



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1523 – Transluminal insertion, management, repositioning, and removal of an intravascular microaxial blood pump (Impella®), for patients requiring mechanical circulatory support

Applicant: Abiomed Inc.

Date of MSAC consideration: MSAC 77th Meeting, 28-29 November 2019

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

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of transluminal insertion, management, repositioning, and removal of an intravascular microaxial ventricular assist device ([IMVAD] Impella®), for patients requiring mechanical circulatory support was received from Abiomed Inc. by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding of transluminal insertion, management, repositioning and removal of an IMVAD (Impella®) for patients requiring mechanical circulatory support. MSAC considered that the evidence for comparative safety and effectiveness was too uncertain relative to standard care in all three populations (high-risk percutaneous coronary interventions [HR-PCI], cardiogenic shock [CS] and right-heart failure [RHF]), 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.

Consumer summary

Abiomed Inc. applied for public funding through the Medicare Benefits Schedule (MBS) for the procedure to insert, manage, reposition and remove the Impella® device in people who have heart failure or heart shock, or who need heart surgery but have a high risk of their heart failing during the surgery.

Impella® aims to help circulate blood through the heart. The device is placed inside the heart and uses a pump with a motor to move blood from the heart to the main artery that leaves the

heart. 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.

MSAC considered that the available evidence showed that Impella[®] might be less effective or no better than other treatment options. It might also be less safe. MSAC thought that Impella[®] could cost more to the MBS than the applicant had estimated.

MSAC's advice to the Commonwealth Minister for Health

MSAC did not support public funding for Impella[®] because the evidence was not high-quality enough to show that it is safe and effective. The economic evaluation and financial impact were also uncertain.

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

Applicant hearing

The applicant was granted a hearing, during which time they presented information to MSAC on the Impella[®] device and data on its effectiveness.

MSAC heard from an Australian clinician who has treated a number of patients requiring mechanical circulatory support with Impella[®]. The clinician described their experience using this therapy and presented a clinical vignette for one patient treated recently for HR-PCI. Overall, the clinician considered Impella[®] provides an important new therapeutic option for patients requiring mechanical circulatory support who have limited other effective treatment options.

MSAC heard from the applicant who indicated that with the right patient selection, Impella[®] has shown to improve outcomes and be cost-effective to the healthcare system. In addition, the applicant expected that as adoption and skills with Impella[®] therapy improves, it can bring equitable healthcare to remote and under-served populations for a morbid indication in Australia.

MSAC asked the applicant if Impella CP is identical to Impella 2.5 for effectiveness. The clinician indicated Impella CP is a similar device to the Impella 2.5 that has been developed to pump more blood (flow rate: 3.8-4.0 L/min vs. 2.5 L/min, respectively). In CS, the clinician indicated Impella 2.5 would provide insufficient mechanical circulatory support and Impella CP would be the most suitable device.

MSAC asked the clinician about what proportion of extracorporeal membrane oxygenation (ECMO) supported HR-PCI patients are performed in Australia. The clinician indicated that due to the complexity of performing ECMO that numbers are very low in Australia and recalled two patients that have been supported with ECMO in the HR-PCI population.

MSAC asked the applicant about their interest in performing future Impella RCTs in the HR-PCI population. The applicant indicated that no RCT was planned, but highlighted that prospective real-world data was available to inform on safety and effectiveness of Impella[®]. The applicant also highlighted the difficulty in completing RCTs in the requested three patient populations, in particular in CS due to difficulty with obtaining patient consent and enrolment.

MSAC discussion

MSAC noted the three proposed populations: HR-PCI, CS and isolated RHF were extremely heterogeneous conditions. However, MSAC acknowledged the clinical need in these populations with limited treatment options (particularly for CS).

MSAC noted that Impella® provides short-term treatment, mainly provided in large teaching hospitals.

MSAC noted that there are four types of devices which vary in the level of circulatory support they provide (see Figure 1 below): Impella 2.5, Impella CP, Impella 5.0 and Impella RP. Impella CP and Impella 5.0 are listed on the Australian Register of Therapeutic Goods (ARTG), and Impella RP is currently under application for registration. MSAC noted that all the clinical studies used in the application for the HR-PCI population used Impella 2.5, but that registration of this model had not yet been applied for in Australia at the time of the application. However, MSAC also noted that the 2.5 model was considered biologically identical to the CP model.

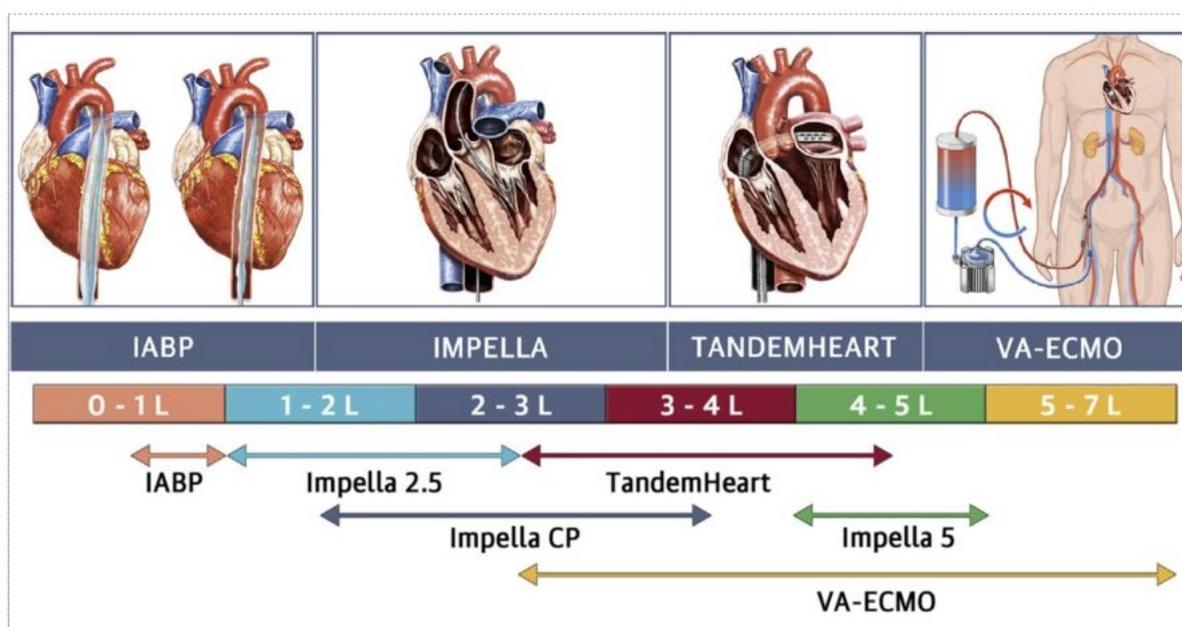


Figure 1 Flow rates provided for devices that provide mechanical circulatory support

MSAC agreed with the comparators as assessed by ESC – that is:

- for HR-PCI, the appropriate comparators were intra-aortic balloon pump (IABP) and ECMO
- for cardiogenic shock, 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
- for RHF, the appropriate comparator was ECMO.

