of statistical significance.

MSAC noted the economic evaluation presented two cost-utility analyses comparing IMPELLA versus VA-ECMO and ECPELLA versus VA-ECMO ± SV. The main driver in both economic models was the differential in 30-day mortality, which was informed by low-certainty evidence. Mortality risks over the extrapolated period (beyond one month) were derived from the limited long-term data available and assumed no difference between treatment groups. MSAC considered that this was appropriate, given that the limited registry data available from other countries indicate that this occurs. MSAC noted the incremental cost-effectiveness ratio (ICER) was $redacted per quality-adjusted life year (QALY) gained for IMPELLA compared with VA-ECMO, and $redacted per QALY gained for ECPELLA compared with VA-ECMO ± SV. Due to uncertainties in the evidence, MSAC considered that these ICERs were also uncertain but noted the sensitivity analysis indicated the ICER for IMPELLA remained cost-effective compared VA-ECMO. MSAC noted the sensitivity analysis indicated there was less certainty that ECPELLA is cost-effective compared to VA-ECMO ± SV.

MSAC noted the utilisation of IMPELLA/ECPELLA would mainly be in a public hospital setting in centres that have ECMO capability and that the potential utilisation via the MBS would be very low (i.e. it was estimated that redacted to redacted patients per year may utilise IMPELLA and/or ECPELLA if MBS listed). The financial impact analysis estimated that MBS listing of IMPELLA/ECPELLA may provide a small net cost saving to the MBS (-$797 in year 1 to -$1,308 in year 6). MSAC also noted there could be a low financial impact to private health insurers of $redacted in year 1, increasing to $redacted in year 5 if an application to list the IMPELLA device on the Prescribed List of Medical Devices and Human Tissue Products (PL) is made and supported by the Medical Device and Human Tissue Advisory Committee (MDHTAC). However, MSAC noted that IMPELLA may be advantageous in centres that do not have ECMO capability, as a temporary measure to stabilise patients until ECMO can be made available or until patients can be transferred to an ECMO centre. If this is the case, this could increase the financial impact to

[1] TGA Recall Reference RC-2024-RN-00205-1

[2] https://www.fda.gov/medical-devices/medical-device-recalls/abiomed-recalls-instructions-use-impella-left-sided-blood-pumps-due-perforation-risks

[3] Steinacher E, et al. (2022) Cardiogenic Shock Does Not Portend Poor Long-Term Survival in Patients Undergoing Primary Percutaneous Coronary Intervention. *J Pers Med*; 12(8): 1193.

the MBS, although MSAC considered that the frequency of utilisation in these circumstances is likely to be low.

Regarding the proposed MBS item descriptors, MSAC considered that the item descriptors should be device agnostic and mention "an intravascular microaxial ventricular assist device" rather than specifying IMPELLA. However, MSAC advice to the department and MDHTAC was that, given the uncertainties already discussed, should other IMVADs also seek PL listing with the intention of using the device agnostic IMVAD MBS items supported by MSAC in this application, then the comparative safety, effectiveness and cost-effectiveness of future IMVADs should be evaluated and the evaluation should include consideration by MSAC. MSAC considered that "(Anaes)" was appropriate for both percutaneous and surgical insertion items, but that "(Assist)" was not required for surgical insertion item. MSAC agreed with ESC that the decision to initiate a patient with CS on an IMVAD (and selection of IMVAD type) should be determined by a multi-disciplinary team (MDT), typically including an interventional cardiologist, cardiothoracic surgeon, heart failure specialist and intensivist. Due to the urgency of CS management, MSAC agreed with ESC that this should be recommended in an Explanatory Note. MSAC noted the concerns raised regarding pre-emptive ECPELLA and considered that the Explanatory Note could include: "ECMO should only be considered after insertion of an IMVAD in the case of continuing clinical deterioration".

MSAC considered that the item descriptors did not need to mention patient age, noting the applicant's pre-MSAC response had confirmed that IMPELLA is only ARTG registered for use in adults and that should the ARTG indication for IMVAD change to include paediatric patients then an application would be made to amend the MBS indication. MSAC considered the potential for reimplantation had been adequately addressed by the applicant and as such did not consider a restriction for this was required.

Overall, MSAC acknowledged the limitations and uncertainty in the clinical evidence but considered there was a high clinical need for the intervention and that the evidence supported the comparative effectiveness and cost-effectiveness of IMPELLA compared with VA-ECMO. MSAC considered that the evidence for ECPELLA was less certain than for IMPELLA but accepted there was also a clinical need for ECPELLA in patients with CS who required LV unloading. MSAC also noted that the very low estimated utilisation would provide a small cost saving to the MBS and a low financial impact to private health insurers (if the IMPELLA device is listed on the PL). Therefore, MSAC supported the creation of new MBS items for transluminal insertion, removal and management of a left IMVAD for the management of patients with CS requiring temporary MCS as shown in Table 1.

Table 1 MSAC supported MBS items for the transluminal insertion and management of an IMVAD for the management of patients with CS

Percutaneous insertion
MBS item *XXXX Percutaneous insertion of an intravascular microaxial ventricular assist device, into the left ventricle only, by arteriotomy: if a) the patient has deteriorating symptoms of cardiogenic shock (with no evidence of significant anoxic neurological injury), which are not controlled by optimal medical therapy; or b) the patient is on VA-ECMO, for; i. deteriorating symptoms of cardiogenic shock (with no evidence of significant anoxic neurological injury); and ii. is not controlled by optimal medical therapy; and iii. due to the effects of established VA-ECMO, requires unloading of the left ventricle.

including all associated intraoperative imaging (Anaes) Fee: $693.65
Surgical insertion
MBS item *XXXX Surgical insertion of an intravascular microaxial ventricular assist device, into the left ventricle only, by arteriotomy: if a) the patient has deteriorating symptoms of cardiogenic shock (with no evidence of significant anoxic neurological injury), which are not controlled by optimal medical therapy; or b) the patient is on VA-ECMO, for; i. deteriorating symptoms of cardiogenic shock (with no evidence of significant anoxic neurological injury); and ii. is not controlled by optimal medical therapy; and iii. due to the effects of established VA-ECMO, requires unloading of the left ventricle. including all associated intraoperative imaging (Anaes.) Fee: $1,040.50
Surgical removal
MBS item *XXXX Surgical removal of a left-sided intravascular microaxial ventricular assist device Fee: $624.30
Management of the first day
MBS item *XXXX Management of the device - first day, including management and monitoring of parameters of the controller for a left-sided intravascular microaxial ventricular assist device Fee: $540.65
Management of the subsequent days
MBS item *XXXX Management of the device - each day after the first day, including management and monitoring of parameters of the controller for a left-sided intravascular microaxial ventricular assist device Fee: $125.75

After the MSAC meeting, the applicant notified MSAC that the results from the Danish–German Cardiogenic Shock (DanGer Shock) trial[4] were published on 7 April 2024. The DanGer Shock trial compared the routine use of a microaxial flow pump in addition to standard guideline-directed therapies in patients with STEMI-related cardiogenic shock versus standard care alone. The PICO elements of the DanGer Shock trial do not fully align with the PICO elements for this application

[4] Møller J et al. (2024) Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock. *The New England Journal of Medicine.* 390(15):1382-1393

(e.g. do not provide a comparison of IMPELLA versus VA-ECMO or ECPELLA versus VA-ECMO ± SV) and the results were not available in time for evaluation as part of MSAC's consideration. The DanGer Shock trial reported a lower risk of death at 180 days for the IMPELLA arm compared to standard care alone. Adverse events were assessed as a composite safety end point that included severe bleeding, limb ischaemia, haemolysis, device failure, or worsening aortic regurgitation. A higher rate of adverse events was observed in the IMPELLA arm compared to standard of care.

4. Background

MSAC previously assessed IMVAD (application 1523) at their November 2019 meeting. MSAC application 1523 sought reimbursement of IMVAD for three populations: CS, high-risk percutaneous coronary intervention (HR-PCI) and isolated right heart failure (RHF). MSAC did not support public funding of IMVAD for any of the proposed populations (Public Summary Document [PSD], November 2019). MSAC considered that the evidence for comparative safety and effectiveness was too uncertain relative to standard care in all three populations, which had flow-on effects to the economic analyses. MSAC considered the financial estimates were also highly uncertain and likely underestimated for all three populations. MSAC considered that additional data from randomised controlled trials (RCTs) would be required to give greater certainty regarding comparative safety, effectiveness and cost-effectiveness.

Following a pre-submission meeting in 2022 between Abiomed and the department, the MSAC Executive advised that it would be reasonable to lodge a resubmission via an expedited pathway bypassing the PASC process (MSAC Executive meeting minutes, 1 July 2022). The MSAC Executive advised that a resubmission could proceed with non-randomised data, noting that it does not preclude MSAC from making its own judgement on whether the further evidence sufficiently addresses its previously identified uncertainties.

The applicant has indicated that MBS listing for IMVAD in a HR-PCI population will be pursued in a separate application (the Applicant Developed Assessment Report [ADAR] stated that the RHF population will not be pursued at this stage).

The key matters of concern raised in relation to the CS population in the PSD for MSAC application 1523 are summarised in Table 2.

Table 2 Summary of key matters of concern raised in the PSD for application 1523

Component	Matter of concern	How the current assessment report addresses it
Clinical need	MSAC acknowledged the clinical need for effective interventions, particularly in the CS population who currently have limited options. However, MSAC considered the need to balance treatment benefit with futility of intervention. MSAC noted the ongoing investigator-run trial in Denmark and Germany for patients with CS (the DanGer Shock trial) and accepted that this was a well-designed trial; results are expected in 3–4 years. [PSD, p.5]	The ADAR noted that since 2006, four of the five RCTs in patients with CS have been discontinued due to low enrolment. The ADAR explained that the DanGer Shock RCT was not designed to directly compare IMPELLA and VA-ECMO in patients with CS and is unlikely to be informative. DanGer Shock reached its recruitment target (N=360) but has not yet published (estimated study completion is January 2024).
Clinical place in therapy	The algorithm suggested that ECMO can also be used in conjunction with IMVAD and pharmacological therapy. This is despite the PICO Confirmation noting concern about the use of IMVAD in addition to other mechanical	Addressed. Justification was provided in the ADAR for the clinical need for IMVAD + VA-ECMO (ECPELLA). The ADAR proposed that ECPELLA be used in a

	circulatory support. The Critique stated that the use of ECMO in addition to IMVAD was not justified in the application. [PSD, p.10]	subset of patients on VA-ECMO who require unloading of their LV. The commentary noted that the clinical evidence used to support the effectiveness and safety of ECPELLA also included 'pre-emptive' use of ECPELLA.
Comparator	MSAC agreed with the comparators as assessed by ESC. For CS, the appropriate comparator was ECMO, although MSAC noted the lack of evidence to support this, and also considered that the use of IMVAD in conjunction with ECMO would require justification in a narrower population. [PSD, p.3]	Addressed. Consistent with the advice in the PSD, the ADAR nominated VA-ECMO as the comparator to IMPELLA. For ECPELLA, the ADAR nominated VA-ECMO with or without SV as the comparator. The ADAR acknowledged that SV is not routine care in Australia; not all patients are suitable for SV, nor is expertise universally available.
Proposed fee / items	MSAC agreed with ESC that, while the time for surgical IMVAD insertion and removal is higher than percutaneous methods, the quantum of reimbursement is not adequately justified. MSAC also agreed that it was reasonable to delete the fee for percutaneous removal of the device. [PSD, p.5]	Addressed. The ADAR provided a clearer rationale for the proposed fees, based on local expert advice, MBS item fees for MCS devices (IABP, VA-ECMO and LVAD) and working relative value units from the United States for MCS devices (IABP, VA-ECMO and IMPELLA).
Comparative safety	MSAC noted the absence of RCTs that directly compared IMVAD and ECMO. Overall, MSAC considered the comparative safety to be uncertain, but noted that IMVAD is less invasive than ECMO. MSAC considered that high-quality RCTs would be required to reduce uncertainty in comparative safety. [PSD, p.3-4] The Critique stated that the indirect comparisons presented in the application, which aggregated results of RCTs and single-arm studies, were naïve and the methodology for conducting these was scientifically flawed. The application did not attempt to match the populations from different studies via propensity score matching or other means. The results were therefore highly uncertain. [PSD, p.11]	Partially addressed. No RCTs that directly compared IMVAD and ECMO in patients with CS have been published since the previous application. The ADAR's clinical evaluation was more rigorous than conducted previously. The 'pivotal' evidence in the ADAR comprised non-randomised studies that used propensity score matching and/or other adjustment methods to account for differences in baseline demographic and disease characteristics.
Comparative effectiveness	For the CS population, 30-day mortality was similar for IMVAD and IABP, although numbers were small. MSAC noted that recent studies have shown that IABP has limited value in this context and is no longer recommended for this indication. Comparative clinical effectiveness in the application showed that IMVAD is non-inferior or less effective compared with IABP, indicating that IMVAD would also be of limited value to patients with CS. MSAC noted that the included studies were small, low quality and used naive indirect comparisons with flawed methodology [simple pooling], but also acknowledged the difficulties in conducting clinical trials in patients with CS. [PSD, p.4] Overall, MSAC considered that IMVAD was non-inferior or less effective compared with IABP, and uncertain compared with ECMO. MSAC considered that additional data from RCTs would be required to give greater certainty	Partially addressed. The ADAR did not consider IABP as a comparator; as such, it is not known whether recent higher-level evidence has shown IMVAD to be more or less effective than IABP for patients with CS. Although the pivotal evidence in the ADAR consists entirely of non-randomised studies, the use of propensity score matching and/or other adjustment methods improves the certainty of the observed effect. However, some residual confounding may still exist, particularly in the studies with suboptimal matching/adjustment for important predictors of mortality.

	regarding comparative safety, effectiveness and cost-effectiveness. [PSD, p.5]	
Economic evaluation	In the economic model, IMVAD was dominant in all populations according to the base case analyses. However, MSAC noted that the applicant revised the economic (base case) models in their pre-ESC response, acknowledging multiple errors made in the analysis and estimates. In addition, MSAC noted several issues or areas of uncertainty: • several structural flaws and highly uncertain inputs, resulting in them not being informative for decision making • use of per-protocol analyses for IMVAD compared with IABP at 30 days, and variable use of PP or ITT analyses for AEs • effectiveness parameters compared with ECMO were based on naïve indirect comparisons • cost-offsets were uncertain – MSAC considered the use of ECMO in 100% of CS patients to be an overestimate, and also noted differences in-hospital or intensive care unit length of stay compared with ECMO (relative to IMVAD). MSAC considered that these issues either favour IMVAD or have uncertain effects on the model, resulting in a highly uncertain ICER. [PSD, p.4]	Addressed. The resubmission evaluated the cost-effectiveness of IMPELLA versus VA-ECMO, and ECPELLA versus VA-ECMO (± SV) in a CS population. The economic analyses were designed to capture key differences identified between IMPELLA/ECPELLA and VA-ECMO from the clinical evaluation of matched/adjusted comparative studies. Short-term mortality data continued to be the key effectiveness outcome in the model; longer-term outcomes were inconsistently reported across the matched/adjusted studies, reducing the reliability of results. The resubmission used a more conservative approach to the costing of intervention and comparator by applying the same LOS for IMPELLA and ECMO (assuming LOS is a function of disease severity rather than type of MCS).
Budget impact model	MSAC noted that the applicant's revised financial estimates provided to ESC had been reviewed and verified by the assessment group. MSAC considered the financial and budgetary impacts to be uncertain for all three populations, and likely to be underestimated. This was particularly influenced by the proposed cost offsets attributed to reduced ECMO use. [PSD, p.5]	Partially addressed. The basis for the ADAR's financial estimates is that IMPELLA will take some market share from VA-ECMO (substitution) whereas ECPELLA will be used together with VA-ECMO in a proportion of patients (add-on). The commentary notes that the financial estimates did not address the potential for increased costs due to the need for reimplantation, 'upgrade' to a more powerful IMPELLA pump, or a switch to VA-ECMO due to respiratory failure or progressive multi-organ failure.

