Population

This Application of the transluminal insertion and management of a left intravascular microaxial ventricular assist device (IMVAD) (IMPELLA®) is seeking listing on the Medicare Benefits Schedule (MBS) for the management of patients with cardiogenic shock (CS) requiring mechanical circulatory support (MCS).

From here on, IMVAD when used alone is referred to as 'IMPELLA' and IMVAD used with venoarterial extracorporeal membrane oxygenation (VA-ECMO) is referred to as 'ECPELLA'.

Describe the population in which the proposed health technology is intended to be used:

CS is a complex clinical syndrome, a medical life-threatening emergency, with poor prognosis, which occurs when the heart suddenly cannot pump enough blood and oxygen to the brain and other vital organs. It is defined as a state of end-organ hypoperfusion caused by left ventricular, right ventricular, or biventricular myocardial injury resulting in systolic and/or diastolic myocardial pump failure (Kar 2011).

It is characterised by a self-propagating cascade of acute, falling cardiac output and hypotension with ensuing compromised end-organ perfusion. Without appropriate intervention, the end result is multi-organ failure and death (National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand 2018 guidelines for the prevention, detection, and management of heart failure in Australia (NHFA CSANZ 2018)).

The most common causes of CS include large acute myocardial functional insults (e.g., acute myocardial infarction (AMI) or acute fulminant myocarditis) (NHFA CSANZ 2018), with CS complicating approximately 5–10% of cases of AMI, and is the leading cause of mortality in those hospitalised due to AMI (Goldberg 1999; Goldberg 2001). Other acute causes of CS include a catastrophic cardiac structural insult (including acute torrential valvular regurgitation). More sub-acute causes of CS present increasingly in the aging, comorbid population with nearing end-stage chronic heart failure (CHF) (NHFA CSANZ 2018). According to the CardShock study, AMI is the cause in 81% of CS cases, with the remaining cases resulting from non-AMI causes (19%) (Harjola 2015). Of the AMI's, 68% were found to be ST-elevation myocardial infarction (STEMI) and 8% representing mechanical complications of myocardial infarction. The most common non-AMI causes included advancing, severe CHF and valvular causes (Harjola 2015).

The incidence of CS in patient with STEMI has observed an upward trend, from 6.5% in 2003 to 10.1% in 2010. In this population, higher incidence of CS was observed in patients aged >75 years of age, in Asian / Pacific islanders versus other racial / ethnic groups and in women versus men (Kolte 2014). Whilst the in-hospital mortality in patients with CS has seen an improvement over time (van Diepen 2017), possibly related to improved early revascularisation, longer-term mortality in CS has remained relatively consistent over the past two decades, with only 40–50% of patients surviving beyond 6 months, highlighting a persistent unmet need for improved treatment strategies to improve mortality (Hochman 1999; Thiele 2013).

High mortality and morbidity in patients with CS continue to drive demand for improved therapeutic options for patients with CS. A major challenge in the treatment of patients with CS is that the initial hemodynamic problem can deteriorate very fast into a downward spiral with progression of hypoperfusion, organ failure and death. Hence, early identification and rapid

intervention are critical to optimise treatment efficacy in this patient population, with the aim to reverse the cascade of CS.

An overview of the central pathophysiology of CS, reduced cardiac output, and the various consequent cascade of events and conditions is provided in Figure 1.

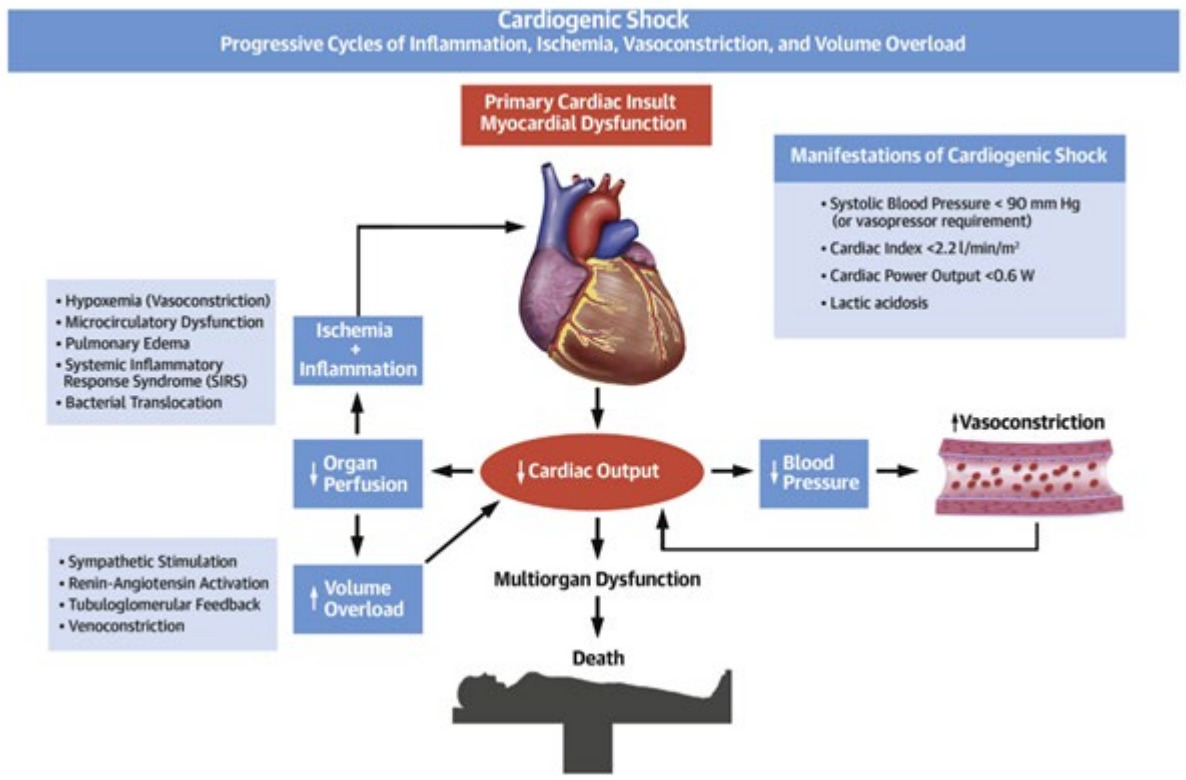

Figure 1 Pathophysiology of CS

Source: Tehrani 2020

Staging of CS

Patients with CS represent a heterogeneous population. To help classify patients based on severity, the Society for Cardiovascular Angiography and Intervention (SCAI) proposed a staging system for CS, categorising patients into five stages (A to E) based on the description of symptoms, physical examination, biochemical markers and haemodynamics. Stage A represents patients 'at risk' and Stage E reflects patients in 'extreme' CS (Baran 2019). Since its introduction, the SCAI staging system has been widely used and a multitude of observational validation studies across the CS spectrum have been conducted, uniformly demonstrating an association between SCAI classification and in-hospital mortality; with higher SCAI classification significantly associated with lower 30-day survival (including Gonzalez-Pacheco 2022; Udesen 2022; Schrage 2020a).

An update of the SCAI staging classification has recently been published (Naidu 2022). The updated SCAI staging maintained the framework of physical examination, biochemical markers and haemodynamics, with the changes relating to the criteria for each Stage having been modified to be more concise and data driven, with the overall objective of optimising sensitivity and specificity to enable increased uptake in clinical practice and hence clinical studies.

Even though the shock stages represent good predictors of mortality in patients with CS, there are a lot of other risk modifiers that can alter this risk, meaning the risk of mortality within each and every one of the stages varies (Kapur 2022). Furthermore, since the condition and severity of patients with CS is a dynamic continuum, the transition between stages is an important consideration, meaning patients should be re-evaluated throughout to guide de-escalation or escalation strategies. An improvement in shock Stage represents a significant prognostic indicator, whilst the converse is true, progression to higher shock Stage is a potent negative marker for survival (Hanson 2020).

CS consists of a heterogeneous population including distinct phenotypes and aetiologies and hence a multitude of factors must be considered in determining the appropriate management, on a case-by-case basis. According to Naidu (2022), "[c]linical decision-making for patients with CS must integrate not only shock severity but also the etiology of shock (particularly ischaemic versus nonischemic and acute versus acute-on-chronic), the presence and reversibility of organ failure, degree of congestion, mixed or vasodilatory shock states, ventricular involvement (LV, right ventricular (RV), or biventricular dysfunction), and a multitude of factors influencing candidacy for supportive therapies such as age, CA [cardiac arrest], and important comorbidities" (pg 940). [To note, given IMPELLA is a LV support device, patients in CS with RV and biventricular failure are not relevant populations for the proposed service for IMPELLA in this ADAR, noting that some patient having their MCS elevated to ECPELLA, eg started on VA-ECMO and added Impella to unload the LV may have biventricular failure].

According to the SCAI framework, patients that require vasoactive drugs or MCS to reverse hypoperfusion or haemodynamic compromise are assigned Stage C, classic CS. If, however, this initial therapy is ineffective, and more intensive therapy is required, including the addition of one more vasoactive drug or additional MCS, then the patient would be designated Stage D, deteriorating. Refractory CS reflects ongoing persistent tissue hypoperfusion despite provision of two adequately dosed vasoactive medications and management of the underlying aetiology (Reyentovich 2016). If despite multiple vasoactive drugs and/or MCS devices perfusion is not restored, then Stage E is present, extremis.

The Joint EAPCI/ACVC (European Association of Percutaneous Cardiovascular Intervention/ Association for Acute Cardiovascular Care) expert consensus document on percutaneous ventricular assist devices, suggests that MCS should be considered for patients with deteriorating shock (Stage C and D) with failure to respond to initial therapy (Chieffo 2021).