Regarding comparative safety, MSAC noted no significant differences overall for IMVAD compared with IABP in the HR-PCI population (although lower rates of stroke and revascularisation were noted). For the CS population, IMVAD was associated with higher rates of major bleeding complications (8/24 patients, 33.3%) than IABP (2/24 patients, 8.3%) in one study (Ouweneel 2017). Evidence for comparative safety in the RHF population was poor quality. MSAC noted the absence of randomised controlled trials (RCTs) that directly compare IMVAD and ECMO. Overall, MSAC considered the comparative safety to be

uncertain, but noted that IMVAD is less invasive than ECMO. High-quality randomised controlled trials would be required to reduce uncertainty in comparative safety.

Regarding clinical effectiveness, MSAC noted several issues, including use of per-protocol analyses rather than intention-to-treat, small studies, low-quality naïve indirect comparisons using flawed methodology, and an absence of RCTs comparing IMVAD with ECMO. For HR-PCI, MSAC noted no significant difference in 30-day mortality in the PROTECT II study, although the results favoured IABP. MSAC also noted that the PROTECT II study was stopped due to futility. For RHF, MSAC noted the poor quality of evidence to inform 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 naïve indirect comparisons with flawed methodology, but also acknowledged the difficulties in conducting clinical trials in patients with CS.

Overall, MSAC considered that IMVAD was non-inferior or less effective compared with IABP, and uncertain compared with ECMO. The number of patients who would be eligible for IMVAD was also uncertain.

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:

- The economic models have several structural flaws and use highly uncertain inputs, resulting in them not being informative for decision making.
- The applicant used per-protocol analyses for IMVAD compared with IABP at 30 days, and included variable use of per-protocol or intention-to-treat analyses for adverse events.
- Effectiveness parameters compared with ECMO was based on naïve indirect comparisons.
- Cost-offsets were uncertain – MSAC considered the use of ECMO in 38% of HR-PCI patients and 100% of cardiogenic shock patients to be overestimates, particularly given the applicant's advice that ECMO-assisted HR-PCI numbers are very low (1 or 2 patients per year in a large Melbourne hospital). One-way sensitivity analysis on the proportion of ECMO-supported HR-PCI patients showed that the ICER was highly sensitive to this parameter. MSAC also noted differences in hospital or intensive care unit length of stay compared with ECMO (relative to IMVAD).
- The applicant used short-term (30-day) follow-up data, when longer follow-up data (90-day) data were available for mortality and adverse event data in HR-PCI patients in the PROTECT II trial.

MSAC considered that these issues either favour IMVAD or have uncertain effects on the model, resulting in a highly uncertain ICER.

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.

In the applicant's pre-MSAC response, the applicant confirmed that CS is not listed as an indication in the TGA registrations for IABP or ECMO. The applicant also noted ongoing trials using IMVAD for acute myocardial infarction with cardiogenic shock, and HR-PCI (PROTECT III study). However, MSAC noted two recent US studies (Dhruva et al. and Amin et al.) that show that IMVAD is associated with higher rates of bleeding complications and death compared with IABP. The applicant considered this analysis to be flawed because of differences in patient risk at baseline and during procedures, and limitations in the data source and analysis (including excluding the most costly IABP patients who were escalated to other therapies). MSAC also noted the rapid adoption and high use of Impella® in the United States (where more than 30% of PCI patients requiring mechanical circulatory support receive the device), but also the large variation in use among hospitals, suggesting clinical equipoise.

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.

MSAC acknowledged the clinical need for effective interventions in these populations, who currently have limited options (particularly for CS). 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 cardiogenic shock (the DanGer Shock trial) and accepted that this was a well-designed trial; results are expected in 3–4 years.

Overall, MSAC did not support public funding of Impella® because of poor-quality evidence leading to uncertain safety, clinical effectiveness and cost-effectiveness in all proposed populations. MSAC considered that additional data from randomised controlled trials would be required to give greater certainty regarding comparative safety and effectiveness and cost-effectiveness.

4. Background

This is the first submission (submission based assessment [SBA]) for transluminal insertion, management, repositioning, and removal of an IMVAD (Impella®), for patients requiring mechanical circulatory support. MSAC has not previously considered this application.

5. Prerequisites to implementation of any funding advice

The Impella CP and 5.0 models, and the control unit are listed on the ARTG. At the time of this application to MSAC, the RP model for right ventricular support is currently under application, while registration of the 2.5 model has not yet been applied for.

6. Proposal for public funding

Separate MBS item numbers were proposed for the insertion (percutaneous [Table 1]; surgical [Table 2]), management (Table 3), repositioning (Table 4) and removal (percutaneous [Table 5]; surgical [Table 6]) of the device in line with current item codes for

intra-aortic balloon pump (IABP) and ventricular assist devices (VAD). The application stated that percutaneous removal of the microaxial ventricular assist device is a simple procedure and it was considered that a fee and hence an item for this was not required and has been removed from the application. The application stated that surgical insertion of a right-sided intravascular microaxial ventricular assist device cannot be conducted by arteriotomy and the term venotomy has been added to the item descriptor in Table 2 (highlighted in red).

Table 1 Proposed MBS item descriptor, percutaneous insertion

Category 3 – THERAPEUTIC PROCEDURES
<p>Percutaneous insertion of a left- or right-sided intravascular microaxial ventricular assist device by arteriotomy/venotomy in patients with cardiogenic shock (with no evidence of significant anoxic neurological injury), right heart failure or who are undergoing high-risk percutaneous coronary intervention.</p> <p>The criteria for high-risk percutaneous coronary intervention are: comorbidities; and</p> <ul style="list-style-type: none"> - left ventricular ejection fraction $\leq 35\%$; and - unprotected left main; or - last patent coronary vessel; or - three-vessel disease. <p>The criteria for right heart failure is isolated right heart failure after LVAD implantation or after cardiac surgery or myocardial infarction</p>
Fee: \$384.95

Source: p49 of the SBA

Table 2 Proposed MBS item descriptor, surgical insertion

Category 3 – THERAPEUTIC PROCEDURES
<p>Surgical insertion of a left- or right-sided intravascular microaxial ventricular assist device by arteriotomy/venotomy in patients with cardiogenic shock (with no evidence of significant anoxic neurological injury), right heart failure or who are undergoing high- risk percutaneous coronary intervention.</p> <p>The criteria for high-risk percutaneous coronary intervention are: comorbidities; and</p> <ul style="list-style-type: none"> - left ventricular ejection fraction $\leq 35\%$; and - unprotected left main; or - last patent coronary vessel; or - three-vessel disease. <p>The criteria for right heart failure is isolated right heart failure after LVAD implantation or after cardiac surgery or myocardial infarction.</p>
Fee: \$1,480.00

Source: p49 of the SBA

Table 3 Proposed MBS Item descriptor, management and monitoring

Category 3 – THERAPEUTIC PROCEDURES
<p>Initial and subsequent daily management and monitoring of parameters of the controller for a left- or right-sided intravascular microaxial ventricular assist device</p>
Fee: \$156.10

Source: p49 of the SBA

Table 4 Proposed MBS Item descriptor, adjustment and repositioning

Category 3 – THERAPEUTIC PROCEDURES
<p>Adjustment and repositioning, in patients supported by of a left- or right-sided intravascular microaxial ventricular assist device.</p>
Fee: \$156.10

Source: p50 of the SBA

Table 5 Proposed MBS Item descriptor, adjustment and repositioning

Category 3 – THERAPEUTIC PROCEDURES
Percutaneous removal of a left- or right-sided intravascular microaxial ventricular assist device.
Fee: \$156.10

Source: p50 of the SBA

Table 6 Proposed MBS Item descriptor, surgical removal

Category 3 – THERAPEUTIC PROCEDURES
Surgical removal of a left- or right-sided intravascular microaxial ventricular assist device.
Fee: \$740.00

Source: p50 of the SBA

The applicant provided the below justification for the proposed MBS fees for the insertion, management, repositioning and removal of Impella® (Table 7).