ADAR = Applicant Developed Assessment Report; CS = cardiogenic shock; ECMO = extracorporeal membrane oxygenation; ESC = Evaluation Sub-committee; HR-PCI = high-risk percutaneous coronary interventions; IABP = intra-aortic balloon pump; ICER = incremental cost-effectiveness ratio; IMVAD = intravascular microaxial ventricular assist device; ITT = intention-to-treat; LOS = length of stay; LV = left ventricle; LVAD = left ventricular assist device; MCS = mechanical circulatory support; MSAC = Medical Services Advisory Committee; PP = per-protocol; PSD = Public Summary Document; RCT = randomised controlled trial; SV = surgical venting; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Source: Compiled from Table 2 of MSAC 1523.1 ADAR+in-line commentary.

5. Prerequisites to implementation of any funding advice

Regulatory approval status

A range of IMPELLA pumps are currently included on the Australian Register of Therapeutic Goods (ARTG) together with an introducer kit (ARTG ID 368070) for insertion of the device. Of the IMPELLA pumps on the ARTG (all with GMDN code 56732 – intracardiac circulatory assist axial-pump catheter), the IMPELLA models shown in Table 3 are relevant to this application. IMPELLA RP is not relevant to the application as it is used for RHF.

Table 3 ARTG numbers and other key information for relevant IMPELLA devices

Device name	ARTG ID	Catheter size	Maximal flow rate (L/min)	Maximum days of use	Intended placement	Additional information
Impella® 2.5	344062	12-Fr	2.5	5	Femoral percutaneous approach	Provides insufficient support for patients with CS according to expert clinical advice (Application 1523 PSD, p.2).
Impella® CP	365210 379190[a]	14-Fr	4.3	5	Femoral percutaneous approach	The most commonly used IMVAD in patients with CS according to ADAR expert clinical advice.
Impella® 5.0	307717	21-Fr	5.0	10	Surgical approach (femoral cut-down or axillary artery)	-
Impella® 5.5	386932	21-Fr	5.5	30	Surgical approach (axillary artery)	Recently brought to market therefore not represented in the included clinical evidence.

ARTG = Australian Register of Therapeutic Goods; CS = cardiogenic shock; Fr = French; IMVAD = intravascular microaxial ventricular assist device; L = litres; MCS = mechanical circulatory support; min = minute; PSD = public summary document.
[a] Refers to the IMPELLA CP® with SmartAssist Set, which consists of one IMPELLA CP with SmartAssist heart pump, one introducer Kit for femoral access, one guidewire to place the pump and one purge cassette.
Source: Compiled from Section 1.5 text, Table 3 and Table 5 of MSAC 1523.1 ADAR.

All IMPELLA devices have a small microaxial rotary pump mounted at one end of a thin, flexible catheter that pumps blood from the left ventricle (LV) through an inlet area near the tip and expels blood into the ascending aorta. The other end of the tube is connected outside the body to the Automated IMPELLA Controller, which powers the drive motor of the IMPELLA catheter and provides a user interface to monitor the correct positioning and functioning of the IMPELLA. The Automated Impella Controller is also listed on the ARTG (288729; GMDN 57808 – Intracardiac circulatory assist axial-pump catheter control unit).

Other than IMPELLA, there are no other IMVADs currently available in Australia.

Device funding status

The applicant intends to submit an application seeking listing of an IMPELLA kit (inclusive of an IMPELLA catheter, introducer kit and one purge cassette) on the Prescribed List of Medical Devices and Human Tissue Products (PL) at a reimbursed price of $redacted per unit.

The commentary noted that if the PL application is unsuccessful, the cost of the IMPELLA kit could be passed on to the patient (although this is unlikely if the service is predominantly performed in large public teaching hospitals). According to the ADAR, additional single-use purge cassettes ($redacted per cassette) are changed every couple of days; these are not expected to be listed on the PL and the ADAR does not address who will pay for these.

The Automated Impella Controller is a non-consumable device and is currently provided by Abiomed to hospitals at redacted. The ADAR advised that this will continue to be the case should IMPELLA be listed on the MBS for treating CS. Whilst the Automated Impella Controller is provided at reacted to hospitals, annual servicing is required, costing $redacted per annum.

Training and certification

Although not mentioned in the ADAR, the PICO Set for MSAC application 1523.1 mentions that IMPELLA is only to be used by clinical staff who have received competency training and certification from Abiomed.

6. Proposal for public funding

The application requested new MBS items for the transluminal insertion, management and removal of a left IMVAD in patients with CS. The ADAR claimed that a left IMVAD supports the native heart in patients with LV dysfunction/failure by unloading the LV, which in turn has a cascade of consequent positive effects on the heart function and physiology, ultimately improving end-organ perfusion.

The ADAR noted that existing utilisation of IMPELLA via the MBS occurs through the left ventricular assist device code (MBS item 38615), illustrating the need for a unique, and fit for purpose code for IMVAD.

Prior to the commencement of an IMPELLA episode, the patient must be evaluated for suitability of placement of the device via fluoroscopy imaging of the vasculature and access sites. The insertion and removal procedure is performed by an interventional cardiologist/intensivist for IMPELLA 2.5® and IMPELLA CP (femoral percutaneous approach), and by a cardiac surgeon for IMPELLA 5.0® and IMPELLA 5.5 (surgical approach). Immediately after implantation, fluoroscopy is used to check for correct IMPELLA positioning. The patient is monitored every day in the intensive care unit (ICU). If necessary, the catheter may be repositioned using echocardiography or using the repositioning guide for devices with the SmartAssist feature (IMPELLA CP and IMPELLA 5.5).

Whilst the setting for the delivery of the IMVAD service will predominantly be inpatients in a public hospital setting (mainly large teaching hospitals), as is the case for VA-ECMO, the ADAR noted that evaluation of IMVAD by MSAC will help to inform public hospitals of the relative safety, effectiveness and cost-effectiveness of IMVAD versus VA-ECMO. The ADAR stated that local experts consider it appropriate to include IMVAD on the MBS consistent with VA-ECMO (which can be used in both public and private settings).

Proposed MBS item descriptors

Several changes have been made to the proposed MBS items since MSAC consideration of application 1523:

1. consistent with MSAC advice, a fee for percutaneous removal has not been included
2. given the introduction of SmartAssist devices with repositioning guidance, a repositioning item has not been included
3. the proposed MBS item descriptors have been adapted to limit use to a population with CS and to a left-sided IMVAD
4. consistent with the MBS item structure for VA-ECMO and LVAD, the single daily management item has been separated into an item for management on the first day, and a separate item for management on subsequent days.

The five proposed new items are presented in Table 4.

Table 4 Proposed item descriptors with edits to align with ESC advice

Percutaneous insertion
MBS item *XXXX Percutaneous insertion of a left-sided intravascular microaxial ventricular assist device by arteriotomy: if (a) the patient has deteriorating symptoms of cardiogenic shock (with no evidence of significant anoxic neurological injury), which are not controlled by optimal medical therapy; or (b) the patient is on VA-ECMO and requires unloading of the left ventricle; and i. has deteriorating symptoms of cardiogenic shock (with no evidence of significant anoxic neurological injury); and ii. is not controlled by optimal medical therapy including all associated intraoperative imaging Fee: $693.65
Surgical insertion
MBS item *XXXX Surgical insertion of a left-sided intravascular microaxial ventricular assist device by arteriotomy: if (a) the patient has deteriorating symptoms of cardiogenic shock (with no evidence of significant anoxic neurological injury), which are not controlled by optimal medical therapy; or (b) the patient is on VA-ECMO and requires unloading of the left ventricle; and i. has deteriorating symptoms of cardiogenic shock (with no evidence of significant anoxic neurological injury); and ii. is not controlled by optimal medical therapy including all associated intraoperative imaging (Anaes.) (Assist.) Fee: $1,040.50[a]
Surgical removal
MBS item *XXXX Surgical removal of a left--sided intravascular microaxial ventricular assist device Fee: $624.30[a]
Management of the first day
MBS item *XXXX Management of the device - first day, including management and monitoring of parameters of the controller for a left-sided intravascular microaxial ventricular assist device Fee: $540.65
Management of the subsequent days
MBS item *XXXX Management of the device - each day after the first day, including management and monitoring of parameters of the controller for a left-sided intravascular microaxial ventricular assist device Fee: $125.75

[a] Refers to fee proposed in Table 15 of MSAC 1523.1 ADAR.
Source: Table 10, Table 11, Table 12, Table 13, Table 14 of MSAC 1523.1 ADAR+in-line commentary with edits to align with ESC advice.

The commentary noted the following:

- MSAC may wish to consider whether an explanatory note or alternative policy advice is required to restrict the provision of the service (1) to providers who have undertaken competency training and certification (provided by Abiomed), and (2) to centres equipped with VA-ECMO that have the appropriate facilities and expertise to provide the service and manage patients in CS. In 2021 there were at least 26 sites in Australia that performed ECMO (5% private)[5].
- The ADAR does not propose that IMVAD will replace VA-ECMO in the setting of transfer to a VA-ECMO centre. However, the Automated Impella Controller is portable and in the U.S., IMPELLA has been qualified for use for patient transport by trained healthcare professionals within healthcare facilities and during medical transport between hospitals (i.e. ambulance, helicopter or fixed-wing aircraft).
- The population described in the proposed item descriptors is consistent with the PICO summarised in the ADAR but is broader than the intended population in the proposed clinical management algorithm. The algorithm proposed that IMVAD should be considered for patients with CS (1) as an add-on to pharmacotherapy in patients with isolated left (or predominantly left) ventricular failure and deteriorating shock (i.e. when end-organ function is not stabilised despite initial pharmacotherapy); and (2) as an add-on in patients who are on VA-ECMO and require LV unloading.
- The proposed item descriptors do not mention that the decision to initiate a patient with CS on an IMVAD (and selection of IMVAD type) should be determined by a multidisciplinary team (MDT), typically including an interventional cardiologist, cardiothoracic surgeon, heart failure specialist and intensivist.
- The proposed item descriptors allow for IMVAD to be used alone or in conjunction with other MCS devices. The descriptors would allow for patients with CS to be initiated on IMVAD before or at the same time as VA-ECMO (i.e. pre-emptive). The ADAR's economic and financial estimates assume 25% of patients on VA-ECMO require LV unloading; for the remaining 75%, ECPELLA would add cost and potentially also harm without benefit.
- The IMVAD insertion approach is dependent on the patient's vasculature (assessed using fluoroscopy) and the IMPELLA model (see Table 3). The ADAR's economic and financial estimates assume 94% of IMPELLA procedures are performed percutaneously and 6% surgically (using the prevalence of peripheral artery disease [PAD] among patients presenting to hospital in the US with acute MI and CS as a proxy for requiring surgical insertion).
- The proposed descriptors do not specify whether fluoroscopy is included in the proposed fee for the IMVAD insertion services. The descriptor for MBS item 13832 (peripheral cannulation for VA-ECMO) includes 'ultrasound guidance where clinically appropriate' and explicitly states that 'no separate ultrasound item is payable with this item'.
- The proposed descriptors do not specify that IMVAD insertion is for temporary or short-term LV support only. Presumably, the number of repeat claims for the proposed item will be limited by the number of days that the IMVAD device can be used (between 5 and 30 days according to TGA registration). However, published studies report longer duration of use of large IMPELLA systems (5.0 or 5.5) in CS patients when used as a bridge to permanent MCS or heart transplantation.
- There is potential for a subset of patients on IMPELLA 2.5 or CP to require transition to an IMPELLA 5.0 or 5.5 for higher level support. There may also be patients who require

[5] Hodgson CL, et al. (2022) *The EXCEL Registry Report 2019-2021*, Monash University, Australian and New Zealand Intensive Care Research Centre. Report No 3, 30 pages.

reimplantation of an IMPELLA device (for example, due to pump thrombosis or accidental dislodgement).

Proposed fees

There were inconsistencies in the proposed MBS item fees presented across the ADAR for the surgical insertion and surgical removal items. The fees presented in the Executive Summary are those used in the economic evaluation and financial analysis for these items.

The ADAR considered existing MBS services for VA-ECMO, IABP and LVAD relevant to informing the proposed MBS fees for IMVAD. The proposed fees were also informed by local experts' advice and working Relative Value Units (RVUs) for the Current Procedure Terminology (CPT) codes used in the U.S. to assign a reimbursement value to procedures performed by healthcare providers.

Justification of the proposed MBS item fees is summarised in Table 5.