Table 1 SCAI classification of CS stages – descriptors, physical exam, biochemical markers and haemodynamics

Stage	Description	Physical exam/bedside findings		Biochemical markers		Haemodynamics	
		Typically includes	May include	Typically includes	May include	Typically includes	May include
A At risk	A patient who is not currently experiencing signs or symptoms of CS, but is at risk for its development. These patients may include those with large AMI or prior infarction acute and/or acute-on-chronic heart failure symptoms	Normal JVP Warm and well perfused • Strong distal pulses • Normal mentation	Clear lung sounds	Normal lactate	Normal labs •Normal (or at baseline) renal function	Normotensive (SBP≥100 mmHg or at baseline)	If invasive haemodynamics assessed • Cardiac index ≥2.5 mL/min/m^2 (if acute) • CVP <10 mmHg • PCWP ≤15 mmHg • PA saturation ≥65%
B Beginning CS	A patient who has clinical evidence of haemodynamic instability (including relative hypotension or tachycardia) without hypoperfusion	Elevated JVP Warm and well perfused • Strong distal pulses • Normal mentation	Rales in lung fields	Normal lactate	Minimal acute renal function impairment Elevated BNP	Hypotension • SBP <90 mmHg • MAP <60 mmHg • >30 mmHg drop from baseline Tachycardia • Heart rate ≥100 bpm	–
C Classic CS	A patient who manifests with hypoperfusion and who requires one intervention (pharmacological or mechanical) beyond volume resuscitation. These patients typically present with relative hypotension (but hypotension is not required)	Volume overload	Looks unwell Acute alteration in mental status Feeling of impending doom Cold and clammy Extensive rales Ashen, mottled, dusky, or cool extremities Delayed capillary refill Urine Output <30 mL/h	Lactate ≥2 mmol/L	Creatinine increase to 1.5 x baseline (or 0.3 mg/dL) or >50% drop in GFR Increased LFTs Elevated BNP	If invasive haemodynamics assessed (strongly recommended) • Cardiac index <2.2 L/min/m^2 • PCWP >15 mmHg	–
D Deteriorating	A patient who is similar to category C but is getting	Any of Stage C and worsening (or not		Any of Stage C and lactate rising and	Deteriorating renal function	Any of Stage C and requiring escalating	

Stage	Description	Physical exam/bedside findings		Biochemical markers		Haemodynamics	
		Typically includes	**May include**	**Typically includes**	**May include**	**Typically includes**	**May include**
	worse. Failure of initial support strategy to restore perfusion as evidenced by worsening haemodynamics or rising lactate	improving) signs/symptoms of hypoperfusion despite the initial therapy.		persistently >2 mmol/L	Worsening LFTs Rising BNP	doses or increasing numbers of pressors or addition of a mechanical circulatory support device to maintain perfusion	
E Extremis	Actual or impending circulatory collapse	Typically unconscious	Near pulselessness Cardiac collapse Multiple defibrillations	Lactate ≥8 mmol/L[a]	CPR (A-modifier) Severe acidosis • pH <7.2 • Base deficit >10 mEq/L[b]	No SBP without resuscitation PEA or refractory VT/VF Hypotension despite maximal support	Need for bolus doses of vasopressors

Abbreviations: AMI, acute myocardial infarction; BNP, B-type natriuretic peptide; BP, blood pressure; bpm, beats per minute; CPR, cardiopulmonary resuscitation; CVP, central venous pressure; GFR, glomerular filtration rate; JVP, jugular venous pressure; LFT, liver function test; MAP, mean arterial pressure; PA sat, pulmonary artery oxygen saturation; PAPI, pulmonary artery pulsatility index; PEA, pulseless electrical activity; RAP, right atrial pressure; SBP, systolic blood pressure; VT/VF, ventricular tachycardia / ventricular fibrillation

a Stage E prospectively is a patient with cardiovascular collapse or ongoing CPR. Source: Naidu 2022

b Base deficit is the amount of base (in mmol) required to titrate a litre of whole arterial blood to a pH of 7.40

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

The proposed population for IMPELLA, consistent with the Ratified PICO for Application 1523, includes patients with CS with no evidence of significant anoxic neurological injury. The proposed population for ECPELLA (IMPELLA added to VA-ECMO) includes patients with CS who are on VA-ECMO and require left ventricular unloading.

Provide a rationale for the specifics of the eligible population:

Given the heterogeneity in the CS population, the dynamic continuum of CS, as discussed above, and the complexity of classifying patients by Stage in a consistent manner that relates specifically to the management of these patients; the proposed population, and consequent proposed MBS item descriptor, is kept intentionally broad given the large element of clinical discretion associated with managing these patients. This is consistent with the MBS item descriptor for VA-ECMO.

The decision to initiate MCS in patients with CS, and selection of the most appropriate device, is made by a multidisciplinary team. As illustrated above, the SCAI staging provides some guidance as to when MCS may be considered and when escalation of support may be warranted. That is, patients in Stage C and beyond, who have not stabilised despite use of vasoactive drugs, would be considered for MCS. In this population, IMPELLA would provide an alternative MCS device to VA-ECMO. (Note. The proposed setting is for the service to be provided in centres with VA-ECMO capability).

Whilst it is difficult to define the exact population in CS for whom IMPELLA would constitute a reasonable device, as per local expert advice, the following considerations are taken into account by the multidisciplinary team in selecting appropriate MCS on an individual patient basis:

- ECMO may be used to provide circulatory support in acute or refractory CS or CA, given the emergency of the condition noting that extracorporeal cardiopulmonary resuscitation (E-CPR) is a specific type of time critical VA-ECMO performed on patients in CA. IMPELLA might not be an ideal MCS device for use in CA given the likely need for simultaneous respiratory and cardiac support.
- Given the IMPELLA device provides direct unloading of the left ventricle, whereas VA-ECMO does not reduce the work or unload the left ventricle, it is a suitable option for patients who have left ventricular failure. In cases of biventricular failure, where the left and right ventricle are failed, VA-ECMO is used as cardiopulmonary support that provide blood oxygenation and circulation like a heart-lung bypass machine whereas IMPELLA would not be used alone. However, since VA-ECMO increases LV afterload leading to LV extension in patients with severely depressed LV function, IMPELLA can be used with VA-ECMO to unload patients with biventricular failure (e.g., ECPELLA).
- IMPELLA would also be considered a suitable MCS option for patients who have AMI complicating CS.

As per their November 2019 consideration, MSAC *"considered that the use of IMVAD in conjunction with ECMO would require justification in a narrower population*" (Application 1523

PSD November 2019, pg 5). Consistent with local expert advice, IMPELLA would be considered as a conjunct device in VA-ECMO patients (ie, ECPELLA) who require unloading of their LV. That is, whilst VA-ECMO is an effective life support device, as a consequence of the circuit, oxygenated blood returning to the body flows retrograde in the aorta and increases LV afterload, hence further compromising the already failing myocardium and creating LV distension, which, in turn, may lead to difficulties and/or the inability to regain native heart function. In order for the aortic valve to open, an equilibrium must exist, between the pressure generated by the LV and the arterial pressure. That is, the LV must be able to produce sufficient pressure to overcome the ECMO-induced rise in arterial pressure (Rao 2018).

The mechanism of action of IMPELLA is specifically to unload the LV, by pumping blood directly from the LV into the aorta. IMPELLA unloads the LV, increases cardiac output, and improves mean arterial pressure (MAP) whilst reducing LV end-diastolic pressure, myocardial workload and oxygen consumption. IMPELLA is the only technology that directly and actively unloads the LV and simultaneously increases cardiac output (Attinger-Toller 2022). Mechanistically, the addition of the IMPELLA device in patients on VA-ECMO who require LV unloading is therefore intuitive – the IMPELLA device in these patients leads to the reduction of pressure and volume, wall stress and myocardial oxygen demand from the heart which, in turn, allows the native heart to rest and recover, thereby improving the patients chance of survival with their native heart.

The proposed population for ECPELLA is therefore narrowly defined as patients in CS on VA-ECMO that require unloading of their LV. According to local experts, this proposed population represents a small number of patients – the addition of another MCS device is considered carefully by the multidisciplinary team, because a fine balance exists between doing enough and doing too much. The experts also indicated that the use of IMPELLA first and then escalating to VA-ECMO is not an approach that would be used; it was noted that only in extremely rare circumstances where, for example, the patients pathology changed from presentation (for example presenting with left heart failure and developing right heart failure), would it perhaps be necessary to add VA-ECMO. According to local expert advice, this is an uncommon occurrence and therefore, IMPELLA first with the addition of VA-ECMO, is not considered in this Application.

Are there any prerequisite tests?

No

Are the prerequisite tests MBS funded?

N/A

Please provide details to fund the prerequisite tests:

N/A

Intervention

Name of the proposed health technology:

The proposed medical service is for the insertion, maintenance and removal of a left IMVAD (IMPELLA®)

When used together with VA-ECMO, the intervention is referred to as ECPELLA.

Describe the key components and clinical steps involved in delivering the proposed health technology:

IMPELLA is a transluminal microaxial ventricular assist device that is inserted percutaneously or surgically.

The IMPELLA devices have a small microaxial pump (at one end of a thin, flexible catheter) that pumps blood from the left ventricle through an inlet area near the tip and expels blood into the ascending aorta. The other end of the tube is connected to an automated control system (AIC-automated Impella controller) outside the body (that controls the pump rate). The IMPELLA technology is part of the latest generation of cardiac assist devices. The device stabilises haemodynamics, unloads the ventricle, augments peak coronary flow, perfuses the end organs, reduces myocardial oxygen demand and allows for recovery of the native heart. It is indicated for clinical use in interventional cardiology and cardiac surgery for supporting the native heart in patients with reduced ventricular function.

The IMPELLA® Ventricular Support System consists of a family of percutaneous heart pumps. To accommodate a range of cardiac output requirements, different sized IMPELLA support catheters are available. The IMPELLA family consists of four left ventricular devices relevant to this Application, IMPELLA® 2.5, CP, 5.0 and 5.5:

1. IMPELLA® 2.5: a 12-Fr (French) catheter-based device with maximal flow rates of 2.5 L/min, placed through a femoral percutaneous approach – via a standard catheterisation procedure through the femoral artery, into the ascending aorta, across the valve and into the left ventricle.
2. IMPELLA® CP (cardiac power): a 14-Fr catheter-based device maximal flow rates of 4.3 L/min, placed through a femoral percutaneous approach – via a standard catheterisation procedure through the femoral artery, into the ascending aorta, across the valve and into the left ventricle.
3. IMPELLA® 5.0: a 21-Fr catheter-based device with maximal flow rates of 5.0 L/min; placed via femoral cut down or through the left or right axillary artery and goes through the ascending aorta, across the valve and into the left ventricle.
4. IMPELLA® 5.5: a 21-Fr catheter-based device with maximal flow rates of 5.5 L/min; placed through the left or right axillary artery and goes through the ascending aorta, across the valve and into the left ventricle or directly into the ascending aorta.