Table 7 Justification for fees applied for in the submission

Proposed service	MBS fee
Percutaneous insertion of device	\$384.95 – based on item 38362 (percutaneous insertion of IABP)
Surgical insertion of device	\$1,480.00 – an amount \$1,000 more than item 38609 (insertion of IABP via arteriotomy \$479.15), but \$50 less than item 38615 (insertion of VAD \$1,532.00)
Surgical removal of device	\$740.00 – based on item 38612 (removal of IABP), but the applicant stated removal of Impella® is more complex than IABP removal
Repositioning of device	\$156.10 – based on item 13847* (IABP management on first day)

*The Intensive Care and Emergency Medicine Clinical Committee of the MBS Review Taskforce recommended item 13847 be deleted and combined with 13848 (management of IABP on subsequent days, MBS fee \$131.05). This is because there is no significant difference in clinical input required on the first and subsequent days of management, other than that already reflected in the separate item covering insertion of the IABP (item 38609).

It was queried whether the price discrepancy in the insertion method would lead to changes in practice. The discrepancy in price reflects the increased time and complexity of surgical insertion vs percutaneous insertion. The application stated that surgical insertion requires a cut-down to expose an artery, then anastomotic connection of a graft conduit. These steps take a long time and therefore justify the reimbursement, given the complexity and length of time required, clinical experts have advised that the surgical procedure would only be conducted if absolutely necessary and the price difference would therefore not influence practice. However, the Critique stated that the application incorrectly provided an explanation for the price discrepancy between the insertion methods rather than the removal methods, and therefore the concern of PASC has not been addressed.

Regarding processes for payment of the device, the application stated while it is still not clear whether Impella® would be funded from on the Prostheses List the advice from the Prostheses List Advisory Committee (PLAC) secretariat was to make an application to test the device against the criteria for listing. This is currently under way.

7. Summary of public consultation feedback/consumer Issues

Consultation feedback was received from two individuals from intensive care, one from cardiology and one professional organisation. In terms of the clinical claim, two respondents agreed that IMVAD was superior in terms of effectiveness and non-inferior in terms of safety compared to standard of care. However, the remaining two respondents disagreed since there was no evidence for improved 30 day mortality and no long term evidence to support superior effectiveness.

8. Proposed intervention's place in clinical management

Impella[®] is a transluminal ventricular assist device that is inserted percutaneously or surgically. The device has a small microaxial pump at one end of a thin, flexible catheter that pumps blood from the ventricle, through an inlet area near the tip and expels blood into the ascending aorta/pulmonary artery. The other end of the tube is connected to an automated control system outside the body that controls the pump rate. The device stabilises haemodynamics, unloads the ventricle, augments peak coronary flow, perfuses the end organs and allows for recovery of the native heart.

There are four variants of the device proposed in the submission, each have a different sized catheter with different flow rates and different insertion techniques: Impella 2.5, Impella CP, Impella 5.0 and Impella RP. The Automatic Impella Controller generates signals required to power the drive motor of the Impella Catheters and provides a user interface.

Impella[®] is indicated for clinical use in cardiology and cardiac surgery in patients with reduced ventricular function. The populations proposed in the application are divided into three subgroups as outlined in the ratified PICO confirmation:

1. Patients undergoing high-risk percutaneous coronary interventions (HR-PCI). This is further defined as having: comorbidities; and left ventricular ejection fraction $\leq 35\%$; and unprotected left main; or last patent coronary vessel; or three-vessel disease.
2. Patients with cardiogenic shock with no evidence of significant anoxic neurological injury
3. Patients with isolated right heart failure (RHF) after left-sided ventricular assist device (LVAD) implantation or after cardiac surgery or myocardial infarction.

The application's current and proposed clinical management algorithms for HR-PCI (Figure 2), cardiogenic shock (Figure 3) and RHF (Figure 4) were based on the ratified PICO, PASC outcomes and expert advice.

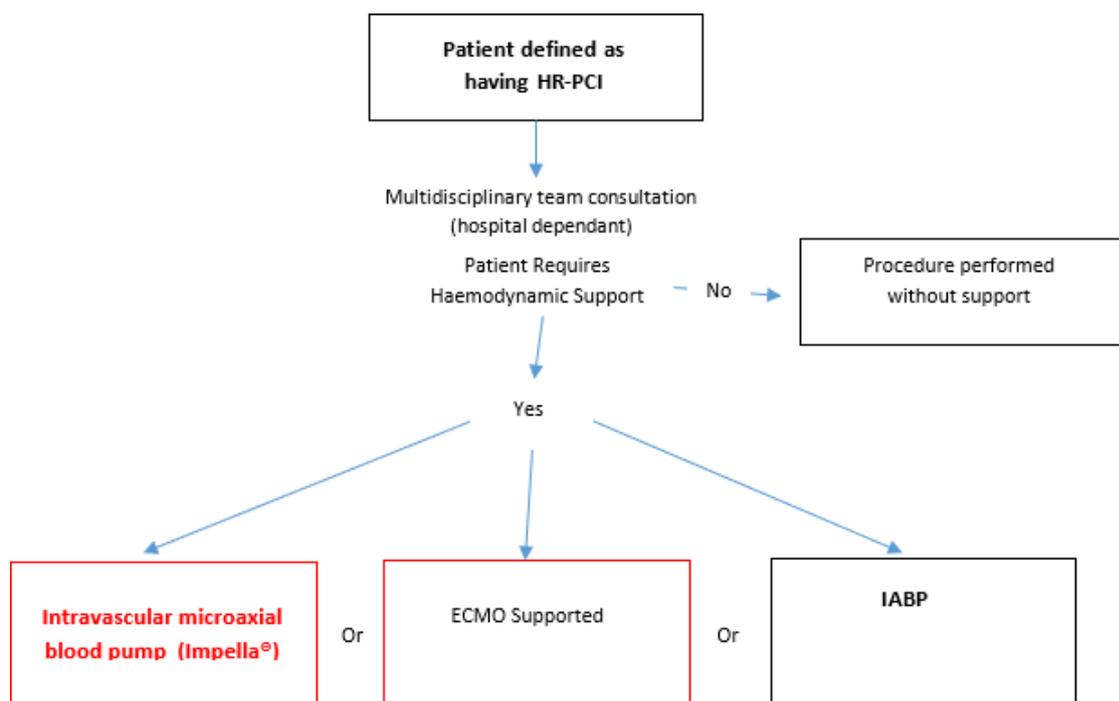


Figure 2 Clinical management algorithm for high-risk PCI

Source: Figure 7, p62 of the SBA

ECMO= Extracorporeal membrane oxygenation; IABP=intra-aortic balloon pump

Note: The Critique stated it is unclear why ECMO is placed in a red box which is intended to be for proposed changes to the current clinical management algorithm. The ratified PICO confirmation does not place ECMO in a red box.

The Critique stated that it is not clear from the application’s clinical management algorithm whether there is a hierarchy in mechanical circulatory support (MCS) choice. The primary comparator nominated by the submission and the ratified PICO confirmation was IABP. ECMO appears to be equally weighted as a comparator in the clinical management algorithm.