Table 5 Justification of proposed MBS item fees

Proposed item	Proposed fee	Basis for proposed fee in ADAR	Comments
Percutaneous insertion	$693.65	RVUs for IABP, IMPELLA and VA-ECMO MBS fees for IABP and VA-ECMO	Higher fee than proposed in MSAC application 1523 ($384.95) based on item 38362 for percutaneous insertion of IABP (fee for item 38362 was $421.55 at Oct 2023).
Surgical insertion	$1,040.50	RVUs for percutaneous and surgical insertion of IABP and VA-ECMO Proposed MBS fee for percutaneous insertion of IMPELLA Larger difference in duration and complexity expected between insertion methods for IMVAD than for VA-ECMO and IABP	Lower fee than proposed in MSAC application 1523 ($1,480.00, $50 less than the LVAD code at the time according to the ADAR). MBS item 38615 (for LVAD insertion), fee at Oct 2023 was $1,677.85.
Surgical removal	$624.30	RVU's for surgical removal versus insertion of VA-ECMO Proposed MBS fee for surgical insertion of IMPELLA	Lower fee than proposed in MSAC application 1523 ($740.00), which was based on MBS item 38612 for IABP removal (fee at Oct 2023 was $588.30). ADAR claims that removal of IMPELLA is more complex than IABP removal.
Management of the device – first day	$540.65	Same as VA-ECMO MBS item 13834 and LVAD MBS item 13851 for the management of the device – first day.	Substantially higher fee than was proposed in MSAC application 1523 ($156.10), which was based on MBS item 13847 (IABP management on first day), which has since been deleted. ADAR considered a similar level of resources would be required for VA-ECMO/LVAD and IMVAD patients.
Management of the device – each day after the first day	$125.75	Same as VA-ECMO MBS item 13835 and LVAD MBS item 13854 for the management of the device – each day after the first day.	ADAR considered the proposed fee appropriate in the context of similar level of resources required for VA-ECMO/LVAD and IMVAD patients.

IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; RVU = relative value units; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Source: Derived from Table 15 of MSAC 1523.1 ADAR+in-line commentary.

7. Population

The ADAR included two patient populations within the one PICO set. The intervention and comparator were different for the two populations, but the outcomes were the same.

The first population included patients with CS with no evidence of significant anoxic neurological injury. The commentary noted this is consistent with the Ratified PICO for MSAC application 1523 but is broader than the intended CS population. According to the ADAR's clinical management algorithm, MCS devices are recommended for use in addition to pharmacotherapy in patients with deteriorating shock after failure to respond to initial pharmacotherapy with inotropes ± vasopressors. The intervention relevant to this population is IMPELLA (as an add-on to pharmacotherapy).

The second population was broadly defined as patients with CS who are on VA-ECMO and require unloading of the LV. As explained in the ADAR, although VA-ECMO is an effective MCS for use in patients with CS, one of the disadvantages is that it causes a marked increase in LV afterload due to the retrograde flow of blood in the aorta, which further compromises the already failing myocardium. The intervention relevant to this population is ECPELLA (IMPELLA added to VA-ECMO).

The ADAR claimed there is no universally accepted definition of LV distension requiring LV unloading. The decision to initiate ECPELLA is made by a MDT who consider echocardiographic, radiological, and clinical signs of impaired LV unloading or LV stasis (stone heart, pulmonary oedema, impending clotting on the LV, significant aortic regurgitation). The ADAR's economic and financial analyses assume 25% of CS patients on VA-ECMO require LV decompression.

The ADAR claimed that the proposed populations, and consequent proposed MBS item descriptors were kept intentionally broad, given the heterogeneity in the population with CS, the complexity in classifying patients by stage in a consistent manner that relates specifically to patient management, and the large element of clinical discretion associated with managing these patients. The commentary noted that the CS populations investigated in clinical studies of IMPELLA/ECPELLA versus VA-ECMO were also broad, with a wide variety of aetiologies.

8. Comparator

IMPELLA

The comparator to IMPELLA in MSAC application 1523 was 'standard care (i.e. pharmacological therapy and/or intra-aortic balloon pump, and ECMO, percutaneous VADs)'. The ADAR for application 1523.1 nominated VA-ECMO as the comparator to IMPELLA. The commentary agreed that this change is consistent with MSAC advice and that omission of IABP and pharmacological therapy as comparators is appropriate.

The commentary queried whether TandemHeart (LivaNova) – a temporary, percutaneously inserted VAD – may also be an appropriate comparator to IMVAD for patients with CS; however, it is unclear whether TandemHeart is widely used in the private setting.

The commentary noted that VA-ECMO can be used in a broader CS population than IMPELLA, including patients with right ventricular or biventricular failure and/or severe concomitant respiratory dysfunction. Therefore, while IMPELLA provides an additional option for use in patients with CS, it is only an alternative to VA-ECMO in patients with isolated LV (or predominantly LV) failure.

ECPELLA

VA-ECMO with or without SV is nominated as the comparator to ECPELLA. This comparator has not been considered by MSAC previously. The commentary considered the comparator reasonable but noted there are other less invasive approaches to decompress the LV during VA-ECMO (for example, escalation of pharmacotherapy, IABP, percutaneous atrial septostomy, pulmonary artery drainage).[6] Given its passive nature, complexity and invasiveness requiring open surgery, not all patients are suitable for SV, nor is expertise universally available, meaning it is not routinely available to all patients requiring LV unloading.

The commentary also noted that although the intention is that IMPELLA is added to VA-ECMO only in patients who develop increased afterload, the clinical evidence included cases where IMPELLA may have been used pre-emptively as protection against LV distension/stasis.

9. Summary of public consultation input

A summary of previous consultation feedback received for MSAC Application 1523 is available in the Public Summary Document:
http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1523-public

Further consultation input for this resubmission was received from three (3) individuals, all of whom were medical specialists. The feedback was supportive of the application.

The applicant also provided letters of support from three (3) organisations:

- Australian and New Zealand Intensive Care Society (ANZICS)
- Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS)
- Cardiac Society of Australia and New Zealand (CSANZ).

Benefits:
The feedback indicated the main benefits include:

- Patients with CS requiring left ventricular support currently have limited treatment options, and this device helps sustain circulatory support while simultaneously reducing the workload on the left ventricle.
- The IMPELLA IMVAD improves systemic perfusion and coronary flow, leading to a decrease in myocardial oxygen demand and improving end-organ profusion.
- Observational study outcome data suggests that IMVAD may be associated with reduction in mortality in patients with cardiogenic shock.
- IMVAD can be inserted in any cardiac centre by a trained interventional cardiologist or intensive care specialist, unlike VA-ECMO therapy which is a complex intervention that needs high volume dedicated centres.
- Public funding will provide equity of access to IMVAD.

Disadvantages
The feedback suggested the following disadvantages:

- If not properly inserted and monitored IMVAD can lead to limb ischaemia by occluding the common femoral artery, which could potentially lead to loss of the patient's leg.
- Risk of haemolysis, which can lead to multi-organ dysfunction, particularly renal failure and risk of bleeding at the site.

[6] Ezad SM et al. (2023) 'Unloading the left ventricle in venoarterial ECMO: In whom, when and how?', *Circulation*, 147(16):1237-1250, doi: 10.1161/CIRCULATIONAHA.122.062371.

Other comments
The feedback noted patient selection is important, as well as providing patients with multi-disciplinary team care (e.g. dieticians, pharmacists, physiotherapists, psychologists and social workers).

10. Characteristics of the evidence base

The ADAR literature searches sought to identify all comparative clinical studies of IMPELLA or ECPELLA versus VA-ECMO in patients with CS. The ADAR identified no relevant RCTs. One RCT currently in-progress (UNLOAD ECMO [NCT05577195]) was identified that could potentially provide data of relevance to the ADAR for the ECPELLA population. According to ClinicalTrials.gov, the study is currently recruiting participants and has an estimated completion date of December 2025.

Included studies were categorised according to whether or not they used propensity score matching (PSM) and/or other adjustment methods to account for differences in demographic and baseline disease characteristics of participants. The ADAR considered studies that were matched or adjusted as 'pivotal' evidence and unmatched/unadjusted studies as 'supportive' evidence. The commentary noted that although this represented an improvement on the naïve comparisons presented in MSAC application 1523, some residual confounding may still exist; a limitation also acknowledged by the ADAR. The commentary noted that the availability of a well-designed and well-conducted RCT would provide the best evidence to inform the clinical therapeutic conclusions.

Overall, there were 25 non-randomised studies included in the ADAR. Some studies provided both matched/adjusted and unmatched/unadjusted data or provided data for multiple treatment arms and may have been included in more than one group.

Eight of the IMPELLA versus VA-ECMO studies and five of the ECPELLA versus VA-ECMO ± SV studies were conducted in larger registries, claims databases, or hospital databases with multiple centres. These studies may be prone to reporting bias relating to consistency and accuracy in reporting (for example diagnosis of CS), and extent of reporting (for example, haemodynamic and laboratory results, procedure details, or procedural complications). While the ADAR reported that this bias is unlikely to influence the study results due its non-differential nature, the commentary disagreed, noting that important differences in the characteristics of the two groups may not have been captured.

The studies included in the ADAR represented a diverse range of CS patients recruited through varied eligibility criteria. While trial populations differed, when taken together the ADAR proposed that the trials reflect the epidemiology of CS; that is, a population that is variable with regards to shock aetiology, physiological parameters and shock severity, with decisions to treat made by an MDT.

The ADAR noted that studies that included patients with post cardiac arrest CS (CA-CS) should be interpreted with caution due to the mortality risk of this group substantially exceeding that of patients with CS alone. These patients may have anoxic brain injury, an exclusion criterion based on the proposed population in the PICO, raising concerns regarding applicability.

IMPELLA versus VA-ECMO

The ADAR included a total of 15 studies that met the inclusion criteria for assessing the safety and effectiveness of IMPELLA compared to VA-ECMO. The matched/adjusted study characteristics are summarised in Table 6.

A key limitation of the included studies was that device selection (IMPELLA or VA-ECMO) and timing of device implantation was decided by the treating physician, guided by local policies, institutional algorithms, individual preferences, and/or experience. This could reduce the comparability of the patients in each study arm and introduce selection bias. While few studies provided details around how the decision for device selection was made, it appeared that patients with unilateral LV failure were treated with IMPELLA, while patients with biventricular failure and/or severe concomitant respiratory dysfunction were treated with VA-ECMO.

Of the six matched/adjusted studies, four used PSM to balance covariates, one conducted propensity score adjusted analyses and one conducted SAVE score-adjusted analyses of mortality.[7] The commentary noted that the extent of matching/adjustment varied across the studies and the selection of matched variables was often influenced by the data fields available rather than important predictors of mortality. The methods of statistical adjustment used in the two adjusted studies are not as effective as PSM in terms of addressing potential confounding.

In general, the ADAR assessed the matched/adjusted studies to be at moderate risk of bias and the unmatched/unadjusted studies to be at high risk of bias. Of note, nearly 10% of patients in Karatolios (2021) received both devices but were analysed according to the first device implanted (20 patients received IMPELLA first and 22 patients received VA-ECMO first). In the VA-ECMO cohort of Schiller (2019), 17% had concomitant support with IMPELLA and 22% of patients were treated with IABP or LV drainage. Lemor (2020) also reported in-hospital use of IABP in 50% of IMPELLA patients and 48% of VA-ECMO patients.

The commentary identified potential for overlap in patients in two propensity matched retrospective cohort studies conducted at the same institution in Germany over a similar time period (Karatolios 2021; Syntila 2021) and two retrospective analyses that included Medicare patients in the U.S. over a similar time period (Lemor 2020; Vetrovec 2020).

ECPELLA versus VA-ECMO with or without surgical venting

The ADAR included a total of 13 studies that met the inclusion criteria for assessing the safety and effectiveness of ECPELLA compared to VA-ECMO ± SV. The matched/adjusted study characteristics are summarised in Table 13 and the unmatched/unadjusted study characteristics are summarised in Table 14.

As for the IMPELLA studies, there is potential for selection bias in the ECPELLA studies relating to device selection and timing of device implantation. The commentary noted variation within and between the ECPELLA studies in the timing of IMPELLA insertion relative to VA-ECMO (before, simultaneous or after).

Of the five matched/adjusted studies, two used PSM to balance covariates, two conducted multivariable adjustment analyses and one conducted inverse probability treatment weighting (IPTW)-adjusted analyses. The ADAR acknowledged that the variables used for matching/adjustment differed across the studies and may not have considered all predictors of mortality in patients with CS.

The ADAR assessed the matched/adjusted studies as moderate risk of bias, and the unmatched/unadjusted studies as high risk of bias. Overall, the commentary agreed, though had concerns in relation to study applicability, conduct and analysis.

[7] SAVE score variables included diagnosis, age, weight, haemodynamics, respiratory values, renal conditions and other organ failures.

Radakovic (2022) was the only matched/adjusted study to compare ECPELLA to VA-ECMO plus a surgical vent. In Patel (2018), 20% of patients in the ECPELLA cohort and 31% in the VA-ECMO cohort also had a surgical vent. IABP use was reported in the ECPELLA and VA-ECMO cohorts in Patel (2018) and Pappalardo (2017).

Of the matched/ adjusted studies, Pappalardo (2017) and Radakovic (2022) were the only studies that restricted the ECPELLA cohort to patients under VA-ECMO support who received IMPELLA for therapeutic LV decompression. Several studies included patients in the ECPELLA cohort who received IMPELLA before VA-ECMO (20% in Patel 2018; 56% in Schrage 2020b; number not reported in Hendrickson 2022).

The commentary noted there was potential for patient overlap in two studies that recruited patients from the same centre in Germany during overlapping time periods (Pappalardo 2017 and Schrage 2020b). Similarly, there was potential that patients included in Patel (2018) and Schrage (2020b) may also be included in Hendrickson (2022) if their data contributed to the National Inpatient Sample database.