[Note: IMPELLA® RP also exists, however, is used for right heart failure, a population for whom listing is not sought, hence not included in the table below].

The femoral and axillary insertions of IMPELLA are depicted in Figure 2.

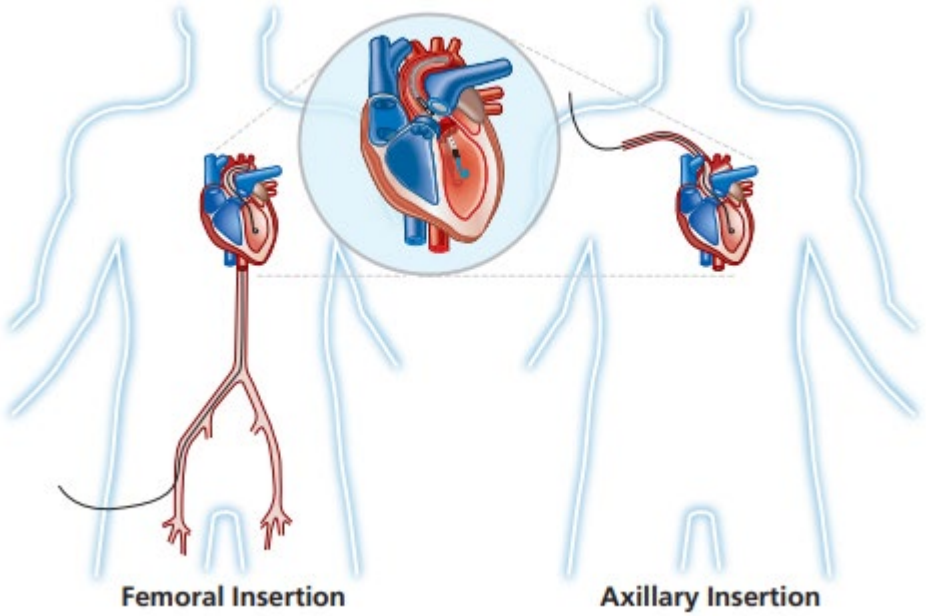

Figure 2 IMPELLA catheter in the heart, via femoral or axillary insertion

All of the IMPELLA catheters consist of a microaxial rotary blood pump mounted on a drive catheter, which is connected to an external controller, the automatic IMPELLA® controller (AIC). The IMPELLA® CP is shown as an example in Figure 3.

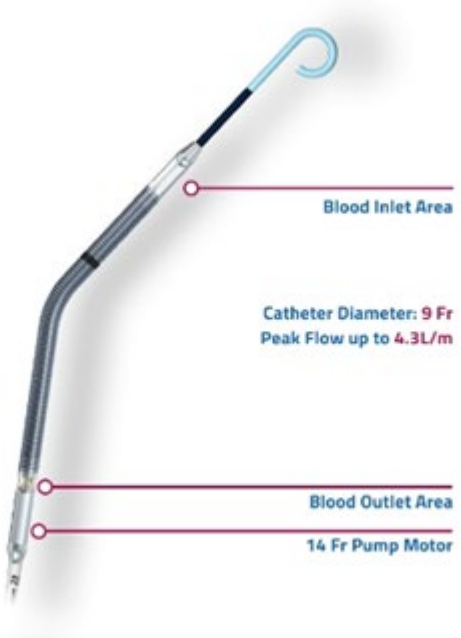

Figure 3 IMPELLA Ventricular Support catheter (IMPELLA® CP)

Source: https://www.mpo-mag.com/contents/view_breaking-news/2018-04-02/fda-approves-abiomeds-IMPELLA-cp-heart-pump-with-smartassist/ (accessed 12 April 2023).

The AIC is used by operators to monitor the correct positioning and functioning of the IMPELLA®. The AIC generates signals required to power the drive motor of the IMPELLA catheters and provides a user interface. The AIC also incorporates the disposable IMPELLA® purge cassette system (each purge system includes five single use purge cassettes), which provides a fluid pressure barrier to prevent blood from entering the IMPELLA Catheters' drive motor. The recommended purge solution is 25 U/mL of unfractionated heparin with 5% dextrose in water. The AIC and IMPELLA purge cassette are shown in Figure 4.

The AIC is portable and, in the U.S., has been qualified for use in patient transport by trained healthcare professionals within healthcare facilities and during medical transport between hospitals (i.e., ambulance, helicopter or fixed-wing aircraft). It should be noted that, whilst technically possible to use IMPELLA in the setting of transport to a VA-ECMO centre, the current VA-ECMO retrieval service is well established and will remain. To this end, it is not intended for IMPELLA to be used during transport.

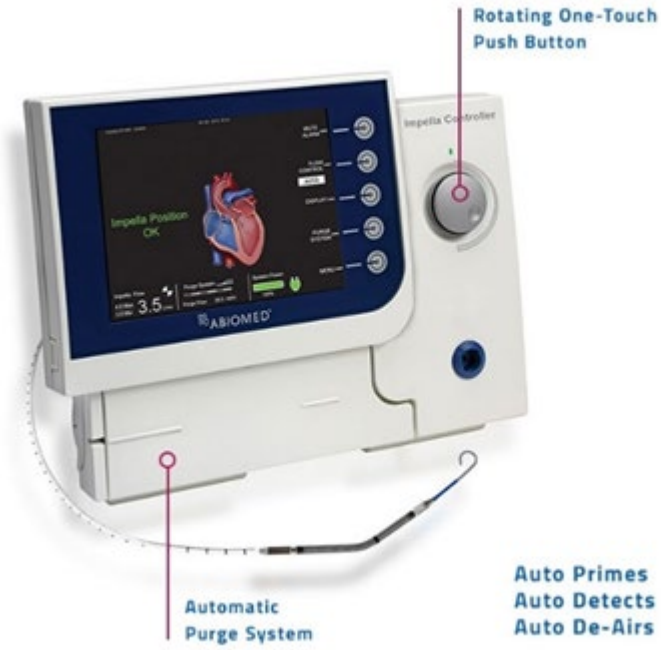

Figure 4 AIC and IMPELLA purge system

Source: http://www.abiomed.com/IMPELLA/automated-IMPELLA-controller

IMPELLA® favourably alters the balance of myocardial oxygen demand and supply, improving myocardial ischaemic reserve. During normal physiological systole, blood is propelled by contraction of the left ventricle through the aortic valve to the systemic circulation via the ascending aorta, blood also enters the left and right coronary arteries via the coronary ostia to perfuse the heart. IMPELLA® generates haemodynamic support by providing active forward flow that increases net cardiac output. By supplementing active forward flow and systemic aortic pressure there is an effective increase in mean arterial pressure and overall cardiac output. As a result, the IMPELLA® devices can assist in maintaining end-organ perfusion and facilitate myocardial recovery from insult.

Identify how the proposed technology achieves the intended patient outcomes:

It provides continuous pumping independent of the cardiac cycle. The IMPELLA device improves haemodynamics by directly unloading the left ventricle (by ejecting blood into the ascending aorta), reducing end-diastolic wall stress and immediately decreasing pulmonary capillary wedge pressure (PCWP) hence improving organ perfusion in patients with CS and at the same time reducing myocardial oxygen demand (Meyns 2003). Figure 5 summarises the mechanism of action of IMPELLA®. In short, it may be summarised that IMPELLA (2.5/CP/5.0/5.5) provides unloading of the left ventricle.

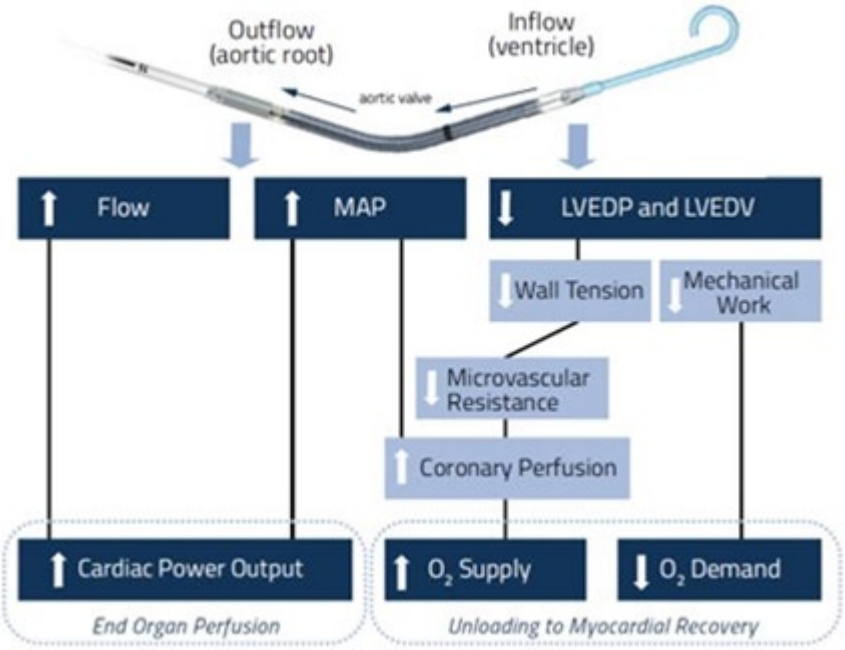

Figure 5 Mechanism of action of IMPELLA

LVEDP = Left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; MAP = mean arterial pressure.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

Yes (IMPELLA®)

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

It is not essential to have this trademark component. It will be at the discretion of MSAC to determine if the MBS item should be specific to the IMPELLA® device. To note there are no other IMVADs currently available in Australia.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

Yes

Provide details and explain:

The limitation on the provision of the proposed service relates to limitations of centres that have the expertise and capability to manage CS patients. Specifically, the proposed setting for IMVAD is in centres with VA-ECMO capability.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

The management of CS involves a multidisciplinary team (MDT), typically including a cardiac surgeon, interventional cardiologist, heart failure specialist and intensivist (critical care specialists).