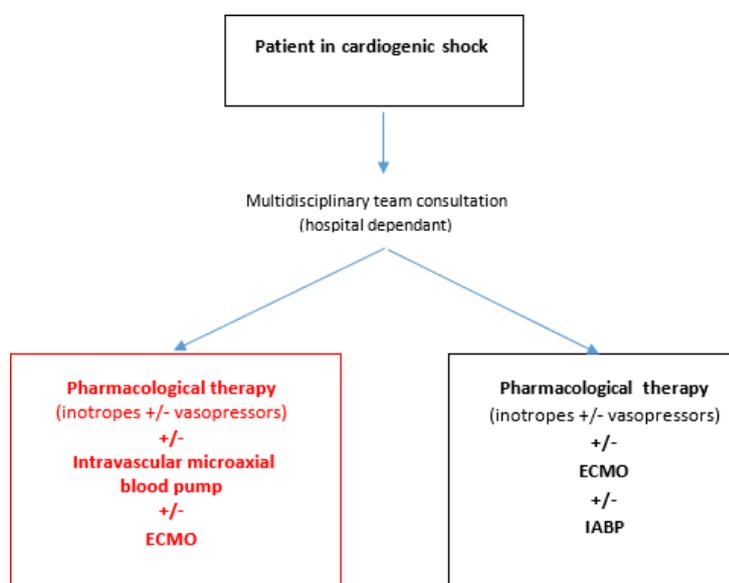


Figure 3 Clinical management algorithm for cardiogenic shock.

Source: Figure 8, p63 of the SBA

ECMO= Extracorporeal membrane oxygenation; IABP=intra-aortic balloon pump

The Critique stated that the application's clinical management algorithm differs to that proposed in the ratified PICO confirmation. The algorithm presented in the application suggests 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 circulatory support. The Critique stated that the use of ECMO in addition to IMVAD was not justified in the application.

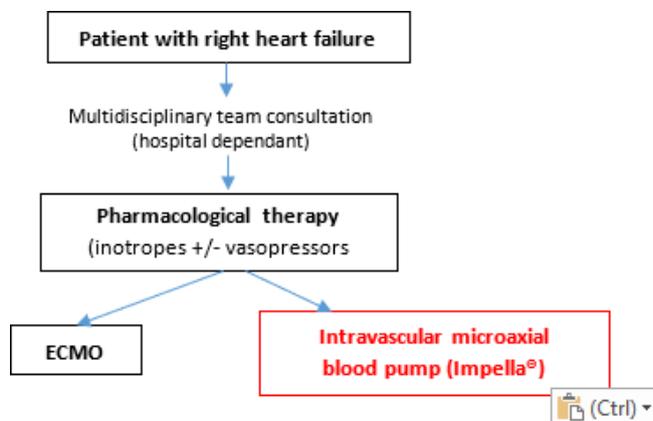


Figure 4 Clinical management algorithm for right heart failure

Source: Figure 9, p64 of the SBA

ECMO= Extracorporeal membrane oxygenation

The Critique stated that application's clinical management algorithm is unchanged from the PICO confirmation and is appropriate.

9. Comparator

HR-PCI

The application's nominated comparator was standard of care which includes a basket of therapies including pharmacological therapy and/or mechanical circulatory support, including IABP, ECMO and ventricular assist devices (VAD). However, IABP was identified as the primary comparator in the ratified PICO confirmation. The application cited local expert advice for its inclusion of ECMO as a comparator; however, the Critique stated that there was insufficient evidence to validate the proportion of ECMO used (ECMO weighted 38% in economic evaluation).

Cardiogenic shock

The application's nominated comparator was standard of care which includes a basket of therapies including pharmacological therapy and/or MCS including IABP and/or ECMO if greater haemodynamic support is required. The application cited local expert advice for its inclusion of ECMO as a comparator; however, the Critique stated that there was insufficient evidence to validate the proportion of ECMO used (ECMO weighted 100% in economic evaluation). In addition, the Critique stated there was inconsistency within the application as ECMO was presented as the only comparator presented in the economic model, however IABP was also included as a comparator in the financial estimates.

RHF

The application's nominated comparator was standard of care, including medical and mechanical circulatory support. The application acknowledged that there was little evidence on the current management algorithm and standard of care in patients with RHF. The application also argued that IABP was not used in patients with RHF. The Critique stated that the use of ECMO alone was appropriate in this population.

10. Comparative safety

The safety outcomes presented in the application were the 30 day major adverse cardiac and cerebral events (MACCE).

HR-PCI

Six studies were included, one of which was a multicentre randomised controlled trial (RCT) comparing IMVAD with IABP (PROTECT II, n=452 [O'Neill 2012]). However, this RCT was not completed as planned on the grounds of futility, therefore the results from the participants who did complete the study (69% of the planned enrolment) are not powered appropriately. The remaining studies were single arm observational studies or company sponsored registries, three of which assessed IMVAD, while two assessed ECMO. The Critique noted the evidence mostly consisted of the IMVAD 2.5; it was uncertain whether results from these studies translate into the same outcomes for other models of IMVAD.

RCT results (vs. IABP)

No clinically relevant differences in safety outcomes were identified from the PROTECT II trial. There were statistically significant differences in stroke and repeat-revascularisations which favoured IMVAD. PROTECT II did not collect information on bleeding.

Cardiogenic shock

Twenty studies were included, two of which were multicentre RCTs directly comparing IMVAD with IABP (IMPRESS, n=48 [Ouweneel 2017]; ISAR-SHOCK, n=25 [Seyfarth 2008]). The Critique stated that the remaining studies were observational studies or company sponsored registries of IABP or ECMO. There were no RCTs identified which directly compared IMVAD with ECMO.

RCT results (vs. IABP)

There were significant differences in the number of major bleeding events (favouring IABP) and the number of repeat-revascularisations (favouring IMVAD) presented in Ouweneel 2017. No other significant differences in safety outcomes were identified.

RHF

Fourteen studies were included. No RCTs were identified comparing IMVAD to either IABP or ECMO. All studies identified were single arm studies. The Critique stated that the evidence presented in the submission was of too poor quality.

The Critique stated that overall and for all three subpopulations the indirect comparisons, which aggregated results of RCTs and single-arm studies in HR-PCI and cardiogenic shock populations (e.g. application's meta analyses of safety results), presented in the application 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.

11. Comparative effectiveness

The primary effectiveness outcome was 30-day mortality. Results from direct RCTs are reported below.

HR-PCI

PROTECT II reported 30 day mortality in both the intention-to-treat (ITT) and per protocol (PP) analyses. Results were statistically insignificant in both analyses, however point estimates favour IABP in both analyses (ITT: IABP 5.9% vs IMVAD 7.6%; PP: 6.2% vs IMVAD 6.9%). PROTECT II also reported 90 day mortality (ITT: IABP 8.7% vs IMVAD

12.1%; PP: 9.0% vs IMVAD 11.6%). Although statistically insignificant, 90-day mortality point estimates also favoured IABP, however there were greater differences between the IABP and IMVAD in the 90 day ITT and PP analyses.

Cardiogenic shock

Ouweneel 2017 and Seyfarth 2008 both reported 30-day mortality. In Ouweneel 2017, 50% of participants died in the IABP arm compared to 45.8% of participants in the IMVAD arm. In Ouweneel 2008, 46.2% of participants died in both arms. The Critique stated small patient numbers limited their interpretability.

RHF

The Critique stated that the evidence presented in the application was of too poor quality.