Table 6 Key features of the pivotal evidence for IMPELLA versus VA-ECMO (matched/adjusted)

Study Country	N	Study design Risk of bias	Population	Intervention	Comparator	Key clinical outcome(s)	Result used in economic model
Karatolios 2021 Germany	IMPELLA = 300 (83 matched) VA-ECMO = 123 (83 matched)	SC, R (Sep 2014 to Sep 2019) PSM analyses Risk of bias: Good *(? Fair, based on commentary)*	Any CS (~86% AMI-CS & ~14% DCM/ myocarditis)	IMPELLA 2.5/ CP	VA-ECMO	Survival (in-hospital, 6 mo); bleeding requiring transfusion; limb ischaemia requiring intervention; stroke; other complications	Yes (1 & 6 mo mortality; bleeding requiring transfusion)
Lemor 2020 U.S.	IMPELLA = 5730 (450 matched) VA-ECMO = 560 (450 matched)	R (Oct 2015 to Dec 2017), National Inpatient Sample (NIS) PSM analyses Risk of bias: Fair	AMI-CS & PCI	IMPELLA (device NS)	VA-ECMO	Mortality (in-hospital); blood transfusions; stroke; haemolysis; other complications	Yes (1 mo mortality; bleeding requiring transfusion)
Schiller 2019 Sweden	IMPELLA = 48 VA-ECMO = 46	SC, R (Jan 2003 to Aug 2015) SAVE score-adjusted analysis (for mortality) Risk of bias: Fair	Any CS (~28% AMI & ~34% post-cardiotomy)	IMPELLA 2.5/ CP/ 5.0/ LD	VA-ECMO (± IMPELLA)	Survival (30 d, 6 mo, 1 y, 2 y, 3 y, 4 y)	Yes (6 mo mortality)
Syntila 2021 Germany	IMPELLA = 105 (40 matched) VA-ECMO = 54 (40 matched)	SC, R (May 2015 to May 2020) PSM analyses Risk of bias: Fair	OHCA due to AMI with post-CA-CS	IMPELLA 2.5/ CP	VA-ECMO	Survival (to discharge, 12 mo); bleeding requiring transfusion; limb ischaemia requiring intervention; stroke; other complications	Yes (1 & 6 mo mortality; bleeding requiring transfusion)
Vetrovec 2020 U.S.	IMPELLA = 2510 (338 matched) VA-ECMO = 340 (338 matched)	R (Jan 2015 to Mar 2017), Medicare claims analysis PSM analyses Risk of bias: Fair *(? Poor, based on commentary)*	AMI-CS (aged 65+ only, Medicare FFS beneficiaries)	IMPELLA (device NS)	VA-ECMO	Mortality (in-hospital)	Yes (1 mo mortality)
Wernly 2021 Europe	IMPELLA = 73 VA-ECMO = 76	MN, R (2005 to 2014), IMPELLA-EUROSHOCK and German LifeBridge registries PS-adjusted analyses Risk of bias: Fair	AMI-CS & CA-CS	IMPELLA 2.5	VA-ECMO	Mortality (30 d); bleeding requiring transfusion; haemolysis; other complications	Yes (1 mo mortality; bleeding requiring transfusion)

AMI = acute myocardial infarction; CS = cardiogenic shock; d = days; DCM = dilated cardiomyopathy; FFS = fee-for-service; mo = months; MN = multinational; N = number of participants; NS = not specified; OHCA = out-of-hospital cardiac arrest; PCI = percutaneous coronary intervention; PS = propensity score; PSM = propensity score matched; R = retrospective; SAVE = Survival After Veno-arterial Extracorporeal membrane oxygenation; SC = single centre; U.S = United States; VA-ECMO = veno-arterial extracorporeal membrane oxygenation; y = years.

Source: Derived from Table 23 of MSAC 1523.1 ADAR+in-line commentary, which also presented the key features of the unmatched/unadjusted studies (not shown here).

Table 7 Key features of the pivotal evidence for ECPELLA versus VA-ECMO with or without surgical venting (matched/adjusted)

Study Country	N	Study design Risk of bias	Population	Intervention	Comparator	Key outcome(s)	Result used in economic model
Hendrickson 2022 U.S.	ECPELLA = 1880 VA-ECMO = 7440	R (2016 to 2018), Healthcare Cost and Utilisation Project National Inpatient Sample (NIS) Adjusted analyses Risk of bias: Fair	Any CS	ECPELLA (device NS)	VA-ECMO	Mortality (in-hospital)	Yes (1 mo mortality)
Pappalardo 2017 Italy, Germany	ECPELLA = 34 (21 matched) VA-ECMO = 123 (42 matched)	MC, R (Jan 2013 to Apr 2015) PSM analyses Risk of bias: Fair	Any, severe refractory CS (~48% STEMI)	ECPELLA 2.5/ CP	VA-ECMO	Mortality (in-hospital); bridge to next therapy or myocardial recovery; major bleeding; haemolysis	Yes (1 mo mortality; bleeding requiring transfusion)
Patel 2018 U.S.	ECPELLA = 30 VA-ECMO = 36	SC, R (2014 to 2016) Adjusted analyses Risk of bias: Fair *(? Poor, based on commentary)*	Any refractory CS	ECPELLA 2.5/ CP/ 5.0	VA-ECMO	Mortality (30 d, 12 mo); major bleeding; stroke; haemolysis	Yes (6 mo mortality)
Radakovic 2022 Germany	ECPELLA = 71 VA-ECMO + SV = 41	SC, R (Jan 2009 to Feb 2020) IPTW-adjusted analyses Risk of bias: Fair	AMI-CS	ECPELLA 2.5/ CP	VA-ECMO plus SV	Mortality (30 d); myocardial recovery or transition to durable MCS; stroke; peripheral ischaemic complications; sepsis	SA only
Schrage 2020b Germany, Italy, U.S., France	ECPELLA = 337 (255 matched) VA-ECMO = 349 (255 matched)	MC, R (2005 to 2019) PSM analyses Risk of bias: Fair	Any CS excl. cardiotomy CS (~63% AMI & ~37% ischaemic)	ECPELLA 2.5/ CP/ 5.0	VA-ECMO	Mortality (30 d); bleeding; stroke; haemolysis; ischaemia	Yes (bleeding requiring transfusion)

AMI = acute myocardial infarction; CS = cardiogenic shock; d = day; ECPELLA = VA-ECMO + IMPELLA; IPTW = inverse probability treatment weighting; MC = multicentre; MCS = mechanical circulatory support; mo = month; N = number of participants; NS = not specified; PSM = propensity score matched; R = retrospective; SA = sensitivity analyses; SC = single centre; STEMI = ST-elevation myocardial infarction; SV = surgical venting; U.S = United States; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.

Source: Derived from Table 23 of MSAC 1523.1 ADAR+in-line commentary, which also presented the key features of the unmatched/unadjusted studies (not shown here).

11. Comparative safety

The safety outcomes presented in the ADAR included bleeding events requiring transfusion, stroke, limb ischaemia, haemolysis and 'other' complications. Short-term mortality (30-day/in-hospital) and long-term mortality (6 months onwards) are presented in Section 10. Results are shown below for the pivotal evidence (matched/adjusted studies) only.

Of note, the ADAR excluded studies that did not report sufficient mortality or survival data. The commentary noted that while this was the key clinical outcome, there may have been additional studies excluded from the ADAR that reported other outcomes of interest (including safety).

Bleeding events requiring transfusion

IMPELLA versus VA-ECMO

Table 8 presents the proportion of patients experiencing bleeding events requiring transfusion in the matched/adjusted IMPELLA versus VA-ECMO studies. Although the largest study, Lemor (2020), reported no statistically significant difference between groups, the ADAR found a statistically significant difference for this study, favouring IMPELLA. The ADAR speculated that the discrepancy may be due to different statistical methods.

Table 8 Bleeding events requiring transfusion in the matched/adjusted IMPELLA versus VA-ECMO studies

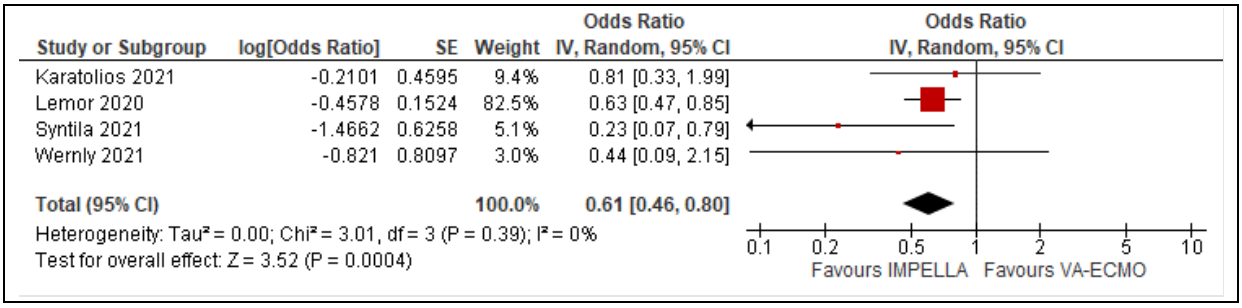
Trial ID	CS type	IMPELLA n/N (%)	VA-ECMO n/N (%)	OR [95% CI] p-value	RR [95% CI] p-value	RD [95% CI] p-value
Karatolios 2021[a]	Any CS	10/83 (12.0%)	12/83 (14.5%)	0.81 [0.33, 1.99] p=0.65	0.83 [0.38, 1.82] p=0.65	−0.02 [−0.13, 0.08] p=0.65
Lemor 2020[b]	AMI-CS	100/450 (22.2%)	140/450 (31.1%)	As reported: 0.63 [0.31, 1.28] p=0.201 ADAR calculated: **0.63 [0.47, 0.85] p=0.003**	**0.71 [0.57, 0.89] p=0.003**	**−0.09 [−0.15, −0.03] p=0.002**
Syntila 2021	OHCA due to AMI with post CS	4/40 (10.0%)	13/40 (32.5%)	**0.23 [0.07, 0.79] p=0.02**	**0.31 [0.11, 0.86] p=0.03**	**−0.23 [−0.40, −0.05] p=0.01**
Wernly 2021[c]	AMI-CS and CA-CS	–	–	As reported: 0.44 [0.09, 2.10] p=0.29	NR	NR
Meta-analysis		114/573 (19.9%)	165/573 (28.8%)	**0.61 [0.46, 0.80] p=0.0004**	**0.67 [0.46, 0.97] p=0.03**	**−0.09 [−0.17, −0.01] p=0.03**
Heterogeneity				I^2=0%; P=0.39	I^2=25%; P=0.26	I^2=49%; P=0.14

AMI = acute myocardial infarction; CA = cardiac arrest; CI = confidence interval; CS = cardiogenic shock; NR = not reported; OHCA = out-of-hospital cardiac arrest; OR = odds ratio; RD = risk difference; RR = relative risk; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Note: Point estimates were calculated for the ADAR using RevMan 5.3, except for Wernly 2021 (OR as reported in study publication) and Lemor 2020 (OR as reported in study publication and also as calculated in the ADAR). Statistically significant results are in bold.
[a] Percentages reported in the matched VA-ECMO cohort in Karatolios (2021) differed to those calculated based on the n/N's provided.
[b] Numerators were calculated based on the percentages reported in the Lemor (2020) publication. Risks relate to the PSM cohorts.
[c] Wernly (2021) only reported percentages for unadjusted data: IMPELLA 20/73 (27.4%) versus VA-ECMO 49/76 (64.5%).
Source: Excerpt from Table 45 of MSAC 1523.1 ADAR+in-line commentary

The meta-analysis (Table 8 and Figure 1) showed statistically significantly lower odds of bleeding events requiring transfusion for patients treated with IMPELLA versus VA-ECMO. GRADE certainty of evidence for this outcome was low. The meta-analysed OR (0.61, 95% CI 0.46, 0.80) was used in the economic analysis. Meta-analysis performed using the Mantel-Haenszel method without Wernly (2021) resulted in a similar risk estimate (OR 0.59; 95% CI 0.36, 0.94; p=0.03).

The commentary noted potential for patient overlap in two retrospective cohort studies that were conducted at the same institution over a similar time period (Karatolios 2021; Syntila 2021).

Figure 1 Forest plot of bleeding events requiring transfusion in the matched/adjusted IMPELLA versus VA-ECMO studies



CI = confidence interval; IV = inverse variance; SE = standard error; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Note: Meta-analysis was conducted using the generic inverse variance method.
Source: Figure 27 of MSAC 1523.1 ADAR+in-line commentary.

ECPELLA versus VA-ECMO with or without surgical venting

Table 9 provides the results for bleeding events requiring transfusion in matched ECPELLA versus VA-ECMO ± SV studies. The commentary noted there is potential for patient overlap and double counting in the meta-analysis as the two studies (Pappalardo 2017; Schrage 2020b) were conducted at the same institution over a similar time period.

The meta-analysis showed a statistically significantly higher odds of bleeding events requiring transfusion for patients treated with ECPELLA versus VA-ECMO. The ADAR commented that this was expected given that patients in the ECPELLA cohort were treated with two MCS devices as opposed to one in the VA-ECMO cohort. The addition of a second device, including the need for a second arterial access, increases the likelihood of bleeding/ischaemic complications, especially because ultrasound-guided vascular access (which could reduce such complications) is not always feasible in CS (Schrage 2020b).

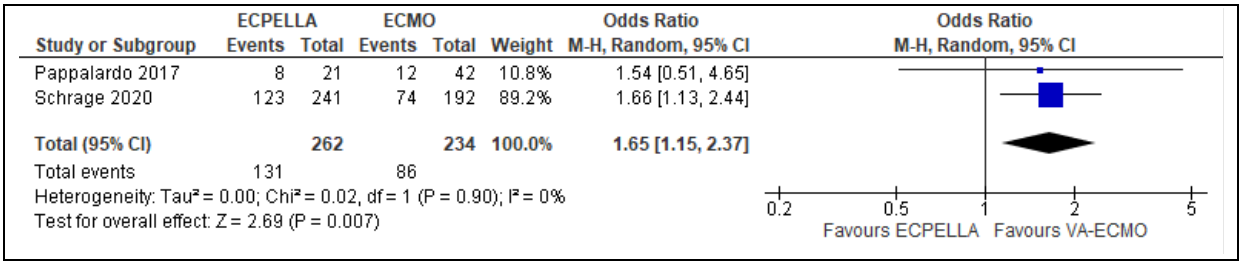
GRADE certainty of evidence for this outcome was low. The meta-analysed OR (1.65, 95% CI 1.15, 2.37) was used in the economic analysis.

Table 9 Bleeding events requiring transfusion in the matched/adjusted ECPELLA versus VA-ECMO studies

Trial ID	CS type	ECPELLA n/N (%)	VA-ECMO n/N (%)	OR [95% CI] p-value	RR [95% CI] p-value	RD [95% CI] p-value
Pappalardo 2017	Severe refractory CS	8/21 (38.1%)	12/42 (28.6%)	1.54 [0.51, 4.65] p=0.45	1.33 [0.65, 2.75] p=0.44	0.10 [−0.15, 0.34] p=0.45
Schrage 2020b[a]	Any CS	123/241 (51.0%)	74/192 (38.5%)	**1.66 [1.13, 2.44] p=0.01**	**1.32 [1.07, 1.65] p=0.01**	**0.12 [0.03, 0.22] p=0.009**
Meta-analysis		131/262 (50.0%)	86/234 (36.8%)	**1.65 [1.15, 2.37] p=0.007**	**1.32 [1.08, 1.63] p=0.008**	**0.12 [0.03, 0.21] p=0.007**
Heterogeneity				I^2=0%; P=0.90	I^2=0%; P=0.99	I^2=0%; P=0.83

CI = confidence interval; CS = cardiogenic shock; VA-ECMO = veno-arterial extracorporeal membrane oxygenation; ECPELLA = IMPELLA + VA-ECMO; OR = odds ratio; RD = risk difference; RR = relative risk.
Note: Point estimates were calculated for the ADAR using RevMan 5.3, except where noted. Statistically significant results are in bold.
[a] Denominator reported was less than the ITT matched population (N=255 for both cohorts), likely due to missing data.
Source: Table 47 of MSAC 1523.1 ADAR+in-line commentary, including commentary corrections

Figure 2 Forest plot of bleeding events requiring transfusion in the matched/adjusted ECPELLA versus VA-ECMO studies



CI = confidence interval; M-H = Mantel-Haenszel; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Source: Figure 29 of MSAC 1523.1 ADAR+in-line commentary

Stroke

IMPELLA versus VA-ECMO

Two matched studies reported any stroke (type not specified). In Karatolios (2021), two patients in each cohort experienced a stroke. No patients in either cohort of Syntila (2021) experienced a stroke.