The insertion/removal procedure is performed by a cardiac surgeon for IMPELLA 5.0 or 5.5 or by an interventional cardiologist/intensivist for IMPELLA 2.5 or CP.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

N/A

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes

Provide details and explain:

Abiomed will offer the following training:

<u>Initial training</u>

- General training on the IMPELLA AIC and catheters

- Comprehensive hands-on training for small groups of physicians and experienced users per department
- Proctored case training facilitated by an Abiomed Clinical Specialist conducted on site for physicians and staff during actual cases
- Competency evaluations and certification for clinical staff

It is Abiomed's policy that without the competency training and certification, Impella will not be allowed to be used.

Continued training

Ongoing online and onsite refresher training depending on usage patterns will be provided. Quick skill videos are available online at Abiomed Academy and IMPELLA Application on mobile.

Onsite clinical assistance

Trained Abiomed / Partner's resources will support and provide onsite clinical assistance from the catheterisation laboratory and operating theatre to the Intensive Care Unit (ICU).

24x7 Clinical Support Centre

The Clinical Support Centre is available 24 hours a day, 7 days a week accessible via domestic phone number. This experienced team, which includes cardiac nurses and technologists, has expertise in hemodynamic support and provides 24x7 clinical assistance from the catheterisation laboratory and operating theatre to the ICU. Phone system directly connects to a clinical consultant not an operator*

Dedicated and highly skilled clinical team to provide assistance with:

- Pre-implant considerations
- Patient Management
- Setup and implantation
- Best Practice Consultation
- ICU Check-In, Proactive Calls
- Troubleshooting
- Positioning
- Hospital-to-hospital transfer
- Purge fluid, cassette, and system change
- Weaning and explant

Indicate the proposed setting(s) in which the proposed health technology will be delivered: (select all relevant settings)

☐ Consulting rooms

☐ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☐ Laboratory
☐ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?
Yes

Please provide additional details on the proposed health technology to be rendered outside of Australia:
N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

VA-ECMO is nominated as the comparator to IMVAD in patients with CS. Similarly, when IMVAD is used in conjunction with ECMO, eg, ECPELLA, the nominated comparator is also VA-ECMO with or without surgical venting.

List any existing MBS item numbers that are relevant for the nominated comparators:

Description	MBS item	Fee
VA-ECMO		
Peripheral cannulation, including under ultrasound guidance where clinically appropriate, for venoarterial cardiopulmonary extracorporeal life support. No separate ultrasound item is payable with this item (See para TN.1.10 of explanatory notes to this Category)	13832	$932.20
Veno–arterial cardiopulmonary extracorporeal life support, management of—the first day (See para TN.1.10 of explanatory notes to this Category)	13834	$521.85
Veno–arterial cardiopulmonary extracorporeal life support, management of—each day after the first (See para TN.1.10 of explanatory notes to this Category)	13835	$121.40
TN.1.10		

Description	MBS item	Fee
Procedures Associated with Intensive Care - (Items 13815, 13818, 13832, 13834, 13835, 13837, 13838, 13840, 13842, 13848, 13851, 13854 and 13857) TN.1.10 Procedures Associated with Intensive Care - (Items 13815, 13818, 13832, 13834, 13835, 13837, 13838, 13840, 13842, 13848, 13851, 13854 and 13857) Item 13815 covers the insertion of a central vein catheter, including under ultrasound guidance where clinically appropriate. No separate ultrasound item is payable with item 13815. Item 13818 covers the insertion of a right heart balloon flotation catheter. Benefits are payable under this item only once per day except where a second discrete operation is performed on that day. Items 13832, 13834, 13835, 13837, 13838 and 13840 These items cover extracorporeal life support services in an ICU. Benefits are payable only once per calendar day for a patient, irrespective of the number of medical practitioners involved. Items 13832 and 13840 include the use of ultrasound guidance where clinically appropriate. No separate ultrasound item is payable with these items. Item 13839 Provides for collection of blood for diagnostic purposes by arterial puncture. Medicare benefits are not payable for sampling by arterial puncture under item 13839 in addition to item 13870 and 13873 on the same day. Item 13842 This item provides for intra-arterial cannulation (including ultrasound guidance) for either or both intra-arterial pressure monitoring or blood sampling. If a service covered by item 13842 is provided outside of an ICU, in association with, for example, an anaesthetic, benefits are payable under item 13842 in addition to item 13870 and 13873 when performed on the same day. Where this occurs, accounts should be endorsed "performed outside of an Intensive Care Unit" against item 13842. Item 13848 Item 13848 covers management of counterpulsation by intra-aortic balloon on each day and includes initial and subsequent consultations and monitoring of parameters. Insertion of the intra-aortic balloon is covered under item 38609. Items 13851 and 13854 Items 13851 and 13854 cover the management of ventricular assist devices in an ICU. Benefits are payable only once per calendar day per patient, irrespective of the number of medical practitioners involved. Item 13851 covers management of ventricular assist devices on the first day where the ICU admission relates to the device implantation or complication. Management on each day subsequent to the first is covered under item 13854. Item 13857 This item covers the establishment of airway access and initiation of ventilation on a patient outside intensive care for the purpose of subsequent ventilatory support in intensive care. Benefits are not payable under item 13857 where airway access and ventilation is initiated in the context of an anaesthetic for surgery even if it is likely that following surgery the patient will be ventilated in an ICU. In such cases the appropriate anaesthetic item/s should be utilised.		

Please provide a rationale for why this is a comparator:

As per the Ratified PICO for Application 1523, the nominated comparator to IMVAD in patients with CS was "standard care (ie pharmacological therapy and/or intra-aortic balloon pump, and/or extracorporeal membrane oxygenation (ECMO), ventricular assist devices)".

However, in their deliberation, "MSAC agreed with the comparators as assessed by ESC – that is:

- 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" (Application 1523 PSD November 2019, pg 3).

- "For the CS population… MSAC noted that recent studies have shown that IABP has limited value in this context and is no longer recommended for this indication" (Application 1523 PSD November 2019, pg 4).

To this end, VA-ECMO is nominated as the comparator to IMPELLA in patients with CS. To note, intra-aortic balloon pump (IABP) was nominated as a comparator to IMVAD as per the PICO for Application 1523 but is not considered in this ADAR, because, and as noted above, MSAC advised that ECMO is the appropriate comparator in patients with CS. This advice is consistent with Australian (NHFA CSANZ Heart Failure Guidelines 2018; Chew 2016) and international clinical guidelines (Bernhardt 2023, Chieffo 2021; McDonagh 2021), where routine use of IABP is not recommended in the management of CS patients.

Similarly, pharmacotherapy, despite being mentioned as forming part of standard of care in the PICO for Application 1523 is not included as a comparator in this Application. This is because patients that require MCS have already trialled pharmacotherapy and stabilisation has not been achieved (consistent with Stage C or higher SCAI stages as discussed above). Implementation of MCS is on top of pharmacotherapy. To this end, pharmacotherapy forms part of the background therapy for patients requiring MCS and is not an appropriate comparator to IMVAD in the proposed patient population. This is further supported by the proposed setting for IMVAD being in VA-ECMO equipped centres; meaning IMPELLA represents an alternative MCS to VA-ECMO.

The PICO for Application 1523 also nominated 'ventricular assist devices' as a comparator. To note, IMVAD is a ventricular assist device. It is possible that the PICO refers to TandemHeart, which is a percutaneous ventricular assist device (LivaNova). The intended purpose of TandemHeart, is to "maintain blood flow through the extracorporeal circuit whilst on heart lung bypass" (ARTG 15880), suggesting this device is used in addition to VA-ECMO. As per the Procedure Kit guidance on the LivaNova website, the TandemHeart system is intended for short term use to pump blood through an extracorporeal circuit, of less than 6 hours. This is in contrast to the markedly longer duration of MCS required in patients with CS (typically around 5 days, Wilson-Smith 2018). TandemHeart, and hence 'ventricular assist devices' is therefore not an appropriate comparator to IMVAD in this ADAR.

As specified above, the proposed population for ECPELLA includes patients in CS who are on VA-ECMO and require unloading of the LV. One of the disadvantages of VA-ECMO is that the oxygenated blood returning to the body flows retrograde in the aorta and, in turn, causes a marked increase in LV afterload, which due to a number of haemodynamic consequences, further compromises the already failing myocardium. These patients on VA-ECMO need LV unloading. The only approach available to physicians that directly vents the LV is surgical venting; however, owing to its passive and complex procedural nature, it is not suitable for all patients, nor is access to expertise universal. To this end, whilst surgical venting represents an option, it is not routinely used in Australia. According to local experts, these patients may also be considered for escalation of vasodilators to reduce LV afterload. However, vasodilators are also passive in nature and do not actively unload blood from LV into the aorta. Therefore, for patients in CS on VA-ECMO who require LV unloading, VA-ECMO with or without surgical venting is the nominated comparator to ECPELLA. The fact that there are no MCS devices currently available that directly unloads the LV highlights the high clinical need for ECPELLA in this small group of patients.

Note, in contrast to 'venting' which is a passive process, 'unloading' is an active approach that reduces the volume and pressure in the ventricle by pumping blood from the right or left ventricle to the pulmonary artery or aortic root, respectively. In this situation, unloading refers to pumping from the left ventricle to the aortic root.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?
(please select your response)

IMPELLA
☐ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☐ Partial – in some cases, the proposed technology will replace the use of the comparator, but not in all cases
☒ Full – subjects who receive the proposed intervention will not receive the comparator

ECPELLA
☒ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☐ Partial – in some cases, the proposed technology will replace the use of the comparator, but not in all cases
☐ Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:

It is anticipated that the uptake of IMVAD in the first year of listing will be **Redacted** of current VA-ECMO procedures used in CS (see UTILISATION ESTIMATES attachment).