Clinical claim

On the basis of the benefits and harms reported in the evidence base, the application proposed that, relative to standard of care, IMVAD has non-inferior safety and superior effectiveness. The Critique stated that overall, and for three subpopulations, the evidence presented in the submission was of too poor quality to justify the clinical claim. Based on the RCTs alone for the HR-PCI and cardiogenic shock populations, 30-day mortality point estimates were greater in participants treated with IABP in the HR-PCI population (although this is statistically insignificant), while there were no differences observed in the cardiogenic shock population.

Pre-MSAC response

The applicant provided updated data collection and several analyses for IMVAD:

- In AMI CS, a prospective protocol based MC study of 250 patients enrolled so far reported 72% survival
- In HR-PCI a FDA-approved study interim analysis for 898 patients including 571 Impella[®] CP supported patients reported 16.8% MAACE rates at 90 days compared with 31% 90 day MACCE rates in IABP control arm of Protect II (p<0.0001)
- Impella[®] RP FDA post approval study shows similar 72% survival, when used as per FDA approved criteria.

12. Economic evaluation

The economic evaluation was based on three economic models of cost-utility analysis, one for each patient population (Table 8).

Table 8 Summary of the economic evaluation

Perspective	Health care provider
Comparator	Model 1: HR-PCI patient group: Standard care (IABP or ECMO) The base case used 38% ECMO as the comparator Model 2: Cardiogenic shock patient group: Standard care (IABP or ECMO) The base case used 100% ECMO as the comparator Model 3: RHF patient group: Standard care (ECMO) ECMO was the only comparator included in the model
Type of economic evaluation	Cost-utility
Sources of evidence	Systematic review of randomised and single arm studies A combination of RCT, observational studies and naïve indirect comparisons of low quality studies
Time horizon	Five years in the model base case
Outcomes	LYG and QALYs
Methods used to generate results	Markov microsimulation model ^a
Health states	Cycle 1 (procedure): no complications, stroke, major bleeding, acute renal dysfunction, repeat revascularisation, death Cycle 2 and beyond: Healthy, heart failure, stroke, MI, death
Cycle length	30 days
Discount rate	5%
Software packages used	TreeAge Pro 2019

ECMO=extracorporeal membrane oxygenation; HR-PCI=high-risk percutaneous coronary intervention; IABP=intra-aortic balloon pump; LYG=life-years gained; MI=myocardial infarction; QALY=quality-adjusted life years; RCT=randomised controlled trial; RHF=right heart failure

^a ESC noted this was incorrect term, and should be "Individual-based state-transition model"

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, and using the base case assumptions, are shown in the tables below. However, the Critique stated that the application's results do not accurately represent the cost-effectiveness of listing IMVAD and thereby are not informative for MSAC decision making purposes.

Table 9 Model 1: Incremental costs and effectiveness of IMVAD compared to Standard of Care in HR-PCI

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Standard of Care (ECMO 38%) <i>Critique's values</i>	\$115,783 \$85,203 ^a		2.46		
IMVAD <i>Critique's values</i>	\$81,269	-\$34,514 -\$3,935	2.57	0.11	Dominant

ICER = Incremental Cost-Effectiveness Ratio; IMVAD= intravascular microaxial ventricular assist device; QALY=quality-adjusted life years
a Critique values use the correct value for the length of stay in ICU in patients treated with IABP. The base case in the results from the economic model utilised the same value as ECMO for ICU length of stay in the IABP arm, however the SBA stated this value is the same was based on IMVAD (see Table 173, p214 of the SBA)

Table 10 Model 2: Incremental costs and effectiveness of IMVAD compared to Standard of Care in CS

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Standard of Care (ECMO 100%)	\$145,331		0.99		
IMVAD	\$123,688	-\$21,643	1.51	0.52	Dominant
<i>Critique's values^a</i>	<i>\$123, 874</i>	<i>-\$21, 456</i>	<i>1.50</i>	<i>0.51</i>	

ICER = Incremental Cost-Effectiveness Ratio; IMVAD= intravascular microaxial ventricular assist device; QALY=quality-adjusted life years
^a Recalculated during the critique from the base case model provided with the SBA

Table 11 Model 3: Incremental costs and effectiveness of IMVAD compared to Standard of Care in RHF

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Standard of Care (ECMO 100%)	\$162,561		2.11		
IMVAD	\$83,526	-\$79,035	2.29	0.18	Dominant

ICER = Incremental Cost-Effectiveness Ratio; IMVAD= intravascular microaxial ventricular assist device; QALY=quality-adjusted life years

The Critique stated multiple errors were identified in aspects of the economic model structure, inputs and assumptions. The Critique provided a list of the model issues in Table 12. For ease of understanding what changes were made by the Applicant, a brief summary of the applicant Pre-ESC response is included below (shaded in Table 12).

Table 12 Changes which should be made to a base case evaluation (raised in Critique)

Issue	Current	Change to be made	Comment	Applicant-Pre ESC response ^a
Model inputs				
Proportion of ECMO used in standard of care arm	38%	0%	<p>The use of ECMO for HR-PCI in the Australian setting is unclear.</p> <p>The normalisation of transition probabilities is inappropriate and may underestimate the amount of MACCE in the model.</p> <p>The assumption in the model that no patient is free from an MACCE following HR-PCI with ECMO is uncertain and inappropriate.</p>	<p>Argue ECMO is treatment choice for HR-PCI, CS and RHF. Cite Australian 2019 study in HR-PCI with small numbers (n=15)</p> <p>Argue this method is normal practice in these situations.</p> <p>Identified studies report high incidence of MACCE, specifically bleeding and acute renal disease (both >60%), reducing the likelihood of patients supported with ECMO experiencing “no MACCE.</p>
LOS ICU IABP	0.6 days specified in SBA but 9 days used in model	0.6 days	Input error in Tree Age	Artifact of SA. Insist ICER based on correct value (9 days).