Lemor (2020) reported a numerically higher proportion of patients experiencing acute ischaemic stroke in the VA-ECMO arm (5.6%) compared to the IMPELLA arm (1.1%) in the PSM population. However, the OR reported in the publication for the PSM population was not statistically significant (p=0.134).

ECPELLA versus VA-ECMO with or without surgical venting

Two matched/adjusted studies reported rates of ischaemic stroke. Schrage (2020b) reported ischaemic stroke in 7.0% of ECPELLA patients and 9.1% of VA-ECMO patients. Radakovic (2022) reported a RR that indicated no difference between the two cohorts. Meta-analysis showed no statistically significant difference between cohorts (RR 0.84, 95% CI 0.50, 1.41; p=0.50).

Schrage (2020b) reported haemorrhagic stroke in 3.2% of ECPELLA patients and 5.5% of VA-ECMO patients (p=0.27).

Limb ischaemia

IMPELLA versus VA-ECMO

Two matched studies reported rates of limb ischaemia requiring intervention. In Karatolios (2021), 8.4% of the IMPELLA cohort and 14.5% of the VA-ECMO cohort reported limb ischaemia (p=0.23). Syntila (2021) reported a significantly lower rate of limb ischaemia in the IMPELLA cohort compared with VA-ECMO (2.5% versus 20.0%; p=0.04). Meta-analysis showed no statistically significant difference between the two cohorts (OR 0.31, 95% CI 0.06, 1.49; p=0.14) and moderate heterogeneity.

ECPELLA versus VA-ECMO with or without surgical venting

Radakovic (2022) was the only adjusted study to report limb ischaemia for ECPELLA versus VA-ECMO plus surgical vent. The RR indicated that numerically fewer VA-ECMO plus SV patients experienced limb ischaemia compared with ECPELLA patients, though the difference was not statistically significant (2.10, 95% CI 0.80, 5.56; p=0.13).

Haemolysis

IMPELLA versus VA-ECMO

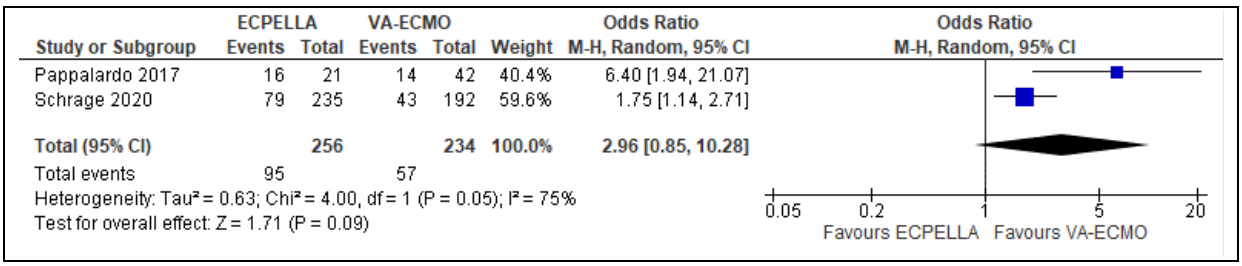
Two matched/adjusted studies reported the proportion of patients experiencing haemolysis (no definitions were provided). Lemor (2020) reported identical rates of haemolysis in the IMPELLA and VA-ECMO cohorts (1.1%). Wernly (2021) reported an adjusted OR of 0.63 (95% CI 0.08, 5.23; p=0.67). Meta-analysis showed no statistically significant difference between the two cohorts (OR 0.89, 95% CI 0.30, 2.60; p=0.83).

ECPELLA versus VA-ECMO with or without surgical venting

Haemolysis was reported in two matched studies (Pappalardo 2017; Schrage 2020b), though different definitions were used. Both studies reported a statistically significantly higher proportion of ECPELLA patients with haemolysis compared with VA-ECMO patients. The meta-analysis showed no statistically significant difference between the cohorts in terms of OR (see Figure 3), but a highly statistically significant difference in RR (1.78, 95% CI 1.18, 2.69; p=0.006) –Forest plot not shown in ADAR.

Of note, there is potential for patient overlap and double counting in the meta-analysis as the studies were conducted at the same institution in Germany over a similar time period.

Figure 3 Forest plot of haemolysis in the matched/adjusted ECPELLA versus VA-ECMO studies



CI = confidence interval; M-H = Mantel-Haenszel; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Source: Figure 42 of MSAC 1523.1 ADAR+in-line commentary

Other complications

IMPELLA versus VA-ECMO

Rates of other complications (including acute kidney injury, myocardial reinfarction, acute respiratory failure, acute liver failure, vascular complications, renal failure, multi-organ failure) were reported in the ADAR for the matched/adjusted studies. Few studies contributed data towards individual complications/adverse events, hence firm conclusions cannot be drawn.

ECPELLA versus VA-ECMO with or without surgical venting

Rates of other complications were reported by three matched/adjusted studies (Pappalardo (2017; Schrage 2020b; Radakovic 2022). Only one study contributed data for each adverse event, with the exception of sepsis, which affected more ECPELLA patients than VA-ECMO patients, though the difference did not reach statistical significance (OR 1.30, 95% CI 0.96, 1.76; p=0.09). Several adverse events were more common in patients treated with ECPELLA than VA-ECMO, though firm conclusions cannot be drawn on the basis of the limited evidence available.

12. Comparative effectiveness

The primary outcome reported in the ADAR was mortality. The ADAR noted a range of variables that potentially predict mortality in patients with CS, suggesting that at a minimum the following are important to consider when attempting to match study cohorts to mitigate potential confounding: age, pH, lactate, alanine transaminase (ALT), systolic blood pressure, out-of-hospital cardiac arrest, and the number of devices utilised. The commentary noted that very few of the included studies matched/adjusted using these variables.

None of the included studies included quality of life as an outcome.

30-day/in-hospital mortality

IMPELLA versus VA-ECMO

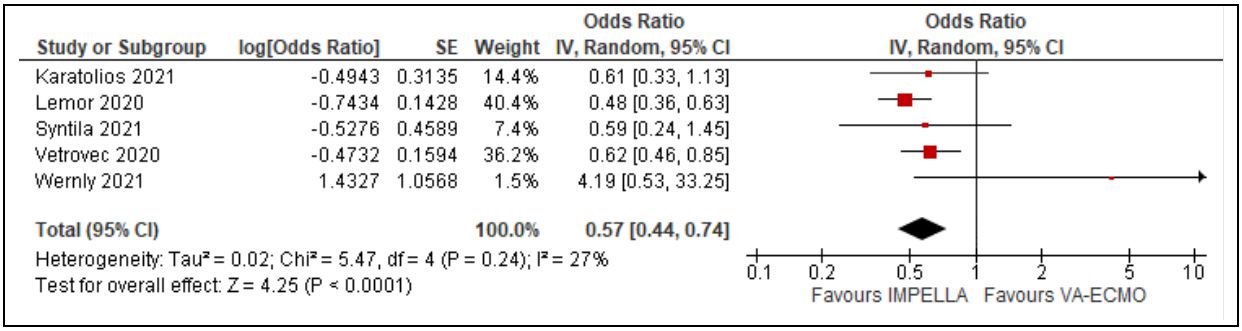
Table 10 and Figure 4 present 30-day/in-hospital mortality after temporary MCS in the matched/ adjusted IMPELLA versus VA-ECMO studies.

Table 10 30-day/in-hospital mortality in the matched/adjusted IMPELLA versus VA-ECMO studies

Trial ID (timing)	CS type	IMPELLA n/N (%)	VA-ECMO n/N (%)	OR [95% CI] p-value	RR [95% CI] p-value	RD [95% CI] p-value
Karatolios 2021 (In-hospital)	Any CS	41/83 (49.4%)	51/83 (61.4%)	0.61 [0.33, 1.14] p=0.12	0.80 [0.61, 1.06] p=0.12	-0.12 [-0.27, 0.03] p=0.12
Lemor 2020[a] (In-hospital)	AMI-CS	120/450 (26.7%)	195/450 (43.3%)	As reported: **0.48 [0.25, 0.89] p=0.021** ADAR calculated: **0.48 [0.36, 0.63] p<0.00001**	**0.62 [0.51, 0.74] p<0.00001**	**-0.17 [-0.23, -0.11] p<0.00001**
Syntila 2021 (In-hospital)	OHCA due to AMI with post CS	22/40 (55.0%)	27/40 (67.5%)	0.59 [0.24, 1.46] p=0.25	0.81 [0.57, 1.16] p=0.26	-0.13 [-0.34, 0.09] p=0.25
Vetrovec 2020 (In-hospital)	AMI-CS	178/338 (52.7%)	217/338 (64.2%)	**0.62 [0.46, 0.84] p=0.002**	**0.82 [0.72, 0.93] p=0.003**	**-0.12 [-0.19, -0.04] p=0.002**
Wernly 2021[b] (30-day)	AMI-CS and CA-CS	–	–	As reported: 4.19 [0.53, 33.25][c] 4.37 [0.51, 37.27][d] p=0.17	NR	NR
Meta-analysis excl. Wernly 2021		361/911 (39.6%)	490/911 (53.8%)	**0.55 [0.45, 0.66] p<0.00001**	**0.75 [0.64, 0.89] p=0.0006**	**-0.14 [-0.19, -0.10] p<0.00001**
Heterogeneity				I^2=0%; P=0.63	I^2=57%; P=0.07	I^2=0%; P=0.75
Meta-analysis incl. Wernly 2021[e]				**0.57 [0.44, 0.74] p<0.0001**	–	–
Heterogeneity				I^2=27%; P=0.24	–	–

AMI = acute myocardial infarction; CA = cardiac arrest; CI = confidence interval; CS = cardiogenic shock; NR = not reported; OHCA = out-of-hospital cardiac arrest; OR = odds ratio; RD = risk difference; RR = relative risk; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Note: Survival rates from Karatolios (2021) and Syntila (2021) were converted to mortality rates to enable comparison. Point estimates were calculated for the ADAR using RevMan 5.3, except for Wernly 2021 (OR as reported in study publication) and Lemor 2020 (OR as reported in study publication and also as calculated in the ADAR). Statistically significant results are in bold.
[a] Risks relate to the PSM cohorts.
[b] Wernly (2021) only reported percentages for unadjusted data: IMPELLA 51/73 (69.9%) versus VA-ECMO 63/76 (82.9%).
[c] Reported OR is adjusted for lactate.
[d] Reported OR is adjusted for lactate plus procedural feasibility and vascular injury.
Source: Excerpt from Table 34 of MSAC 1523.1 ADAR+in-line commentary

Figure 4 Forest plot of 30-day/in-hospital mortality in the matched/adjusted IMPELLA versus VA-ECMO studies



CI = confidence interval; IV = inverse variance; SE = standard error; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Source: Figure 13 of MSAC 1523.1 ADAR+in-line commentary.

The ADAR concluded there was a statistically significantly lower probability of death within 30 days/hospital discharge for IMPELLA compared with VA-ECMO, with the number needed to treat (NNT) to avoid one death being eight. GRADE certainty of evidence for this outcome was low. The meta-analysed OR (0.57, 95% CI 0.44, 0.74) was used in the economic analysis.

The commentary noted the potential for double counting because Karatolios (2021) and Syntila (2021) were conducted at the same institution over a similar time period. Patients in Karatolios (2021) were analysed according to the first device implanted. Lemor (2020) reported use of IABP in 50% of IMPELLA patients and 48% of VA-ECMO. Wernly (2021) included patients with CA-CS who have a substantially higher mortality risk than patients with CS alone.

Although not reported in the ADAR's clinical evaluation, the Cox regression curve adjusted (using the SAVE score) for survival in Schiller 2019 showed a 30-day survival that was similar for IMPELLA and VA-ECMO (60% and 61.9%, respectively).

ECPELLA versus VA-ECMO with or without surgical venting

Table 11 and Figure 5 present 30-day/in-hospital mortality after temporary MCS in the matched/ adjusted ECPELLA versus VA-ECMO ± SV studies.

The ADAR concluded that ECPELLA is associated with a statistically significant lower probability of death within 30 days/hospital discharge compared with VA-ECMO. The meta-analysed OR (0.71, 95% CI 0.19, 2.60; p=0.60) was used in the economic analysis. The commentary noted that none of the meta-analyses reached the threshold for statistical significance ($p< 0.05$) and GRADE certainty of evidence was very low (OR) and low (RR and HR).

The commentary noted the potential for double counting due to patient overlap in Pappalardo (2017) and Schrage (2020b). The commentary also noted the use of IMPELLA prior to VA-ECMO in 56% of the ECPELLA cohort in Schrage (2020b) and 20% of the ECPELLA cohort in Patel (2018). Patel (2018) also reported that 20% of patients in the ECPELLA group and 31% of patients in the VA-ECMO group received SV. Furthermore, there were notable differences between cohorts at baseline in Patel (2018) that may have biased the mortality results in favour of ECPELLA.