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

Type	Outcome	Outcome claim for IMPELLA versus VA-ECMO comparison	Outcome claim for ECPELLA versus VA-ECMO with/without surgical vent comparison
Health benefit	Short-term mortality (In-hospital/30-days)	IMPELLA is expected to improve in-hospital/30-day mortality relative to VA-ECMO	ECPELLA is expected to improve in-hospital/30-day mortality relative to VA-ECMO with or without surgical vent
Health benefit	Longer-term mortality (6-12 months)	IMPELLA is expected to improve 6-month/1-year mortality relative to VA-ECMO	ECPELLA is expected to improve 6-month/1-year mortality relative to VA-ECMO with or without surgical vent
Health harm	Bleedings requiring transfusion	IMPELLA is expected to reduce the proportion of patients experiencing bleedings requiring transfusions relative to VA-ECMO	A higher proportion of patients treated with ECPELLA experience bleedings requiring transfusion relative to VA-ECMO with or without surgical vent, as to be expected considering patients are treated with two MCS devices
Health harm	Stroke	IMPELLA is expected to reduce the proportion of patients experiencing stroke relative to VA-ECMO	A higher proportion of patients treated with ECPELLA experience stroke relative to VA-ECMO with or without surgical vent, as to be expected considering patients are treated with two MCS devices
Health harm	Other complications	In general, IMPELLA had a numerically favourable safety profile relative to VA-ECMO Other complications included events such as haemolysis, limb ischemia and myocardial reinfarction	In general, ECPELLA had a less favourable safety profile relative to VA-ECMO, as to be expected considering patients are treated with two MCS devices Other complications included events such as acute kidney injury, limb ischemia, haemolysis and myocardial reinfarction

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

N/A

Proposed MBS items

How is the technology/service funded at present? (for example: research funding; State-based funding; self-funded by patients; no funding or payments):

IMPELLA is currently not funded for the proposed population in CS.

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention:

Proposed item details

Percutaneous insertion

MBS item number (where used as a template for the proposed item)	NA
Category number	3
Category description	THERAPEUTIC PROCEDUES
Proposed item descriptor	Percutaneous insertion of a left-sided intravascular microaxial ventricular assist device by arteriotomy in patients with CS with no evidence of significant anoxic neurological injury
Proposed MBS fee	$669.55
Indicate the overall cost per patient of providing the proposed health technology	Refer to Cost breakdown attachment
Please specify any anticipated out of pocket expenses	Anticipated out of pocket expenses are unknown; it may reflect 25% of the fee for patients with private health funds that do not cover this part of the arrangement.
Provide any further details and explain	Refer to Cost breakdown attachment

Surgical insertion

MBS item number (where used as a template for the proposed item)	NA
Category number	3
Category description	THERAPEUTIC PROCEDUES
Proposed item descriptor	Surgical insertion of a left-sided intravascular microaxial ventricular assist device by arteriotomy in patients with CS with no evidence of significant anoxic neurological injury)
Proposed MBS fee	$1,004.33
Indicate the overall cost per patient of providing the proposed health technology	Refer to Cost breakdown attachment

Please specify any anticipated out of pocket expenses	Anticipated out of pocket expenses are unknown; it may reflect 25% of the fee for patients with private health funds that do not cover this part of the arrangement.
Provide any further details and explain	Refer to Cost breakdown attachment

Surgical removal

MBS item number (where used as a template for the proposed item)	NA
Category number	3
Category description	THERAPEUTIC PROCEDUES
Proposed item descriptor	Surgical removal of a left--sided intravascular microaxial ventricular assist device.
Proposed MBS fee	$602.60
Indicate the overall cost per patient of providing the proposed health technology	Refer to Cost breakdown attachment
Please specify any anticipated out of pocket expenses	Anticipated out of pocket expenses are unknown; it may reflect 25% of the fee for patients with private health funds that do not cover this part of the arrangement.
Provide any further details and explain	Refer to Cost breakdown attachment

Management – first day

MBS item number (where used as a template for the proposed item)	NA
Category number	3
Category description	THERAPEUTIC PROCEDUES
Proposed item descriptor	Management of the device - first day, including management and monitoring of parameters of the controller for a left-sided intravascular microaxial ventricular assist device
Proposed MBS fee	$521.85
Indicate the overall cost per patient of providing the proposed health technology	Refer to Cost breakdown attachment
Please specify any anticipated out of pocket expenses	Anticipated out of pocket expenses are unknown; it may reflect 25% of the fee for patients with private health funds that do not cover this part of the arrangement.
Provide any further details and explain	Refer to Cost breakdown attachment

Management – subsequent days

MBS item number (where used as a template for the proposed item)	NA

Category number	3
Category description	THERAPEUTIC PROCEDUES
Proposed item descriptor	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
Proposed MBS fee	$121.40
Indicate the overall cost per patient of providing the proposed health technology	Refer to Cost breakdown attachment
Please specify any anticipated out of pocket expenses	Anticipated out of pocket expenses are unknown; it may reflect 25% of the fee for patients with private health funds that do not cover this part of the arrangement.
Provide any further details and explain	Refer to Cost breakdown attachment

Justification of proposed MBS item fees.

Justification of the proposed MBS item fees are provided in Table 2. VA-ECMO services, along with IABP and left ventricular assist device (LVAD) services, are considered relevant to informing the proposed MBS fees for IMVAD (see Table 3). In addition to current MBS items for IABP, VA-ECMO and LVAD; local expert advice was sought to help inform the MBS fees for the proposed IMVAD items pertaining to percutaneous insertion, surgical insertion, as well as surgical removal of the IMVAD device working relative value units (RVUs) for the Current Procedure Terminology (CPT) codes used in the U.S. of IABP, VA-ECMO and IMPELLA (Table 4).

Consistent with MSAC's advice *"that it was reasonable to delete the fee for percutaneous removal of the device"* (MSAC Application 1523 PSD pg 5), an item for percutaneous removal of the device is not proposed.

Consistent with VA-ECMO and LVAD items for IMVAD for the management of the device on the first day and subsequent days are proposed with the same corresponding fees. Notably, management of patients on IABP is also reimbursed via the MBS, with a different structure (daily management at a higher fee than daily management for VA-ECMO, with no management on the first day fee) (Table 3). Notably, Application 1523 additionally included an MBS item code for repositioning of the IMVAD device – however, given the introduction of SmartAssist devices with repositioning guidance, the process of repositioning is typically relatively straight forward and as such is expected to be captured in the daily management MBS item fee. To this end, a reposition item is not proposed in the current Application.

In their evaluation of the MBS item fees proposed in the original submission, MSAC considered that *"while the time for surgical IMVAD insertion and removal is higher than percutaneous methods, the quantum of reimbursement is not adequately justified"* (MSAC Application 1523 PSD pg 5).

The applicant sought advice from the following societies representing the health professionals involved in the management of patients on IMVAD, to inform the proposed MBS items and corresponding fees:

- Cardiac Society of Australia and New Zealand (CSANZ)

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

The societies support the proposed items and corresponding item fees for IMVAD.

Table 2 Justification of proposed MBS item fees

Proposed item	Proposed fee	Justification
Percutaneous insertion of a left-sided intravascular microaxial ventricular assist device by arteriotomy in patients with CS (with no evidence of significant anoxic neurological injury)	$669.55	According to the U.S. CPT code RVU relativities of IABP (CPT code 33967, work RVU 4.48), IMPELLA (CPT code 33990, work RVU 6.75), and VA-ECMO (CPT code 33952, work RVU 8.15), percutaneous insertion of IMPELLA is halfway between IABP (MBS item 38362; fee=$406.90) and VA-ECMO (MBS item 13832; fee=$932.20).
Surgical insertion of a left-sided intravascular microaxial ventricular assist device by arteriotomy in patients with CS (with no evidence of significant anoxic neurological injury)	$1,004.33	The U.S. CPT code RVUs of IABP percutaneous insertion and VA-ECMO percutaneous insertion relative to their corresponding surgical insertions reflect an increase of 12% and 39% respectively. Given a larger difference in duration and complexity is expected between axillary and femoral insertion of IMVAD than between surgical and percutaneous insertion of VA-ECMO and IABP due to the need for anastomotic connection of a graft conduit after cut down to expose the artery, not required for IABP or VA-ECMO. As such, an MBS fee of $1,004.33 is proposed for axillary insertion of IMPELLA, reflecting a fee that is 50% higher than the proposed fee for femoral insertion. This is lower than proposed in Application 1523 ($1,480.00, $50 less than the LVAD code at the time).
Surgical removal of a left-sided intravascular microaxial ventricular assist device	$602.60	The proposed MBS fee of $602.60 for axillary removal of IMVAD reflects 60% of the proposed axillary insertion fee for IMPELLA. This assumption is based on relative work RVU's for surgical removal versus insertion of VA-ECMO on the NPFS, e.g., 40% less work RVU's for removal (5.46) compared to insertion (9.11).
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: $521.85	Same as per VA-ECMO code 13834 and LVAD code 13851 for the management of the device – first day. This is considered to be appropriate in the context of similar the level of resources required for VA-ECMA/LVAD and IMVAD patients.
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: $121.40	Same as per VA-ECMO code 13835 and LVAD code 13854 for the management of the device – each day after the first day. This is considered to be appropriate in the context of similar the level of resources required for VA-ECMA/LVAD and IMVAD patients.

RVU, Relative Value Units.