Issue	Current	Change to be made	Comment	Applicant-Pre ESC response ^a																				
IMVAD price	\$redacted in SBA, \$redacted in model		Sponsor to confirm which price is to be used	Artifact of SA. ICER based on correct value (\$redacted)																				
Costs (all)	No attempt to adjust to current price year	Adjust to current price year	The costs listed in Table 31 are from a variety of international sources and outdated local sources. Consistency is needed with prices converted to a recent common price year.	<p>Cost of post-MAACE in Table 178 of SBA were adjusted by CPI to 2019 AUD.</p> <p>Updated costs</p> <table border="1"> <tr> <td>ECMO hospitalisation cost/day</td> <td>\$2,489</td> </tr> <tr> <td>ECMO ICU cost/day</td> <td>\$9,445</td> </tr> <tr> <td>Stroke</td> <td>\$23,264</td> </tr> <tr> <td>AMI</td> <td>\$21,555</td> </tr> <tr> <td>Acute kidney failure</td> <td>\$4,626</td> </tr> <tr> <td>Post MAACE /year</td> <td></td> </tr> <tr> <td>Post MCS</td> <td>\$3,475</td> </tr> <tr> <td>Post-stroke</td> <td>\$10,790</td> </tr> <tr> <td>Post AMI</td> <td>\$3,864</td> </tr> <tr> <td>Post HF</td> <td>\$7,387</td> </tr> </table>	ECMO hospitalisation cost/day	\$2,489	ECMO ICU cost/day	\$9,445	Stroke	\$23,264	AMI	\$21,555	Acute kidney failure	\$4,626	Post MAACE /year		Post MCS	\$3,475	Post-stroke	\$10,790	Post AMI	\$3,864	Post HF	\$7,387
ECMO hospitalisation cost/day	\$2,489																							
ECMO ICU cost/day	\$9,445																							
Stroke	\$23,264																							
AMI	\$21,555																							
Acute kidney failure	\$4,626																							
Post MAACE /year																								
Post MCS	\$3,475																							
Post-stroke	\$10,790																							
Post AMI	\$3,864																							
Post HF	\$7,387																							
Transition Probabilities	Mix of PP and ITT data from O'Neill 2012	ITT data from O'Neill 2012	<p>There is no consistency in the choice of analyses to inform transition probabilities from O'Neill 2012.</p> <p>The argument in the SBA that the PP analysis was chosen for 30 day mortality due to the results of the ITT analysis not favouring IMVAD is inappropriate.</p>	<p>PP chosen (for HR-PCI patients) as it included 427 patients who met the protocol mandated eligibility criteria. Further, use of ITT value for stroke for the Impella supported arm was of little consequence to the result as risk of stroke in both the ITT and PP populations in the PROTECT II trial were reported to be zero.</p>																				
Bleeding Utility	0.30	0.70	<p>The utility value chosen was as assumption used in Roos 2013.</p> <p>The approach used in OHTA 2017 may be more accurate.</p>	Utility value was changed to 0.7.																				
Post-stroke Utility	0.41	0.68	Without justification of the value, the utility used in previous evaluations (OHTA 2017 and Roos 2013) should be used. See Table 34.	<p>Justified that value was chosen from systematic review in Post 2001. Reported utilities of 0.32 and 0.71 for major and minor stroke. Also reported EurQol utility in stroke survivors utilities of 0.32 and 0.71</p>																				

Issue	Current	Change to be made	Comment	Applicant-Pre ESC response ^a
				for major and minor stroke. Argued OHTA 2017/Roos 2013 was derived by a single earlier study (Haacke 1999).
Model structure				
Bleeding health state	Evidence is uncertain	Removal of bleeding as an outcome from HR-PCI procedure	The clinical evidence for bleeding is based on a naïve indirect comparison of low quality evidence and is highly uncertain. Given the low cost of bleeding post procedure, removal of bleeding will not significantly change the result	Disagree, as bleeding is a significant AE in first cycle (potential procedural outcome). In addition bleeding is significant AE for ECMO. Reiterate evidence in HR-PCI was sourced from Roos 2014 CEA for IABP (25%) and from Europella registry for Impella (6%), which supports improved safety for Impella.
Costs of initial MACCE occurring in cycle 2 and beyond	Different formulas for initial cost, incremental cost, and final cost in Tree Age file. See <i>Costs and utilities of CHF and other MAACE (p114-115 of the Critique)</i>	Use same IF statement as per the initial cost for the incremental and final cost formulas.	Initial costs of a MACCE are not accrued where that MACCE occurs for the first time in cycle 2 or later.	Acknowledged formula error. This error was rectified in all models. Note as error applied in both model arms- relative ICER and outcomes of dominance remain unchanged.
Utilities of initial MACCE occurring in cycle 2 and beyond	Different formulas for initial utilities, incremental utilities, and final utilities in Tree Age file. See <i>Costs and utilities of CHF and other MAACE (p114-115 of the Critique)</i>	Use same IF statement as per the initial cost for the incremental and final cost formulas	Initial utilities of a MACCE are not accrued where that MACCE occurs for the first time in cycle 2 or later.	As above.
Inclusion of costs of procedure (proposed MBS price)	Not included in model	Include	Disaggregated costs in Table 37 and Table 38 suggest that the cost of procedures (MBS items) are not included in the model. This is inappropriate considering the purpose of the SBA is to receive MBS listing for these services.	Not reported.

CHF=chronic heart failure; ECMO=extracorporeal membrane oxygenation; HR-PCI=high-risk percutaneous coronary intervention; IABP=intra-aortic balloon pump; ICU=intensive care unit; ITT=intention-to-treat; LOS, length of stay; MACCE= major adverse cardiac and cerebral events; MBS=Medicare Benefits Scheme; MI=myocardial infarction; PP=per protocol; SBA=submission-based assessment
^a Refer to Applicant Pre-ESC response for full description of discussion of modelling issues and submission's model changes

Revised model results: Applicant Pre-ESC response

The pre-ESC response stated saying that rather than identifying structural issues, the Critique identified several assumptions in the model they disagree with. However, the pre-ESC response did acknowledge some errors and made changes to modelling inputs (as described above in brief). The resulting base case ICERs for HR-PCI (model 1), cardiogenic shock (model 2) and RHF (model 3) are provided in Table 13, Table 14 and Table 15, respectively.

Table 13: Costs and outcomes of Model 1: for HR-PCI patients (base case)

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Standard care (ECMO 38%)	\$135,650		2.47		
Impella	\$116,535	-\$19,115	2.57	0.10	Dominant

Table 14: Costs and outcomes of Model 2: for CS patients (base case)

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Standard care (ECMO 100%)	\$234,997		1.00		
Impella	\$175,619	-\$59,378	1.50	0.50	Dominant

Table 15: Costs and outcomes of Model 3: for RHF patients (base case)

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Standard care (ECMO 100%)	\$257,477		2.11		
Impella	\$114,618	-\$142,859	2.30	0.19	Dominant

For HR-PCI (model 1), the applicant also provided updated one-way sensitivity analysis investigating the impact of lower use of ECMO in the base case model (Table 16).

Table 16: One-way sensitivity analysis: proportion of ECMO supported patients in Standard Care for HR-PCI patients

	Cost		Incremental cost	Effectiveness (QALYs)		Incremental effectiveness	ICER
	Impella	SC		Impella	SC		
0.0	\$116,535	\$79,500	-\$37,035	2.57	2.56	0.01	\$3,296,310
0.09	\$116,535	\$92,719	-\$23,815	2.57	2.54	0.03	\$731,757
0.22	\$116,535	\$112,083	-\$4,451	2.57	2.51	0.06	\$70,307
0.28	\$116,535	\$121,313	\$4,778	2.57	2.49	0.08	Impella dominant
0.38 (Base case)	\$116,535	\$135,650	\$19,116	2.57	2.47	0.10	Impella dominant

Pre-MSAC response

The applicant provided a sensitivity analysis of using the intention-to-treat data alone (rather than per protocol data) in HR-PCI (model 1) [Table 17].

Table 17: Costs and outcomes of Model 1: for HR-PCI patients (base case)

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Standard care (ECMO 38%)	\$135,720		2.47		
Impella	\$116,298	-\$19,422	2.55	0.08	Dominant

13. Financial/budgetary impacts

A mixed epidemiological and market share approach was used to estimate the financial implications of listing IMVAD on the MBS (Table 18). The Critique stated that the application did not provide information relating to the broader impact on the MBS, and impact on State and Territory government health budgets. ESC noted the current financial estimates did not include the cost of the device (e.g. prosthesis cost), and noted that a submission for the device to PLAC was underway.