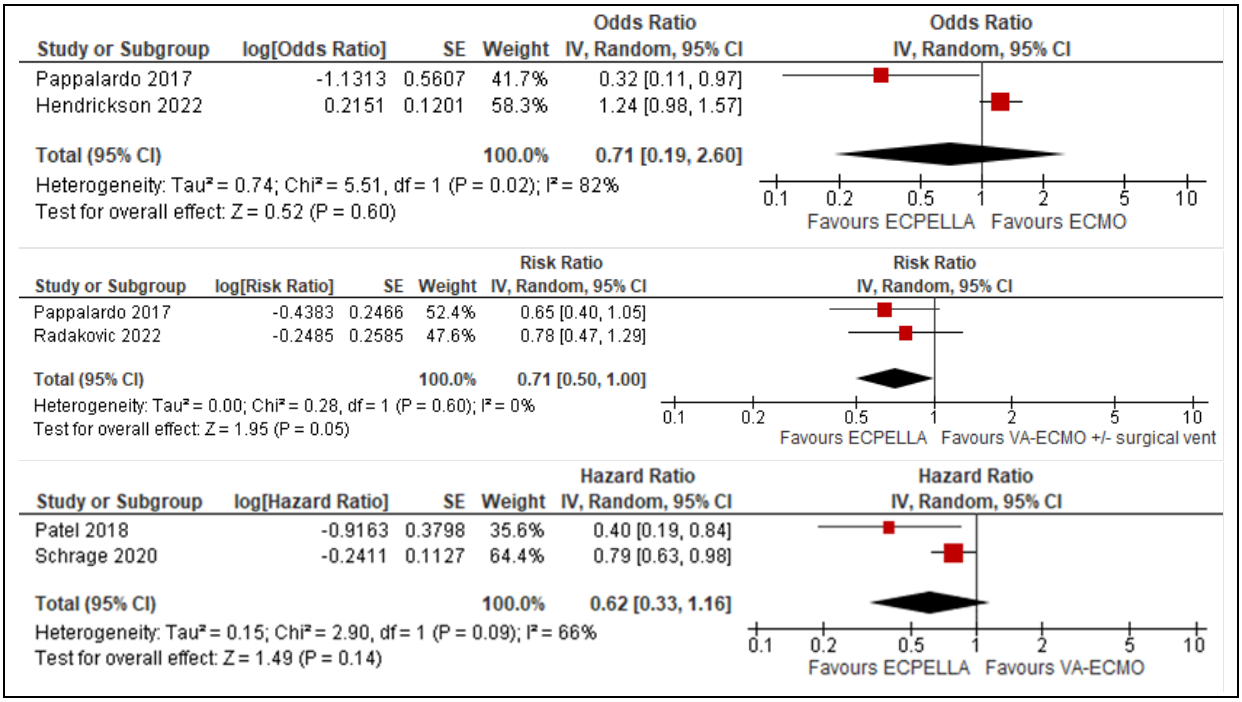
The commentary concluded that given the heterogeneity across the studies, applicability issues, inconsistency in methods of analysis and direction of effect, and concerns that attempts to rectify selection bias may not have entirely eliminated residual confounding, the findings for ECPELLA versus VA-ECMO with regards to 30-day/in-hospital mortality were uncertain.

Table 11 30-day/in-hospital mortality in the matched/adjusted ECPELLA versus VA-ECMO ± surgical vent studies

Trial ID (timing)	CS type	ECPELLA n/N (%)	VA-ECMO n/N (%)	OR [95% CI] p-value	RR [95% CI] p-value	RD [95% CI] p-value
Hendrickson 2022[a] (In-hospital)	Any CS	–	–	As reported: 1.24 [0.98, 1.57] p=0.07	NR	NR
Pappalardo 2017 (In-hospital)	Severe refractory CS	10/21 (47.6%)	31/42 (73.8%)	As reported: **0.32 [0.11, 0.97] p=0.04**	As reported: 0.65 [0.40, 1.05] p=0.08	**−0.26 [−0.51, −0.01] p=0.04**
Radakovic 2022[b] (30-day)	AMI-CS	–	–	NR	As reported: 0.78 [0.47, 1.30] p=0.35	NR
Meta-analysis				0.71 [0.19, 2.60] p=0.60	0.71 [0.50, 1.00] p=0.05	-
Heterogeneity				I^2=82%; P=0.02	I^2=0%; P=0.60	-

AMI = acute myocardial infarction; CI = confidence interval; CS = cardiogenic shock; ECPELLA = IMPELLA + VA-ECMO; NR = not reported; OR = odds ratio; RD = risk difference; RR = relative risk; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Notes: Effect sizes were calculated using RevMan 5.3 using the proportions reported, unless effect sizes were reported in the publications. Meta-analyses used the generic inverse variance method. Statistically significant results are in bold.
[a] Hendrickson (2022) only reports percentages for unadjusted data: ECPELLA 1065/1880 (56.6%) versus VA-ECMO 3845/7440 (51.7%).
[b] Radakovic (2022) only reports percentages for unadjusted data: ECPELLA 38/71 (53.5%) versus VA-ECMO+SV 26/41 (63.4%).
Source: Table 36 of MSAC 1523.1 ADAR+in-line commentary.

Figure 5 Forest plots of 30-day/in-hospital mortality in the matched/adjusted ECPELLA versus VA-ECMO ± surgical vent studies



CI = confidence interval; ECPELLA = IMPELLA plus VA-ECMO; IV = inverse variance; SE = standard error; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Source: Figure 15, Figure 16, and Figure 17 of MSAC 1523.1 ADAR+in-line commentary.

Long-term mortality

IMPELLA versus VA-ECMO

Only three of the matched/adjusted IMPELLA versus VA-ECMO studies measured mortality beyond 30 days/in-hospital. The longer-term mortality results from these studies are presented in Table 12. Meta-analysis of the two studies that reported 6-month mortality (converted from survival) found no statistically significant difference between IMPELLA and VA-ECMO. The commentary noted the potential for double counting due to patient overlap.

The ADAR stated that whilst the analysis likely lacked power to detect a statistically significant difference, studies reporting multiple timepoints indicated that patients surviving to 30 days/ hospital discharge are likely to survive over the longer-term, meaning the benefit is expected to be maintained. The commentary noted that in studies with data at multiple timepoints, mortality continued to increase (albeit slowly) in the IMPELLA cohort but was constant in patients receiving VA-ECMO. The only study that reported 5-year data found numerically higher mortality in the IMPELLA cohort.

Table 12 Longer-term mortality in the matched/adjusted IMPELLA versus VA-ECMO studies

Trial ID	CS type	IMPELLA n/N (%)	VA-ECMO n/N (%)	OR [95% CI] p-value	RR [95% CI] p-value	RD [95% CI] p-value
6-month mortality						
Karatolios 2021	Any CS	45/83 (54.2%)	51/83 (61.4%)	0.74 [0.40, 1.38] p=0.35	0.88 [0.68, 1.15] p=0.35	−0.07 [−0.22, 0.08] p=0.34
Syntila 2021	OHCA due to AMI with post CS	23/40 (57.5%)	27/40 (67.5%)	0.65 [0.26, 1.62] p=0.36	0.85 [0.60, 1.20] p=0.36	−0.10 [−0.31, 0.11] p=0.35
Meta-analysis		68/123 (55.3%)	78/123 (63.4%)	0.71 [0.43, 1.19] p=0.19	0.87 [0.71, 1.07] p=0.19	−0.08 [−0.20, 0.04] p=0.19
Heterogeneity				I^2=0%; P=0.81	I^2=0%; P=0.87	I^2=0%; P=0.83
12-month mortality						
Syntila 2021	OHCA due to AMI with post CS	24/40 (60.0%)	27/40 (67.5%)	0.72 [0.29, 1.80] p=0.49	0.89 [0.64, 1.24] p=0.49	−0.08 [−0.29, 0.14] p=0.48
5-year mortality						
Schiller 2019	Any CS	NR/48	NR/46	HR 1.05 [95% CI 0.58, 1.91] p=0.87		
	Any CS (excl. PC-CS)	NR/39	NR/23	HR 1.56 [95% CI 0.56–2.38] p=NR		

AMI = acute myocardial infarction; CI = confidence interval; CS = cardiogenic shock; HR = hazard ratio; NR = not reported; OHCA = out-of-hospital cardiac arrest; OR = odds ratio; PC-CS = post-cardiotomy cardiogenic shock; RD = risk difference; RR = relative risk; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Notes: Survival rates from Karatolios (2021) and Syntila (2021) were converted to mortality rates, consistent with mortality rates at 30 days/in-hospital.
Source: Table 38 of MSAC 1523.1 ADAR+in-line commentary.

ECPELLA versus VA-ECMO with or without surgical venting

Long-term mortality was not reported by any of the matched/adjusted ECPELLA versus VA-ECMO ± SV studies besides Patel (2018), which reported an adjusted HR for 12-month all-cause mortality of 0.39 (95% CI 0.19, 0.81), indicating statistically significantly lower mortality in the ECPELLA cohort versus the VA-ECMO cohort. GRADE certainty of evidence was very low.

The ADAR commented that this HR and the associated CIs are almost identical to the adjusted HR for 30-day mortality reported by Patel (2018), suggesting the relative benefit of effect is maintained over the longer-term. The commentary noted that Patel (2018) was a small study (30 ECPELLA and 36 VA-ECMO) with minimal statistical adjustment (STEMI and PCI only). There were notable differences between cohorts at baseline in age and lactate levels that were not variables in the adjusted analyses and may have biased the mortality results in favour of ECPELLA.

Clinical claim

In previous deliberations of IMPELLA (MSAC application 1523), MSAC concluded that the effectiveness and safety of IMPELLA was uncertain compared with VA-ECMO. The analysis of matched/adjusted studies in the ADAR for application 1523.1 is more rigorous than previously undertaken but the clinical claims continue to rely entirely on non-randomised studies and low or very low certainty evidence.

IMPELLA versus VA-ECMO

The ADAR concluded that the use of IMPELLA results in **superior effectiveness** compared with VA-ECMO with respect to mortality. The GRADE certainty of evidence for this outcome was low (30-day/in-hospital and 6-month mortality) and very low (12-month mortality). Furthermore, superiority only holds for 30-day/in-hospital mortality; there were no statistically significant differences between groups in longer-term mortality (at 6 months, 12 months or 5 years).

The ADAR concluded that the use of IMPELLA results in **superior safety** compared with VA-ECMO with respect to bleeding events requiring transfusion. The GRADE certainty of evidence for this outcome was low.

ECPELLA versus VA-ECMO with or without surgical venting

The ADAR concluded that the use of ECPELLA results in **superior effectiveness** compared with VA-ECMO (with or without SV) with respect to mortality. The commentary noted the evidence for superiority was not compelling and the GRADE certainty of evidence for this outcome was low to very low (30-day/in-hospital mortality) and very low (12-month mortality). The commentary's interpretation was that the use of ECPELLA results in **uncertain effectiveness** compared with VA-ECMO (with or without SV) with respect to mortality.

The ADAR concluded that the use of ECPELLA results in **inferior safety** compared with VA-ECMO (with or without SV) with respect to bleeding events requiring transfusion. The GRADE certainty of evidence for this outcome was low. Based on the limited evidence available, ECPELLA may also result in increased haemolysis. However, ECPELLA is non-inferior to VA-ECMO in terms of 30-day/in-hospital stroke.

13. Economic evaluation

A summary of the economic evaluation is provided in Table 13. On the basis of the ADAR's clinical claims of superior effectiveness of IMPELLA and ECPELLA compared with the comparator, two cost-utility analyses (IMPELLA and ECPELLA) were presented. The commentary noted that the appropriateness of a cost-utility analysis for ECPELLA versus VA-ECMO ± SV is questionable given that (i) ECPELLA is more costly than VA-ECMO ± SV, (ii) ECPELLA is inferior in terms of safety, and (iii) the clinical claim for superior effectiveness of ECPELLA is uncertain with respect to mortality.

Table 13 Summary of the economic evaluation

Component	Description
Perspective	Healthcare system
Population	Population 1: Patients with refractory cardiogenic shock Population 2: Patients with cardiogenic shock on VA-ECMO who require unloading of the left ventricle
Intervention	Population 1: IMPELLA Population 2: IMPELLA added to VA-ECMO (ECPELLA)
Comparator	Population 1: VA-ECMO Population 2: VA-ECMO with or without surgical venting
Type(s) of analysis	Cost-utility analysis
Outcomes	Life years gained, QALYs gained
Time horizon	Lifetime (5-, 10- and 20-year time horizons were tested in sensitivity analyses)
Computational method	Markov cohort
Generation of the base case	Modelled analysis Step 1: Matched/adjusted study-based analysis; Step 2: extrapolation of survival; Step 3: translation of life years to QALYs
Health states	Alive and Dead
Cycle length	Monthly, then yearly
Transition probabilities	Patients are attributed a mortality risk each cycle. Matched/adjusted study-based mortality risks are applied in the first cycle (one month), derived from identified matched studies (see Section 10) reporting 30-day or in-hospital mortality. Mortality risks in cycle 2 to cycle 6 are derived from the limited long-term data available from matched/adjusted studies, assuming no difference between treatment arms. Mortality risks in cycle 7 onwards are based on age- and sex-matched general population mortality risks (i.e. lifetables).
Quality of life inputs	Berger (2021) – patients in Germany treated with VA-ECMO for cardiogenic shock who underwent urgent LVAD implantation
Cost inputs	MBS, AR-DRG (PHDB); NBPL; Alfred Hospital (personal communication)
Discount rate	5% for costs and for outcomes
Software	Excel

AR-DRG = Australian-Refined Diagnosis Related Groups; MBS = Medicare Benefits Schedule; NBPL = National Blood Products List; PHDB = Private Hospitals Data Bureau; QALY = quality-adjusted life years; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.
Source: Table 63 of MSAC 1523.1 ADAR+in-line commentary, with commentary additions

All costs applied in the models were accumulated as a part of the initial hospitalisation. The models included a lump sum cost in cycle one to account for differences in safety (incidence of bleeding events requiring transfusion) between the treatments.

Based on the limited procedural information provided in the matched studies, the base case models assumed the same 5-day duration of MCS for the intervention and comparator. Likewise, the hospital length of stay was assumed to be the same for the intervention and comparator (11 days for Population 1 and 14 days for Population 2).

The results of the stepped economic analysis for IMPELLA versus VA-ECMO are presented in Table 14.

Table 14 Results of the stepped economic analysis: IMPELLA versus VA-ECMO

Step	IMPELLA	VA-ECMO	Increment	ICER
Step 1: Matched/ adjusted study-based analysis				
Costs	$**redacted**	$54,302	$**redacted**	$**redacted** per patient alive at 30 days/ hospital discharge
Outcomes (% alive at 30 days/ hospital discharge)	58.1%	44.1%	14.0%	
Step 2: Extrapolation of survival				
Costs	$**redacted**	$54,302	$**redacted**	$**redacted** per LY
Outcomes (LYs)	11.681	8.883	2.798	
Step 3: Translation of life years to QALYs				
Costs	$**redacted**	$54,302	$**redacted**	$**redacted** per QALY
Outcomes (QALYs)	5.038	3.832	1.206	

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality adjusted life years; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Note: Cost inputs were taken from the ADAR, not updated to reflect current MBS fees.
Source: Derived from Table 98, Table 100, Table 101 and Table 71 of MSAC 1523.1 ADAR+in-line commentary.

The results of the stepped economic analysis for ECPELLA versus VA-ECMO ± SV are presented in Table 15. Slightly different results were obtained by the commentary due to a discrepancy between the ADAR and commentary in the weighted average 30-day/in-hospital mortality risks calculated from the included studies.