Table 3 MBS items related to VA-ECMO, IABP and LVAD

Description	MBS item	Fee
VA-ECMO		
Peripheral cannulation, including under ultrasound guidance where clinically appropriate, for venoarterial cardiopulmonary extracorporeal life support	13832	$932.20
Venoarterial cardiopulmonary extracorporeal life support, management of—the first day	13834	$521.85
Venoarterial cardiopulmonary extracorporeal life support, management of—each day after the first	13835	$121.40
IABP		
Insertion of intra-aortic balloon pump, percutaneous	38362	$406.90
Insertion of intra-aortic balloon pump, by arteriotomy	38609	$506.55
Removal of intra-aortic balloon pump, with closure of artery by direct suture	38612	$567.85
Counterpulsation by intra-aortic balloon-management including associated consultations and monitoring of parameters by means of full haemodynamic assessment and management on several occasions on a day – each day	13848	$165.05
LVAD		
Insertion of a left or right ventricular assist device	38615	$1,619.55
Insertion of a left and right ventricular assist device	38618	$2,018.75
Left or right ventricular assist device, removal of, as an independent procedure	38621	$805.95
Left and right ventricular assist device, removal of, as an independent procedure	38624	$905.60
Ventricular assist device, management of, for a patient admitted to an intensive care unit for implantation of the device or for complications arising from implantation or management of the device - first day	13851	$521.85
Ventricular assist device, management of, for a patient admitted to an intensive care unit, including management of complications arising from implantation or management of the device - each day after the first day	13854	$121.40
ECMO/bypass/LVAD		
Extracorporeal membrane oxygenation, bypass or ventricular assist device cannulae, adjustment and repositioning of, by open operation	38627	$707.85

Table 4 2023 National Physician Fee Schedule – RVUs for ECMO, IABP, LVAD and IMPELLA services

Device	CPT code	Description	Work RVU
Insertion			
VA-ECMO	33952	Insertion of peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older	8.15
	33954	Insertion of peripheral (arterial and/or venous) cannula(e), open, 6 years and older	9.11
	33956	Insertion of central cannula(e) by sternotomy or thoracotomy, 6 years and older	16.00
IABP	33967	Percutaneous insertion of intra-aortic balloon pump	4.48
	33970	Surgical insertion of intra-aortic balloon pump through the femoral artery	6.74
LVAD	33979	Insertion of ventricular assist device, implantable, intracorporeal, single ventricle	37.50
IMPELLA	33990	Insertion of ventricular assist device (including radiological supervision and interpretation), percutaneous, left heart arterial access only	6.75

Device	CPT code	Description	Work RVU
	34715	Open axillary/subclavian artery exposure for delivery of endovascular prosthesis, by infraclavicular or supraclavicular incision, unilateral	6.00
	34716	Open axillary/subclavian artery exposure with creation of conduit for delivery of endovascular prosthesis or for establishment of cardiopulmonary bypass, by infraclavicular or supraclavicular incision, unilateral	7.19
	33975	Insertion of ventricular assist device; extracorporeal, single ventricle	25.00
Removal			
VA-ECMO	33966	Removal of peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older	4.50
	33984	Removal of peripheral (arterial and/or venous) cannula(e), open, 6 years and older	5.46
	33986	Removal of central cannula(e) by sternotomy or thoracotomy, 6 years and older	10.00
IABP	33968	Percutaneous removal of intra-aortic balloon pump	0.64
	33971	Surgical removal of intra-aortic balloon pump	11.99
LVAD	33980	Removal of ventricular assist device, implantable, intracorporeal, single ventricle	33.50
IMPELLA	33992	Removal of percutaneous left heart ventricular assist device, arterial or arterial and venous cannula(s)	3.55
	33977	Removal of ventricular assist device; extracorporeal, single ventricle	20.86

Abbreviations: IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

The management of CS involves a MDT, typically including a cardiac surgeon, interventional cardiologist, heart failure specialist and intensivist (critical care specialists).

Patients in CS will undergo a series of assessments, including clinical signs and symptoms, tests of biochemical markers and haemodynamics. Patients will typically receive pharmacotherapy, including vasodilators and inotropes, however, if the patient does not stabilise MCS will be considered. The decision to commence MCS will be made by the MDT.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

There are no differences between the proposed and the comparator technologies in terms of the work up of patients prior to accessing the services.

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

Capital equipment	AIC (one unit)
Consumables, single use	The IMPELLA catheter Purge cassette
Theatre time, facility requirements	Cardiac catheter laboratory, ICU unit or operation theatre (for insertion, time unclear), and time in ICU unit (for episode of care)
Staffing resources	Intensivist, cardiac surgeon/interventional cardiologist, anaesthetist, ICU nurse
Anaesthetics	Dependent on procedure duration

Explain what other healthcare resources are used in conjunction with the comparator health technology:

The capital and consumable cost of the VA-ECMO technology was informed by local expert advice.

Capital equipment	ECMO console
Consumables	ECMO tubing pack set kit Cannulas (arterial and venous) Percutaneous insertion kit
Theatre time, facility requirements	Cardiac catheter laboratory, ICU unit or operation theatre (for insertion, time unclear), and time in ICU unit (for episode of care)
Staffing resources	Intensivist, cardiac surgeon/interventional cardiologist, anaesthetist, ICU nurse, perfusionist
Anaesthetics	Dependent on procedure duration

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

Similar level of health care resources used in conjunction with IMPELLA and VA-ECMO are required. The same healthcare professionals are involved in the management of patients with cardiogenetic shock irrespective of if IMPELLA or VA-ECMO is used, noting that a perfusionist may additionally be involved in the management of VA-ECMO patients.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

See below

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:

The maintenance phase of VA-ECMO and IMVAD commences once the haemodynamic and respiratory goals have been achieved. This stage of the episode requires continual monitoring of blood flow, assessment of the need for diuresis and monitoring of left ventricular function.

Separation from VA-ECMO/IMVAD, can occur when either of these conditions take place:

- The patient improves clinically, and weaning can commence, or
- The patient deteriorates clinically, and a decision to stop ECMO is made.

The decision to cease VA-ECMO/IMVAD should take place in consultation with the patient (if possible), family members and the MDT following the multistep process as illustrated in Figure 6 (noting the process pertains to VA-ECMO but the principles would apply to patients on IMVAD as well).

After weaning from VA-ECMO/IMVAD the patient will remain in the ICU until the team is confident that the patient is stable, when the patient will be moved to a ward for the after care.

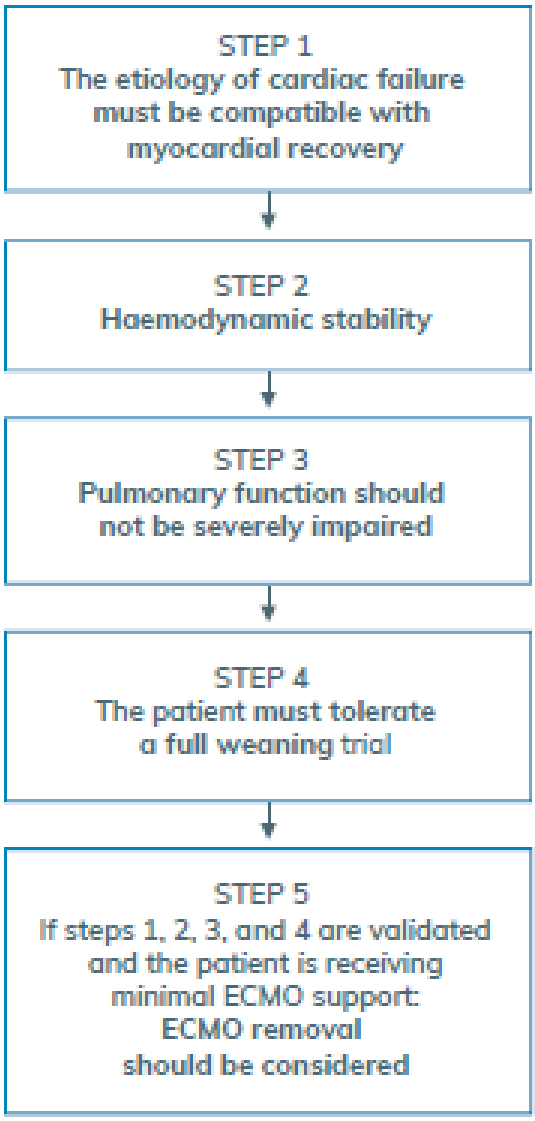

Figure 6 Steps in weaning and discontinuation of ECMO
Source: Ortuno 2019

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

There are no differences in the healthcare resources used after IMVAD versus after VA-ECMO.

Algorithms

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Current algorithm:

The current algorithm is provided in Figure 7. A MDT consultation will occur when a patient with CS arrives to intensive care at the hospital. The patient may arrive via emergency or from within the hospital (admitted patient). First line treatment consisting of pharmacotherapy, including inotropes (such as epinephrine, dobutamine, dopamine, milrinone, levosimendan) and/or vasopressors (such as norepinephrine, vasopressin), are administered. If the patient does not stabilise despite pharmacotherapy, temporary MCS is considered.

The proposed setting for use of IMVAD is in centres that are equipped with VA-ECMO equipment. In these centres, VA-ECMO is the MCS initiated in patients in CS who have not stabilised despite pharmacotherapy. As per treatment guidelines, IABP is not recommended for use in patients with CS (NHFA CSANZ Heart Failure Guidelines 2018; Chew 2016, Chieffo 2021, McDonagh 2021, Bernhardt 2023). In centres that do not have VA-ECMO, an ECMO transfer may be arranged. Either the patient, first treated with pharmacotherapy, travels to the ECMO centre via ambulance or helicopter, or the VA-ECMO centre provides a retrieval service whereby the patient is collected and VA-ECMO is initiated prior to transport to the ECMO centre.

MCS is continued until weaning is indicated, which may occur in one of two ways. Either the patient improves clinically and can be weaned off MCS, or the patients deteriorates clinically (or dies), and a decision is made to wean off MCS.

Whilst VA-ECMO is an effective MCS for use in patients with CS, one of its disadvantages is that due to the retrograde flow blood in the aorta, it causes a marked increase in left ventricular afterload, which due to a number of haemodynamic consequences further compromises the already failing myocardium.