Table 18 Total costs to the MBS associated with IMVAD

	2020-21	2021-22	2022-23	2023-24	2024-25
Increase in MBS services due to listing IMVAD					
Number of patients	9	17	26	36	54
Number of services	32	59	90	126	188
Sub-total cost	\$8,734	\$15,874	\$25,547	\$35,134	\$52,801
Reduction in MBS services due to listing IMVAD (combined IABP, ECMO)					
Number of services	55	108	171	237	370
Sub-total cost	\$16,957	\$33,945	\$54,735	\$76,385	\$119,026
Net Impact to the MBS					
Total services	-23	-49	-81	-111	-182
Total cost	-\$8,223	-\$18,071	-\$29,188	-\$41,250	-\$66,225

Source: Table 202, p238-39 of the SBA

ECMO = extracorporeal membrane oxygenation; IMVAD= intravascular microaxial ventricular assist device; MBS=Medicare Benefits Schedule

The application proposed that nine patients would be treated with IMVAD in the first year of listing, increasing to 54 patients in the fifth year. The Critique stated that there is potential for the net cost/year to the MBS to be greater than estimated in the application due to the uncertainty in the eligible population, and the uncertainty relating to the reduction of ECMO services.

Additional financial analyses: Applicant Pre-ESC response

The applicant stated that the key area of financial uncertainty is the number of patients with RHF after heart surgery. The applicant acknowledged there is limited data on the incidence of RHF after cardiac surgery therefore estimates from the congenital heart disease population were used. The applicant performed additional sensitivity analyses to assess the impact of this. The applicant stated that the Critique incorrectly stated the item for percutaneous IMVAD removal is withdrawn, resulting in incorrect financial implications. An item for percutaneous removal has been requested and the financial estimates appropriately estimated the cost of IMVAD removal. Additional sensitivity analyses were performed assuming more IABP insertions and no use of IABP for cardiogenic shock. A sensitivity analysis assuming a 30% increase in the post-surgical RHF population did not increase net costs to the MBS although this scenario is unlikely (Table 19).

Table 19: Financial implications to the MBS

	2020-21	2021-22	2022-23	2023-24	2024-25
Base case	-\$8,223	-\$18,071	-\$29,188	-\$41,250	-\$66,225
<i>Corrected ECMO use for PCI to 10% (base case 9%)^a</i>	-\$8,223	-\$16,279	-\$29,188	-\$41,250	-\$66,225
<i>More IABP insertions (base case 301 to 270 per year)^b</i>	-\$8,213	-\$15,384	-\$28,249	-\$39,331	-\$61,902
<i>No IABP for cardiogenic shock (base case 19%)</i>	-\$9,571	-\$19,019	-\$33,283	-\$46,539	-\$73,826
<i>30% increase in post-surgical RHF population^c</i>	-\$12,030	-\$24,747	-\$40,611	-\$57,647	-\$94,045

^a Input B17 = 9% (10% was correct value for % of cardiac ECMO for high risk PCI [van den Brink 2018])

^b MBS items M6:R6 = AVERAGE(\$C\$6:\$L\$6)

^c Patient numbers B21:F21×1.3

Pre-MSAC response

The applicant again provided an updated budget impact for the introduction of IMVAD to the MBS (Table 20), including the removal of percutaneous removal MBS item (Table 5).

Table 20 Updated financial implications to the MBS

	2020-21	2021-22	2022-23	2023-24	2024-25
Cost of Impella® to MBS	\$5,614	\$5,614	\$5,325	\$5,325	\$5,325
Cost-offsets of Impella® to the MBS	-\$9,910	-\$9,910	-\$9,504	-\$9,504	-\$9,504
Net Cost of listing Impella® to the MBS	-\$4,296	-\$4,296	-\$4,179	-\$4,179	-\$4,179

Source: Table 6 of pre-MSAC response

MBS=Medicare Benefits Schedule

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Target populations	Population includes extremely heterogeneous conditions. Consider the need for separate applications, which will allow better characterisation of populations to inform the descriptor. No RCT evidence available for the right heart failure (RHF) population.
Comparators	Agree with applicant's pre-ESC response that correct comparators are: <ul style="list-style-type: none"> • for high-risk percutaneous coronary interventions (HR-PCI) – intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO) • for cardiogenic shock (CS) – ECMO (probably true, but no evidence); algorithm for both intravascular microaxial ventricular assist device (IMVAD) + ECMO justified within a very narrow patient population • for RHF – ECMO.
Evidence regarding safety	No RCT evidence to compare IMVAD with ECMO. Poor-quality data from the RCTs in HR-PCI and CS. IMVAD may not be as safe as IABP, which highlights the importance of conducting better quality studies.
Evidence regarding effectiveness	No randomised controlled trial (RCT) evidence to compare IMVAD with ECMO. Poor-quality data in HR-PCI and CS. Methodology for naïve indirect comparisons is flawed.
Item numbers / service fees	Although the time for surgical IMVAD insertion and removal is higher than percutaneous methods, the quantum of reimbursement is not adequately justified. It is reasonable to remove the percutaneous removal item. A case to remove management/monitoring fee could be made.
Uncertainties that could significantly impact the base case analysis	<ul style="list-style-type: none"> • Inconsistent comparators, especially for the CS population • Uncertain weighting of comparator in economic evaluation (38% ECMO for HR-PCI and 100% ECMO for CS); not in line with PICO; favours the intervention • Unclear applicability issues, especially for studies of CS and RHF populations • Structural issues/assumptions favour the intervention • Highly uncertain and low-quality evidence (and data analysis) to estimate key model inputs with a high risk of bias.

ESC discussion

ESC noted the six proposed MBS item descriptors for insertion, management, repositioning and removal of an intravascular microaxial ventricular assist device ([IMVAD] Impella®). ESC suggested that an item for daily management and monitoring is not warranted. ESC also considered that a separate item for percutaneous removal is not necessary and could be removed. ESC noted that surgical insertion would be used as a last resort (i.e. only if percutaneous insertion is not possible) and this should be reflected in the descriptor.

ESC noted that the application is supported by consumer and professional groups, but acknowledged that IMVAD use is proposed in a small group of patients expected to have very poor health outcomes, who would be likely to support any intervention that might have a positive impact on their life. ESC noted that the intervention would need to be provided in a tertiary hospital with associated out-of-pocket costs and access issues. Although expensive, it is the only therapeutic option some of these patients have.

ESC noted that the proposed algorithm for cardiogenic shock (CS) allows for extracorporeal membrane oxygenation (ECMO) to be used in addition to IMVAD despite the PICO confirmation requesting otherwise. ESC considered that there could be a case for using both

in patients who require better oxygenation. ESC noted that there is an active trial in the USA using Impella to complement ECMO for CS (NCT03431467).

ESC considered that a price differential between percutaneous and surgical insertion procedures is appropriate, but the quantum of reimbursement has not been adequately justified. ESC considered that the price differential between methods is unlikely to influence practitioner behaviour and patient choice.

ESC noted there are no current restrictions on the proposed MBS item descriptors on the number of times the device can be used (including insertion, and removal) in a single period of care. ESC noted the device would remain insitu for a number of days and require regular review by the treating doctor in either an intensive care, high dependency or a coronary care unit setting.

ESC noted the complexity and uncertainty regarding appropriate comparators for each of the proposed populations. ESC confirmed that the appropriate comparators are:

- for patients undergoing high-risk percutaneous coronary interventions (HR-PCI) – intra-aortic balloon pump (IABP) and ECMO
- for patients with CS – ECMO (though no evidence for this)
- for patients with isolated right heart failure (RHF) – ECMO.