The cost-utility estimates are subject to considerable uncertainty because the 30-day mortality risks applied in the first cycle (favouring ECPELLA) were based on a meta-analysis that showed no statistically significant difference between ECPELLA and VA-ECMO ± SV. If ECPELLA is considered non-inferior to VA-ECMO ± SV in terms of mortality (which is a reasonable interpretation of evidence available) and inferior in terms of safety, consideration of cost-effectiveness may not be appropriate.

Table 15 Results of the stepped economic analysis: ECPELLA versus VA-ECMO ± surgical venting

Step	ECPELLA	VA-ECMO ± SV	Increment	ICER
Step 1: Matched/ adjusted study-based analysis				
Costs	$**redacted**	$63,853	$**redacted**	$**redacted** per patient alive at 30 days/ hospital discharge
Outcomes (% alive at 30 days/ hospital discharge)	59.9%	62.7%	7.9%	
Outcomes – commentary revised[a]	54.4%	62.7%	8.2%	-
Step 2: Extrapolation of survival				
Costs	$**redacted**	$63,853	$**redacted**	$**redacted** per LY
Outcomes (LYs)	8.960	7.206	1.753	
Outcomes – commentary revised[a]	10.185	8.341	1.844	$23,435 per LY
Step 3: Translation of life years to QALYs				
Costs	$**redacted**	$63,853	$**redacted**	$**redacted** per QALY
Outcomes (QALYs)	3.512	2.826	0.686	
Outcomes – commentary revised[a]	3.922	3.270	0.722	$**redacted** per QALY

ECPELLA = VA-ECMO + IMPELLA; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality adjusted life years; SV = surgical venting; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Note: Cost inputs were taken from the ADAR, not updated to reflect current MBS fees.
[a] Alternative 30-day/in-hospital mortality risk weightings were used in the commentary calculations (Table 72 of MSAC 1523.1 ADAR+in-line commentary).
Source: Table 99, Table 102, Table 103 and Table 74 of MSAC 1523.1 ADAR+in-line commentary.

The ADAR's economic evaluation does not take into consideration several factors that could increase costs relating to IMPELLA and change the cost-effectiveness estimates:

- some patients who receive IMPELLA may receive VA-ECMO afterwards due to respiratory failure, RHF, hemodynamic deterioration or progressive multi-organ failure
- some patients on IMPELLA 2.5 or CP may require transition to an IMPELLA 5.0 or 5.5
- some patients with IMPELLA 5.0 or 5.5 may require reimplantation
- duration of support on IMPELLA may be longer in practice because the IMPELLA 5.5 can be used for up to 30 days, which is advantageous when waiting for a heart transplant.

Both economic evaluations were most sensitive to the applied time horizon, short-term mortality and long-term standardised mortality rates.

The results of key univariate sensitivity analyses are summarised below.

Table 16 Sensitivity analyses: IMPELLA versus VA-ECMO

Analyses	Incremental cost	Incremental QALY	ICER
Base case	**$redacted**	**1.2055**	**$redacted**
Time horizon (base case: lifetime, 37 years)			
20 years	**$redacted**	1.0720	**$redacted**
10 years	**$redacted**	0.7233	**$redacted**
5 years	**$redacted**	0.4323	**$redacted**
Relative mortality in cycle 1 (base case: OR = 0.57)			
Lower confidence limit (OR = 0.44)	**$redacted**	1.7361	**$redacted**
Upper confidence limit (OR = 0.74)	**$redacted**	0.6479	**$redacted**
Mortality cycle 7 onwards (base case: SMR = 1.0)			
SMR = 2	**$redacted**	1.0346	**$redacted**
SMR = 5	**$redacted**	0.7782	**$redacted**

ICER = incremental cost-effectiveness ratio; OR = odds ratio; QALY = quality adjusted life year; SMR = standardised mortality rate; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Source: Excerpt from Table 106 of MSAC 1523.1 ADAR+in-line commentary.

Table 17 Sensitivity analyses: ECPELLA versus VA-ECMO ± surgical venting

Analyses[a]	Incremental cost	Incremental QALY	ICER
Base case	**$redacted**	**0.722**	**$redacted**
Time horizon (base case: lifetime, 43 years)			
20 years	**redacted**	0.601	**$redacted**
10 years	**$redacted**	0.395	**$redacted**
5 years	**$redacted**	0.234	**$redacted**
Relative mortality in cycle 1 (base case: OR = 0.71)			
Lower confidence limit (OR = 0.19)	**$redacted**	3.351	**$redacted**
Upper confidence limit (OR = 2.61)	**$redacted**	-1.631	Dominated
Mortality cycle 7 onwards (base case: SMR = 1.0)			
SMR = 2	**$redacted**	0.639	**$redacted**
SMR = 5	**$redacted**	0.507	**$redacted**

ICER = incremental cost-effectiveness ratio; OR = odds ratio; QALY = quality adjusted life year; SMR = standardised mortality rate; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
[a] Commentary alternative 30-day/in-hospital mortality risk weightings were used in the calculations shown here.
Source: Excerpt from Table 107 of MSAC 1523.1 ADAR+in-line commentary.

14. Financial/budgetary impacts

A market share approach was used to estimate the financial impact of listing services for the insertion, management, and removal of IMPELLA on the MBS for CS patients requiring MCS, and the associated IMPELLA kit on the Prescribed List.

The market share approach employed historical MBS data for VA-ECMO services to estimate the number of patients requiring MCS in a private (MBS) setting, and Extracorporeal Life Support Organisation (ELSO) registry data to estimate the proportion of these patients with a CS indication.

Estimated use of the proposed technology

The estimated uptake of IMPELLA and ECPELLA on the MBS is summarised in Table 18. The estimates assume that IMPELLA will substitute some VA-ECMO services on the MBS, and that ECPELLA will be added to a proportion of VA-ECMO services on the MBS.

Table 18 Estimated uptake of IMPELLA and ECPELLA on the MBS

Row		2024 (Year 1)	2025 (Year 2)	2026 (Year 3)	2027 (Year 4)	2028 (Year 5)	Source/ calculation
A	Estimated VA-ECMO services	37	38	38	39	39	Extrapolated from Medicare statistics
B	% VA-ECMO for CS	60.7%	60.7%	60.7%	60.7%	60.7%	ELSO Registry 2016
C	Total patients requiring MCS for CS	23	23	23	24	24	A x B
D	Uptake of IMPELLA, %	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%	ADAR assumption
E	Uptake of IMPELLA, n	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	C x D
F	Uptake of ECPELLA, %	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%	ADAR assumption
G	Uptake of ECPELLA, n	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	C x F

ADAR = Applicant Developed Assessment Report; CS = cardiogenic shock; ELSO = Extracorporeal Life Support Organisation; MCS = mechanical circulatory support; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Source: Compiled from Table 110 and Table 111 of MSAC 1523.1 ADAR+in-line commentary.

The commentary noted that although it is reasonable to assume that the uptake of IMPELLA-related services by hospitals for CS patients will be gradual during the first year to allow for necessary equipment and expertise to be acquired, no references or data were provided to support the uptake estimates. Although not explicitly mentioned in the ADAR:

- a proportion of CS patients will not be suitable for IMPELLA (for example, patients with RVF or biventricular failure)
- LV unloading is required in approximately 25% of CS patients on VA-ECMO.

Estimation of financial impact to the MBS

The net financial implications to the MBS resulting from the proposed listing of IMPELLA and ECPELLA are summarised in Table 19. The ADAR noted that listing of IMPELLA/ECPELLA on the MBS for CS is estimated to be effectively cost neutral, with marginal cost savings expected each year over the first five years of listing.

The commentary noted that these estimates do not take into consideration several factors (outlined in Section 11) that could increase costs relating to IMPELLA and the total cost to the MBS.

Table 19 Net financial implications of listing IMPELLA and ECPELLA for CS to the MBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated use and cost of the proposed health technology					
Total cost of IMPELLA/ECPELLA-related services	$40,908	$56,508	$72,567	$73,655	$74,760
- co-payments	$10,222	$14,121	$18,134	$18,406	$18,682
- net cost to MBS	$30,685	$42,387	$54,433	$55,250	$56,078
Change in use and cost of other health technologies					
Substituted VA-ECMO-related services	$41,970	$57,881	$74,259	$75,373	$76,504
- co-payments	$10,488	$14,464	$18,556	$18,835	$19,117
- net cost to MBS	$31,482	$43,417	$55,703	$56,538	$57,387
Net financial impact to the MBS					
Total net cost	-$1,062	-$1,373	-$1,693	-$1,718	-$1,744
- co-payments	-$265	-$343	-$423	-$429	-$436
- net cost to MBS	-$797	-$1,030	-$1,270	-$1,289	-$1,308

CS = cardiogenic shock; MBS = Medicare Benefits Schedule; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.
Source: Table 118 of MSAC 1523.1 ADAR+in-line commentary.

Estimation of impact to other health budgets

The applicant intends to submit an application seeking listing of an IMPELLA kit (includes the single use IMPELLA IMVAD and one purge cassette) on the Prescribed List at a reimbursed price of $**redacted** per unit. As such, listing of IMPELLA on the MBS is expected to result in a financial impact to private health insurers (see Table 20).

The commentary noted that the total cost to private health insurers of IMPELLA kits does not take into consideration that some patients may need more than one device:

- a small proportion of patients using IMPELLA 2.5 or CP may need to 'upgrade' to an IMPELLA 5.0 or 5.5 for higher level support
- a small proportion of patients with IMPELLA 5.0 or 5.5 may require reimplantation due to pump thrombosis or accidental dislodgement.

In the ADAR economic analysis, the ADAR included costs for a two purge cassettes per episode of care (5 days duration). If the IMPELLA kit is listed on the PL, it will cover the cost of one purge cassette. The ADAR did not provide clarity on who would pay for second purge cassette or any additional purge cassettes (for longer episodes of care), that are changed every couple of days at a cost of $**redacted** per cassette.

Table 20 Net impact to private health insurers of listing the IMPELLA kit on the Prescribed List

Row		Year 1	Year 2	Year 3	Year 4	Year 5	Source / calculation
A	IMPELLA/ECPELLA procedures	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	Table 26
B	IMPELLA kits per procedure	1.0	1.0	1.0	1.0	1.0	Assumption
C	Total IMPELLA kits used	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	A x B
D	Price per IMPELLA kit	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	Proposed
E	Total cost to Private Health Insurers	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	C x D

Source: Table 119 of MSAC 1523.1 ADAR+in-line commentary.

The ADAR acknowledged there is uncertainty surrounding several inputs applied in the financial estimates, including the proportion of VA-ECMO services used for CS and the uptake of IMPELLA/ECPELLA. However, as IMPELLA/ECPELLA are expected to substitute for existing VA-ECMO (± SV), these uncertainties do not significantly impact the projected financial impact to the MBS of listing IMPELLA and ECPELLA for CS.

The commentary noted the net financial impact to the MBS may increase if:

- private hospitals develop appropriate facilities and expertise to manage patients in CS
- IMPELLA is used in settings where VA-ECMO is not available for use as an alternative treatment option
- ECPELLA is used pre-emptively rather than to unload patients on VA-ECMO with increased LV afterload.

15. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The previous application 1523 was based on low-quality clinical evidence for effectiveness and safety, and the quality of the evidence in this resubmission 1523.1 has not improved substantially. The proposed population has been appropriately narrowed on MSAC advice to only those patients with cardiogenic shock (CS) with no evidence of significant anoxic neurological injury.
- No randomised clinical trials (RCT) were available comparing the intervention with either comparator in the proposed population. Therefore, the key clinical evidence base is informed by matched/adjusted non-randomised studies. However, selection bias and the potential for confounding remain a threat to internal validity for the non-randomised studies. ESC considered the quality of evidence was low even in the matched/adjusted studies presented in the ADAR. However, ESC acknowledged that the evidence may not improve in the near future.
- The low-quality evidence indicated that IMPELLA had superior safety (reduced bleeding events requiring transfusion) and effectiveness (reduced in-hospital/30-day mortality) compared to VA-ECMO. However, no statistically significant difference in mortality was observed at 6-months and 12-months post intervention.
- The low-quality evidence indicated that ECPELLA (IMPELLA in addition to VA-ECMO) had inferior safety compared to VA-ECMO ± surgical venting (SV). Although, the evidence indicated that ECPELLA reduced in-hospital/30-day mortality compared to VA-ECMO ± SV, this reduction was not statistically significant. The evidence also indicated the mortality reduction was sustained to 12-months post-intervention; however, this outcome was based on one small (n=66) low-quality observational study.
- The potential need for re-implantation of the initial device, or transition to an IMVAD offering a higher level of support has not been considered in the assessment of cost-effectiveness or total costs.
- Confirmation is needed as to whether the proposed population would include paediatric patients, if paediatric sized devices become available.

Economic issues:

- The magnitude of the mortality differential at 30 days is the most important driver in the economic models and was informed by low- to very low-certainty evidence. Mortality risks

over the extrapolated period (beyond one month) were derived from the limited long-term data available and assumed no difference between treatment groups. MSAC may wish to consider that the within-trial estimates presented the most confidence for calculating cost-effectiveness.

- The cost-utility analysis for ECPELLA versus VA-ECMO ± SV is subject to considerable uncertainty given the effectiveness of ECPELLA compared with VA-ECMO ± SV is equivocal with respect to mortality. Further, the evidence indicates ECPELLA has inferior safety compared to ECMO ± SV. MSAC wish to consider whether a cost-utility analysis is appropriate for population proposed to receive ECPELLA (i.e. patients with CS who are on VA-ECMO and requiring LV).

Financial issues:

- The financial impact to the MBS may increase if:
  - private hospitals develop appropriate facilities and expertise to manage patients in CS, or
  - IMPELLA is used in settings where VA-ECMO is not available, or
  - ECPELLA is used pre-emptively rather than to unload patients on VA-ECMO with increased LV afterload.

ESC discussion

ESC noted this reapplication from Abiomed requested Medicare Benefits Schedule (MBS) listing of transluminal insertion and management of IMPELLA, an intravascular microaxial left ventricular assist device (IMVAD), for the management of patients with cardiogenic shock (CS) requiring temporary mechanical circulatory support (MCS).

ESC noted that acute myocardial infarction (AMI) with left ventricular (LV) dysfunction accounts for 81% of patients with CS. Further, CS-complicated AMI is the leading cause of mortality in patients hospitalised due to AMI. Other causes of CS include heart failure, cardiac arrest, cardiomyopathy, myocarditis and endocarditis. Although the in-hospital mortality in patients with CS has improved over time, longer-term mortality in CS has remained relatively consistent over the past two decades, with 40–50% of patients surviving beyond 6 months.