Whilst there is no universally accepted definition of LV distention requiring LV unloading, distension of the LV can be readily diagnosed on echocardiography – as evidence by a dilated and hypercontractile LV with or without severe mitral valve insufficiency. Stagnation of blood in the LV is cause for concern that could lead to mural thrombus formation, and the pulmonary artery diastolic pressure and PCWP may serve as good measures to indicate whether or not the patient needs unloading of the LV. If the VA-ECMO patient's heart is able to eject blood during the cardiac cycle, with the aortic valve opening with every contraction, and the pulsatility is maintained at > 10 mmHg between systolic and diastolic values, and PCWP remain low, it would suggest the LV is adequately compressed and does not require unloading (Cevasco 2019).

As per the current algorithm, patients on VA-ECMO who require unloading of the left ventricle, may be considered for surgical venting in addition to VA-ECMO. Surgical venting is the only available approach that provides direct venting of the left ventricle. However, given the complexity (requires open chest surgery), passive nature of the procedure and the potential for complications, some patients are not suitable for the procedure, and not all hospitals have specialists with the required expertise to perform this procedure at the time of need. To this end, surgical venting is not performed routinely in Australia.

In patients that do not have access to surgical venting or are not suitable for the procedure, the multidisciplinary heart team may consider escalating pharmacotherapy (increase in dose and/or number of agents) to attempt to unload the left ventricle. Other potential options include IABP and atrial septostomy, however, neither of these approaches provide direct unloading of the LV.

IABP provides an unreliable degree of unloading and is not recommended as per clinical guidelines for use in CS. Atrial septostomy provides indirect LV unloading but it is possible that the procedure will result in atrial septal defect closure after decannulation, meaning this is not an ideal option for the proposed population (Rao 2018). To this end, and as depicted in the algorithm, patients on VA-ECMO who require left ventricular unloading will continue VA-ECMO with pharmacotherapy escalation and surgical venting considered.

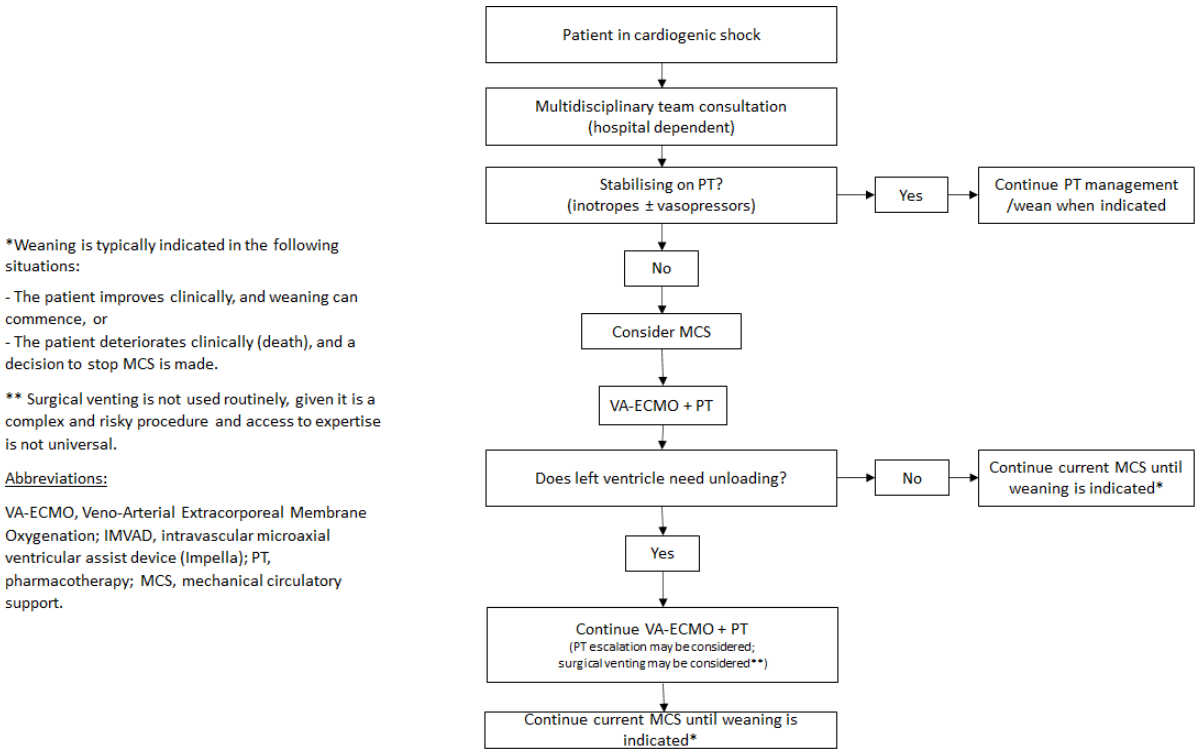

Figure 7 Current clinical management algorithm of temporary circulatory support in CS

Proposed algorithm

As per the proposed algorithm (Figure 8), the addition of IMVAD represents an alternate MCS option to VA-ECMO in patients with CS who have not stabilised on pharmacotherapy. The most appropriate MCS device will be selected by the MDT on an individual patient basis. Based on local expert advice, it is understood that VA-ECMO (ie, E-CPR) is the device of choice for patient in CA because of the emergency of such a condition and the likely requirement of respiratory support. Given the IMPELLA device provides unloading of the left ventricle, it is a suitable option for patients who have left ventricular failure. For the same reason, VA-ECMO is the device of choice in patients with biventricular failure and VA-ECMO for right heart failure (noting the IMPELLA RP device, which is indicated for right heart failure is not pursued in this Application). To note, some patients on ECPELLA may have biventricular failure, if initiated on VA-ECMO and then elevated to include IMPELLA for left ventricular unloading. IMPELLA would also be considered a suitable MCS option for patients who have AMI complicating CS. Therefore, listing IMVAD on the MBS would provide clinicians with an alternative MCS option for use in patients who are in CS.

As discussed above, patients who are on VA-ECMO may require unloading of the left ventricle, if the LV fails to unload this will lead to LV wall stress, increased myocardium oxygen demand, which then further compromises the already failing myocardium. As a result, the recovery of patients with CS may be impaired or even deteriorated to a higher SCAI Stage, further compromising the recovery of the heart. The addition of IMVAD to VA-ECMO, i.e., ECPELLA, is considered an ideal option for these patients, given the fact that the IMPELLA device provides direct unloading of the left ventricle. In the absence of IMVAD, these patients would continue to be managed on VA-ECMO with or without surgical venting (if suitable and available) and may have inotropes and/or vasopressors escalated. Listing ECPELLA on the MBS would address an unmet clinical need for an effective treatment option in patients on VA-ECMO who require unloading of the left ventricle, that is less complex than surgical venting and that can be readily available to the patients. According to local expert advice, few patients would require the addition of IMVAD to VA-ECMO. However, in this targeted population, ECPELLA is shown to improve survival relative to VA-ECMO with or without surgical venting (see Summary of Evidence Section).

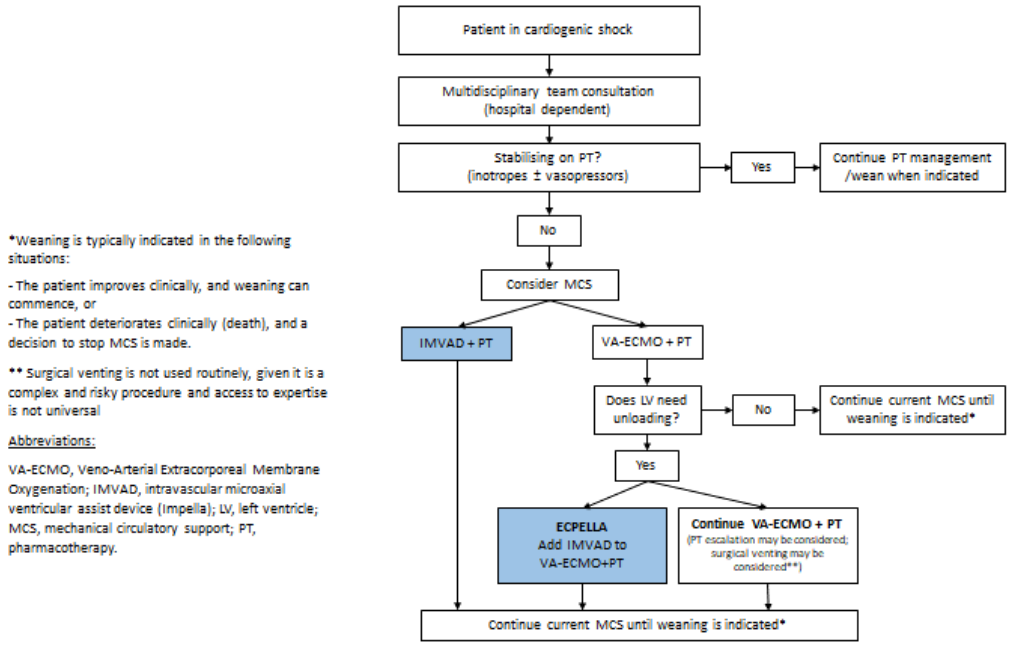

Figure 8 Proposed clinical management algorithm

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?
(please select your response)

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

The use of IMPELLA support in patients with CS results in superior effectiveness relative to VA-ECMO with respect to survival and superior safety with respect to bleeding.
The use of ECPELLA support in patient with CS requiring LV unloading results in superior effectiveness with respect to survival compared with VA-ECMO with or without surgical venting and inferior safety.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

N/A

Identify how the proposed technology achieves the intended patient outcomes:

IMPELLA is a transluminal microaxial ventricular assist device that is inserted percutaneously or surgically. The device stabilises haemodynamics, unloads the ventricle, augments peak coronary flow, perfuses the end organs, reduces myocardial oxygen demand and allows for recovery of the native heart. It is indicated for clinical use in interventional cardiology and cardiac surgery for supporting the native heart in patients with reduced ventricular function.

For some people, compared with the comparator(s), does the test information result in:

N/A

A change in clinical management?	Yes	No
A change in health outcome?	Yes	No
Other benefits?	Yes	No

Please provide a rationale, and information on other benefits if relevant:

N/A

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?
(please select your response)

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

IMPELLA – it is anticipated that IMPELLA will be more costly than the VA-ECMO procedure given the cost of the pump itself exceeds that of the consumables used per procedure for VA-ECMO.