However, ESC noted that for the HR-PCI population, the weightings given to IABP (62%) and ECMO (38%) are not sufficiently justified. Recent studies have shown that IABP has limited value in the context of HR-PCI, and ECMO is now more widely used. ESC also noted that although ECMO is likely to be the treatment of choice for CS, there is no evidence that IABP is not used at all. ESC noted that guidelines quoted in the applicant's pre-ESC response (justifying the choice of ECMO over IABP as comparator) refer to routine use of IABP in CS (European Society of Cardiology, Class IIIB recommendation) and use of IABP in CS associated with acute myocardial infarction (Cardiac Society of Australia and New Zealand).

ESC considered that it would be useful to have more data on the proportions of ECMO and IABP used in practice in HR-PCI and CS subpopulations. ESC suggested that data may be available from the Australian and New Zealand Intensive Care Society ECMO Registry.

ESC noted that the limited randomised controlled trials (RCTs) comparing IMVAD to IABP (in HR-PCI and CS subpopulations) suggested that IMVAD may not be as safe as IABP, which highlights the necessity for better quality studies. However, ESC also acknowledged the difficulty of conducting RCTs in this population due to difficulties in recruitment and gaining consent, especially for patients with CS. ESC also noted the pivotal RCT (PROTECTII) in HR-PCI population was not completed as planned on the grounds of futility. ESC noted that there are no relevant trials currently recruiting for the RHF population.

ESC noted that – because of the lack of RCT data, the poor quality of data (e.g., sourcing from a small single arm study) and flawed naïve indirect comparisons – comparative safety and effectiveness are highly uncertain. The assessments for safety and effectiveness are all subject to bias and confounding.

ESC also noted that there is likely to be anchoring bias among clinicians leading to IMVAD being used despite a lack of evidence.

ESC noted that issues raised in the Critique in relation to 30-day mortality data (primary effectiveness outcome) had not been adequately addressed due to the poor quality of the data,

and the submission's flawed methodology for conducting the naïve indirect comparisons of single-arm studies (e.g. simple pooling).

ESC noted that issues remain about the applicability of study populations to the proposed MBS population (in particular, for studies in CS and RHF subpopulations).

ESC noted the following key structural issues with the model:

- No conceptualisation process or justification for the health states in the model was provided, so it is unclear whether chosen health states and events reflect clinical progression of disease; choosing health states on the basis of available data is inappropriate
- ESC noted the model is split between cycle 1, and cycles 2 and beyond. Cycle 1 is procedure dependent representing short term events (e.g., major bleeding) with stroke as the only long-term state with zero probability for the IMVAD arm. If patients experience stroke, they enter the 'post-stroke' state at cycle 2 and remain for 5 years until death. Cycle 2 and beyond represent long-term events (e.g., heart failure), all events are procedure independent (due to lack of data); only one event can be experienced and patients who experience an event remain for 5 years until death. However, in reality, a patient could experience more than one of the events over the model's 5-year time horizon (e.g. an acute myocardial infarction and then a stroke in a subsequent cycle).

ESC also noted that key model inputs were sourced from low-quality evidence which had inappropriate data analysis at source.

ESC noted that the Applicant revised the economic (base case) models in their pre-ESC response, acknowledging multiple errors made in analysis and estimates including Australian Refined Diagnosis-Related Groups (AR-DRGs), length of hospital and intensive care unit (ICU) stay, cost of device and cost adjustments. ESC suggested that the Assessment Group verify the revised economic models and estimates before the submission proceeds to MSAC, given the significant impact on the base-case models.

ESC noted that the revised incremental cost-effectiveness ratio (ICER) for the HR-PCI group is based on possible incorrect weightings of ECMO vs IABP (weights were based on a Dutch hospital registry). ESC also noted that the primary comparator in the PICO is IABP, and inclusion of ECMO in the economic evaluation favours the intervention. In addition, ESC noted that inconsistent use of per protocol data (rather than intention-to-treat [ITT] data) in the HR-PCI model favours the intervention.

ESC noted that use of ECMO as the comparator for the CS model is inconsistent with the PICO.

ESC noted the Applicant provided additional financial analyses (sensitivity analyses) in their pre-ESC response due to the uncertainty in the eligible population (in particular, the number of patients with RHF after heart surgery).

ESC noted that cost savings to the MBS would mainly result from reduction in the use of ECMO. ESC considered that cost savings may be less than estimated due to uncertainty around the size of the eligible population (especially the RHF population), and the use of ECMO and associated costs associated.

ESC noted that the financial estimates include the item for percutaneous removal of the device. ESC noted contradictory statements in the Critique and the pre-ESC response as to whether the percutaneous removal item was withdrawn. This needs to be clarified.

ESC noted a submission for the device to the PLAC was underway.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

Abiomed is disappointed with MSAC's decision not to recommend Impella for reimbursement for the Australian population on the Medicare Benefits Schedule. Impella® devices are approved as safe and effective by several international regulatory bodies including the U.S. FDA (2015, 2016) and Japan PMDA (2016). Impella heart pumps are supported in eight clinical society guidelines. Based on the best available evidence, the applicant believes that it has demonstrated that Impella® is as effective as IABP in HR-PCI patients and more effective than ECMO in RHF and CS patients. The cardiogenic shock population presents unique challenges for randomized clinical trials (RCTs) and over seven RCTs have been attempted but have been stopped due to low enrolment or methodological flaws. Recent publications from the physician-led National Cardiogenic Shock Initiative have shown CS survival rates over seventy percent with the use of Impella and CS protocols. Impella®, with defined patient selection and protocolized management, is showing improved survival (72% survival in 171 patients) in AMI Cardiogenic Shock (Mir B. Basir. et al.).

Analysis of systematic reviews (Maini et al. 2014) have demonstrated that pVADs achieve better outcomes at lower costs and that they are a dominant therapy (e.g., discharge survival was greater with pVADs than surgical alternatives (56% vs. 42%, $P < 0.001$) with a strong trend toward reduced LOS (13.2 and 17.9 days, respectively, $P = 0.055$) and a lower cost of the index admission (US\$90,929 and US\$144,257, respectively, $P < 0.0001$). Impella has been demonstrated to be cost-effective in several settings. Gregory et al. (2013) found Impella is cost-effective in HR-PCI with an ICER of US\$39,389/QALY and Stretch, et al. (2014) demonstrated that, in cardiogenic shock and other heart disease, pVADs reduced costs by US\$45,000 and US\$54,000 per case, respectively, and reduced mortality by 58%.

References:

[{Atkinson, T.M., et al., *A practical approach to mechanical circulatory support in patients undergoing percutaneous coronary intervention: an interventional perspective*. JACC: Cardiovascular Interventions, 2016. 9(9): p. 871-883}; {Gregory, D. et al., *A value-based analysis of hemodynamic support strategies for high-risk heart failure patients undergoing a percutaneous coronary intervention*. 2013. 6(2): p. 88.}; {Maini, B., D.J. Scotti, and D. Gregory, *Health economics of percutaneous hemodynamic support in the treatment of high-risk cardiac patients: a systematic appraisal of the literature*. Expert review of pharmacoeconomics & outcomes research, 2014. 14(3): p. 403-416}; {Mir B. Basir., et al. *Improved Outcomes Associated with the use of Shock Protocols: Updates from the National Cardiogenic Shock Initiative*, Catheter Cardiovasc Interv. 2019;1-11}; {Stretch, R. et al. *National Trends in the Utilization of Short-Term Mechanical Circulatory Support*. *Journal of the American College of Cardiology*, 2014. 64(14): p. 1407-1415}]

17. Further information on MSAC

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