ESC noted that IMPELLA is a transluminal microaxial ventricular assist device that is inserted percutaneously or surgically. The IMPELLA devices are cardiac-assist devices that are intended to stabilise haemodynamics, unload the ventricle, augment peak coronary flow, perfuse the end organs, reduce myocardial oxygen demand and allow for recovery of the native heart.

ESC noted that MSAC previously considered and did not support public funding of IMPELLA (application 1523) at their November 2019 meeting. MSAC application 1523 sought reimbursement of IMPELLA for patients with CS, high-risk percutaneous coronary intervention and isolated right heart failure. At the time, MSAC considered that the evidence for comparative safety and effectiveness was too uncertain relative to standard care in all three populations, which had flow-on effects to the economic analyses. MSAC considered the financial estimates were also highly uncertain and likely underestimated for all three populations. MSAC considered that additional data from randomised controlled trials (RCTs) would be required to give greater certainty regarding comparative safety, effectiveness and cost-effectiveness.

ESC noted that this resubmission focussed on patients with CS (with no evidence of significant anoxic neurological injury) that were considered as two patient populations with different interventions and comparators:

- Patients with CS who do not respond to pharmacotherapy – the intervention for this population was IMPELLA, which was compared to veno-arterial extracorporeal membrane oxygenation (VA-ECMO).
- Patients with CS who are on VA-ECMO and requiring LV unloading – the intervention for this population was ECPELLA, which was compared to VA-ECMO ± surgical venting (SV).

ESC requested the applicant clarify in its pre-MSAC response to MSAC whether the proposed population would include paediatric patients, if appropriately sized devices for use in paediatric patients were to become available.

ESC noted and welcomed the consultation input received from 1 individual, who was a medical specialist, but noted the lack of consumer input for this reapplication. ESC noted that consumers may be concerned by the apparent selection bias of patients for the studies in that there were more men than women. ESC noted that AMI is more common in men than women, but also acknowledged that women are continually underrepresented in clinical trials. ESC noted the lack of quality-of-life analysis in the clinical evidence presented in applicant-developed assessment report (ADAR) for patients with the IMPELLA device.

ESC noted that the proposed setting for IMVAD devices is centres that are equipped to use VA-ECMO, which is the MCS device used in CS patients who have not stabilised despite pharmacotherapy. IMPELLA used in combination with VA-ECMO is referred to as ECPELLA.

ESC considered that the ADAR proposed MBS descriptors did not sufficiently define the intended population for the percutaneous and surgical insertion MBS items. Therefore, ESC considered the additions suggested by the department (as shown in Section 4, Table 4) to be more appropriate. ESC noted that the applicant's pre-ESC response expressed that the applicant was willing to work with MSAC and the department on the descriptor. ESC did not recommend any additional wording for the three removal and management MBS items. ESC considered it appropriate to include "anaes" and/or "assist" for the open surgical insertion MBS item, but not for the percutaneous insertion MBS item. ESC also confirmed that it was appropriate to include associated imaging for both insertion items.

ESC considered it appropriate to include an explanatory note advising that provision of the service should be limited to providers who have undertaken competency training and certification (provided by Abiomed), and to centres equipped with VA-ECMO that have the appropriate facilities and expertise to provide the service and manage patients in CS. ESC also considered it appropriate to include in an explanatory note that the decision to initiate a patient with CS on an IMVAD (and selection of IMVAD type) should be determined by a multidisciplinary team (MDT), typically including an interventional cardiologist, cardiothoracic surgeon, heart failure specialist and intensivist.

ESC noted that the IMVAD insertion approach depends on the patient's vasculature (assessed using fluoroscopy) and the IMPELLA model. The descriptor for MBS item 13832 (peripheral cannulation for VA-ECMO) includes "ultrasound guidance where clinically appropriate" and explicitly states that "no separate ultrasound item is payable with this item". ESC advised that the proposed descriptors should include fluoroscopy in the proposed fee for the IMVAD insertion services and that no additional fluoroscopy item should be payable.

ESC noted the clinical management algorithm. ESC noted that IMVAD devices on the MBS would provide clinicians with an alternative MCS option for patients who are in CS, with a different mechanism of action to VA-ECMO. A disadvantage of VA-ECMO is that oxygenated blood returning to the body flows retrograde in the aorta, causing a marked increase in LV afterload. ECPELLA (IMPELLA used in combination with VA-ECMO) is proposed to be used in a narrowly defined population of patients who are on VA-ECMO and require LV unloading. ESC also noted the

intended duration of uses for the IMPELLA devices is stated in the Australian Register of Therapeutic Goods (ARTG) and acknowledged that extended duration of use, beyond the ARTG specified durations, was a clinical possibility if the patient was showing clinical improvement. ESC considered this appropriate to be a clinical decision and for this reason, ESC considered it unnecessary to include duration suggestions in any explanatory notes.

ESC noted that the evidence base for the comparative safety and effectiveness of IMPELLA did not include any data from RCTs. ESC noted the applicant's pre-ESC response stated that although there have been multiple attempts to conduct RCTs, most have been discontinued due to low enrolment and asserted that, because of the urgent nature of the clinical scenario, recruiting patients and conducting RCTs in this therapeutic area is difficult. ESC was uncertain this meant an RCT could not be completed and noted there is a current ongoing RCT (UNLOAD ECMO [NCT05577195]) comparing ECPELLA with VA-ECMO in patients with CS (primary outcome is 30-day mortality and 12-month mortality is a secondary outcome). Although ESC acknowledged the applicant's argument creates uncertainty regarding when and whether this RCT will be completed, ESC noted the RCT may provide information that could impact decision making if completed.

ESC noted the resubmission presented non-randomised studies that used matching and/or other adjustment methods as the key evidence (N=6 for IMPELLA versus VA-ECMO and N=5 for ECPELLA versus VA-ECMO ± SV). ESC noted the ADAR attempted to present the next best level of evidence by selecting matched/adjusted studies as the key evidence, however. ESC considered the concerns raised by the commentary to be valid. ESC noted concerns regarding potential participant duplication across some studies. Further, covariates (patient characteristics, comorbidities, haemodynamic and laboratory values) were often not reported for the included studies, meaning the selection and extent of matching/adjusting varied such that selection bias and the potential for confounding remain a threat to internal validity for the non-randomised studies. Therefore, ESC considered the clinical evidence to be of low to very low quality. ESC queried whether retrospective analysis to obtain the missing covariate information could improve the matching/adjustment.

Regarding comparative safety, ESC noted the main safety outcome was bleeding events requiring transfusion. For IMPELLA versus VA-ECMO, the evidence suggested that IMPELLA resulted in a reduction in bleeding events requiring transfusion (odds ratio [OR] = 0.61, range 0.46–0.80, n = 1,295, four observational studies). ESC considered that this appeared to support the ADAR's claim of superior safety, but there remained uncertainty due to the low-quality evidence. For ECPELLA versus VA-ECMO ± SV, the evidence suggested ECPELLA results in an increase in bleeding events requiring transfusion (OR = 1.65, range 1.15–2.37, n = 496, two observational studies). ESC considered that this indicated ECPELLA had inferior safety compared to VA-ECMO ± SV, but again noted this was based on low-quality evidence.

Regarding comparative effectiveness, ESC noted the main effectiveness outcome was in-hospital/30-day mortality. For IMPELLA versus VA-ECMO, the evidence suggested that IMPELLA resulted in a decrease in in-hospital/30-day mortality (OR = 0.57, range 0.44–0.74, n = 1,971, five observational studies). ESC considered that this appeared to support the ADAR's clinical claim of superior effectiveness but that there remained uncertainty due to the low-quality evidence at 30 days. However, ESC noted that the limited data (of low to very-low quality) available at 6- and 12-months post-intervention did not demonstrate a difference in mortality at these longer time points. For ECPELLA versus VA-ECMO ± SV, the evidence suggested ECPELLA results in a non-statistically significant reduction in in-hospital/30-day mortality (risk ratio [RR] = 0.71, range 0.50–1.00, n = 175, two observational studies). ESC noted there was also some evidence to suggest this improvement is sustained to 12 months post-intervention; however, this was based on one small (n=66) low quality observational study.

Overall, ESC considered the comparative safety and effectiveness of IMPELLA versus VA-ECMO and ECPELLA versus VA-ECMO ± SV remained highly uncertain due to the low to very-low quality evidence, and therefore, the clinical claims were highly uncertain. However, ESC acknowledged that it was unlikely that any better-quality evidence would be available in the near future.

ESC noted the ADAR presented two stepped cost-utility analyses (CUA) comparing IMPELLA versus VA-ECMO and ECPELLA versus VA-ECMO ± SV:

- Step 1: matched/adjusted study-based analysis (comparative non-randomised studies) – percentage alive at 30 days
- Step 2: extrapolation of survival to lifetime
- Step 3: translation of life years to quality-adjusted life years (QALYs).

ESC considered that the comparator, structural model issues and assumptions that favoured the intervention in the previous application (MSAC 1523) had been addressed in this resubmission. However, ESC noted that the uncertainty from the low-quality clinical evidence remained a key issue that created high uncertainty in the economic evaluation.

For IMPELLA versus VA-ECMO, ESC noted the within-trial estimates (step 1) resulted in an incremental cost-effectiveness ratio (ICER) of $redacted per patient alive at 30 days/ hospital discharge. After step 2, the ICER dropped to $redacted per life year (LY) and after step 3, the ICER increased again to $redacted per quality adjusted life year (QALY). ESC noted that the magnitude of the in-hospital/30-day mortality differential (informed by low to very-low certainty evidence) was the most important driver in the economic model. ESC considered it reasonable that the ADAR assumed no difference (between the groups) in mortality risks over the extrapolated period (beyond one month), but noted that this resulted in the highly uncertain difference in the in-hospital/30-day mortality being extrapolated out over a lifetime horizon. Because of this, ESC considered the results of the within-trial estimates (step 1) to be the most reliable ICER.

For ECPELLA versus VA-ECMO ± SA, ESC noted the model assumed clinical difference in mortality in the first month, even though the trial did not demonstrate a statistically significant difference in in-hospital/30-day mortality between ECPELLA and VA-ECMO ± SV (RR=0.17; range 0.50–1.00), and then assumed no difference (between the groups) in mortality risks over the extrapolated period (beyond one month). ESC agreed with the commentary that, given the clinical evidence indicated inferior safety and equivocal effectiveness with respect to mortality, the use of a CUA may not be justified. ESC noted that ADAR base case ICERs were $redacted per patient alive at 30 days/ hospital discharge (step 1_, $redacted per LY (step 2), and $redacted per QALY (step 3). The commentary provided alternative 30-day/in-hospital mortality risk weightings, which resulted in slight decreases to the ICERs after steps 2 and 3 to $redacted per LY and $redacted per QALY, respectively.

ESC noted the commentary's concerns that the following factors could increase costs relating to IMPELLA and thereby reduce the cost-effectiveness for the population proposed to receive IMPELLO (i.e. patients with CS who do not respond to pharmacotherapy):

- the need for subsequent ECMO
- the need for reimplantation
- a switch to an IMPELLA device offering higher-level support
- the extended duration of support on IMPELLA 5.5.

ESC considered that about 25% of patients would require subsequent VA-ECMO, but that it was unlikely to be used routinely in combination as ECPELLA. ESC considered it appropriate for this to be a clinical decision.

Regarding reimplantation (e.g. due to pump thrombosis or dislodgement), ESC acknowledged that device thrombosis was a possibility for IMPELLA. However, ESC noted that this had not been observed in the included evidence, and that the risk can be minimised by adherence to anticoagulation protocols and guidelines. ESC noted the applicant's pre-ESC response stated that in persistent thrombosis cases, Abiomed will provide a free-of-charge replacement. It is also the global Abiomed policy to warrant the replacement working pump for the same patient and procedure. ESC also considered it important to note that device thrombosis could also occur with VA-ECMO devices, which may require exchange of the whole circuit.

Regarding transitioning to a higher level of IMPELLA support, ESC noted that the applicant's pre-ESC response stated that were no such occurrences reported in the included evidence and that, since implementation in 2019, no patients who have received an IMPELLA device in Australia (n = 227) have required escalation. The applicant's pre-ESC response stated the Shock Team can determine the appropriate pump size for any given patient before implantation based on the patient's haemodynamic conditions and body size, type of CS, and ejection fraction, which ESC inferred would decrease the chances of needing to be transitioned to a different device.

ESC noted the financial impact analysis suggested a cost savings to the MBS of $797 in year 1 to $1,308 in year 5. However, ESC noted that the utilisation of IMPELLA is likely to be predominately in the public hospital setting. Similarly, the comparator VA-ECMO is predominately used in a public setting. In 2022, there were 36 services for VA-ECMO first-day management (MBS item 13834), which accounted for ~19% of all Australian VA-ECMO patients captured in the EXCEL Registry that year.

ESC noted that the costs to the MBS may increase if:

- private hospitals develop appropriate facilities and expertise to manage patients in CS (which ESC considered unlikely; see discussion below), or
- IMPELLA® is used in settings where VA-ECMO is not available, or
- ECPELLA is used pre-emptively rather than to unload patients on VA-ECMO with increased LV afterload.

ESC noted main financial impact would be to private health insurers ($redacted in year 1 to $redacted in year 5) if the IMPELLA device is listed on the IMPELLA device is not currently listed on the Prescribed List of Medical Devices and Human Tissue Products (PL). However, ESC noted that the IMPELLA device's cost of $redacted may fall to hospitals or be borne as out-of-pocket costs by patients if it is not listed on the PL. If to be borne by the patient, ESC questioned the ability to get informed patient financial consent for a device that costs $redacted noting the applicant's pre-ESC comments on the difficulty of conducting RCTs for this intervention. ESC considered that the likelihood of private hospitals providing this service in the future was low, as the private hospital would need to be collocated with an appropriate public centre, thus limiting the options. ESC also noted the Australian and New Zealand Intensive Care Society's strong preference for IMPELLA to be delivered in the public system.

17. Applicant comments on MSAC's Public Summary Document

Abiomed welcomes MSAC's recommendation to create new MBS items for the insertion and removal of an IMVAD device in patients with CS. Abiomed believes this is an important step in addressing a high clinical need of improved outcomes in CS patients with life-threatening condition. We believe that this positive recommendation by MSAC shows a significant milestone for Abiomed in improving the outcomes for patients with CS in Australia and a testament of the safety, clinical effectiveness, and cost-effectiveness of Impella and ECPELLA to treat patients with CS in Australia Healthcare System.

18. Further information on MSAC

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