ECPELLA –IMPELLA is used with VA-ECMO, hence more costly than VA-ECMO alone.

Summary of Evidence

A systematic literature review was undertaken to identify all comparative clinical studies of IMPELLA versus VA-ECMO or ECPELLA versus VA-ECMO with or without surgical vent in patients with CS. The review did not identify any randomised controlled trials (RCTs) comparing IMPELLA versus VA-ECMO or ECPELLA versus VA-ECMO with or without surgical venting. The lack of RCTs in CS more broadly illustrates the difficulties recruiting patients and obtaining consent for randomisation given the emergency setting of the condition.

Given the evident difficulties in enrolling a sufficient number of patients into RCTs in this therapeutic area, non-randomised studies reflect the best level evidence informing the clinical therapeutic conclusion in this Application. However, confounding by indication is a potential source of bias in non-randomised studies, with MCS device selection at the discretion by the physician and likely based on various patient characteristics. In this context, it is important to try and account for differences in baseline characteristics and disease severity between the cohorts, which may be achieved by means of matching cohorts based on characteristic or analysing outcomes using an adjusted model that incorporates important covariates. To this end, trials have been categorised according to the intervention (IMPELLA or ECPELLA) and whether or not the study included 'matching' of participants or adjusted analyses of mortality/survival to control for confounding patient characteristics that could influence the trial results. Matched/adjusted studies must have reported sufficient data for comparison with other trials (i.e., trials that reported a p-value only for the matched/adjusted population were not included).

In total, there were six matched/adjusted studies comparing IMPELLA versus VA-ECMO, and five matched/adjusted studies comparing ECPELLA versus VA-ECMO with or without surgical venting at the time of writing this Application. For simplicity, only the matched/adjusted studies have been described in the table below, however, unmatched/unadjusted results will be provided in the submission as supportive evidence. In total, the literature search of clinical evidence identified 13 relevant studies providing unmatched data for the IMPELLA versus VA-ECMO comparison, and 11 relevant studies providing unmatched data for the ECPELLA versus VA-ECMO comparison.

Whilst there are few forthcoming RCTs including IMPELLA or ECPELLA listed on ClinicalTrials.gov, it is worth noting that almost all RCTs commenced in the past 20 years of IMPELLA in CS have been terminated due to low enrolment (for example, but not limited to the following: NCT00314847 and NCT00972270). One trial in particular (DanShock/DanGer Shock [NCT01633502]) has been in the 'recruiting' phase since 2012 and it is unclear when it will be completed. Given the high clinical need for life-saving treatment for patients with CS, and the unsuccessful completion of previous RCTs; it is considered that MSAC should not delay the evaluation of IMPELLA or ECPELLA as it would delay access for patients who would benefit from the treatment for the sake of trials which may never be completed.

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
IMPELLA versus VA-ECMO (matched/adjusted)					
1	R, SC, cohort study with PSM analyses (Germany)	**Karatolios 2021** Comparison of mechanical circulatory support with venoarterial extracorporeal membrane oxygenation or IMPELLA for patients with cardiogenic shock: a propensity-matched analysis	Population: Any CS Comparison: IMPELLA 2.5/CP vs. VA-ECMO After PSM, there were 83 participants in each study group. After PSM, in-hospital survival was 50.6% vs. 38.6% (p=0.16), and 6-month survival was 45.8% vs. 38.6% (p=0.43) for IMPELLA v ECMO, respectively.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8405518/	2021
2	R, analysis of National Inpatient Sample (U.S.), PSM analyses	**Lemor 2020** IMPELLA Versus Extracorporeal Membrane Oxygenation for Acute Myocardial Infarction Cardiogenic Shock	Population: AMI-CS Comparison: IMPELLA (device NS) vs. VA-ECMO The study included 5730 patients treated with IMPELLA and 560 patients treated with VA-ECMO, with both groups consisting of 450 participants each following PSM. After PSM, the ECMO cohort had significantly higher in-hospital mortality compared to the IMPELLA cohort (43.3% vs. 26.7%, OR=2.10, p=0.021).	https://pubmed.ncbi.nlm.nih.gov/32605901/	2020
3	R, SC, cohort study with SAVE-score adjustment (Sweden)	**Schiller 2019** Survival after refractory cardiogenic shock is comparable in patients with IMPELLA and venoarterial extracorporeal membrane oxygenation when adjusted for SAVE-score	Population: Refractory CS Comparison: IMPELLA 2.5/CP/5.0 vs. VA-ECMO The study included 48 patients treated with IMPELLA and 46 treated with VA-ECMO who were SAVE-score adjusted. 30-day survival was lower in the VA-ECMO cohort (59%) versus the IMPELLA cohort (65%). The SAVE-score adjusted HR for mortality was 1.05 (0.58–1.91, p=0.87) for the IMPELLA patients compared with the VA-ECMO patients.	https://pubmed.ncbi.nlm.nih.gov/30406678/	2019
4	R, SC, cohort study with PSM analyses (Germany)	**Syntila 2021** Comparison of Mechanical Support with IMPELLA or Extracorporeal Life Support in Post-Cardiac Arrest Cardiogenic Shock: A Propensity Scoring Matching Analysis	Population: OHCA due to AMI with post CS Comparison: IMPELLA 2.5/CP vs. VA-ECMO After PSM, there were 40 participants in each treatment group. In the matched cohort, the hospital and 12-month survival rates were comparable in the IMPELLA group compared to the ECLS group (hospital survival: 45% vs. 32.5%, p=0.36 and 12 months survival: 40% vs. 32.5%, p=0.64).	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8396971/	2021

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5	R, claims analysis with PSM analyses (U.S.)	**Vetrovec 2021** Cost savings for pVAD compared to ECMO in the management of acute myocardial infarction complicated by cardiogenic shock: An episode of care analysis	Population: AMI-CS Comparison: IMPELLA 2.5/CP (pVAD) vs. VA-ECMO The study included 2,510 patients in the IMPELLA cohort and 340 patients in the VA-ECMO cohort. After PSM, there were 338 participants in each treatment arm. Index in-hospital mortality rates were 53% for pVAD versus 64% for VA-ECMO (p=0.0023).	https://pubmed.ncbi.nlm.nih.gov/32790231/	2021
6	R, MN, MC, cohort study with PSM analyses (Europe)	**Wernly 2021** IMPELLA versus extracorporeal life support in cardiogenic shock: a propensity score adjusted analysis	Population: AMI-CS & CA-CS Comparison: IMPELLA (device NS) vs. VA-ECMO (ECLS) There were 73 participants in the IMPELLA group and 76 participants in the VA-ECMO group. There was a trend towards higher 30-day mortality in ECLS patients vs IMPELLA patients (83% vs. 70%; OR [95% CI]=2.09 [0.22–1.04; p=0.06) in univariable analysis. After correction for propensity score, the aOR [95% CI] was 1.06 [0.17–6.75]; p=0.95.	https://pubmed.ncbi.nlm.nih.gov/33560591/	2021
ECPELLA versus VA-ECMO with or without surgical vent (matched/adjusted)					
1	R, registry analysis of National Inpatient Sample with multivariable adjustment (U.S.)	**Hendrickson 2022** Trends in Venoarterial Extracorporeal Life Support With and Without an IMPELLA or Intra-Aortic Balloon Pump for Cardiogenic Shock	Population: Any CS Comparison: ECPELLA (VA-ECMO [VA-ECLS] plus IMPELLA [device NS]) vs. VA-ECMO [VA-ECLS] The study included 7,440 patients in the VA-ECLS arm and 1,880 patients in the ECPELLA arm. The adjusted overall in-hospital mortality was similar between the VA-ECLS group (52%) and ECPELLA group (57%) (aOR [95% CI] = 1.24 [0.98, 1.57]).	https://www.ahajournals.org/doi/10.1161/JAHA.121.025216	2022
2	R, MN, MC, PSM study (Italy & Germany)	**Pappalardo 2017** Concomitant implantation of IMPELLA® on top of venoarterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock	Population: Severe, refractory CS Comparison: ECPELLA (VA-ECMO plus IMPELLA 2.5/CP) vs. VA-ECMO The study included 34 patients treated with ECPELLA and 123 patients treated with ECMO alone. After PSM, there were 21 and 42 patients treated with ECPELLA and ECMO, respectively. Patients in the ECPELLA group had a significantly lower hospital mortality (48% vs. 74%, p=0.04) compared with VA-ECMO patients.	https://pubmed.ncbi.nlm.nih.gov/27709750/	2017

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3	R, SC cohort study with multivariable adjustment for STEMI and PCI (U.S.)	**Patel 2019** Simultaneous Venoarterial Extracorporeal Membrane Oxygenation and Percutaneous Left Ventricular Decompression Therapy with IMPELLA Is Associated with Improved Outcomes in Refractory Cardiogenic Shock	Population: Refractory CS Comparison: ECPELLA (VA-ECMO plus IMPELLA 2.5/CP) vs. VA-ECMO The study included 30 patients treated with ECPELLA and 36 patients treated with VA-ECMO. After adjusting for STEMI and PCI, 30-day mortality and 1-year mortality were significantly lower in the ECPELLA arm versus the VA-ECMO arm (aHR [95% CI]=0.40 [0.19–0.84]; p=0.016; and aHR [95% CI]=0.39 [0.19–0.81]; p=0.011, respectively).	https://pubmed.ncbi.nlm.nih.gov/29489461/	2019
4	R, SC cohort study with IPTW adjustment (Germany)	**Radakovic 2022** Left ventricular unloading during extracorporeal life support for myocardial infarction with cardiogenic shock: surgical venting versus IMPELLA device	Population: AMI-CS Comparison: ECPELLA (VA-ECMO plus IMPELLA 2.5/CP) vs. VA-ECMO plus surgical vent The study included 71 patients treated with ECPELLA and 41 patients treated with VA-ECMO plus surgical vent. Using IPTW-adjusted analyses, the 30-day mortality rate was lower in the ECPELLA group (54%) compared to the VA-ECMO plus surgical vent group (63%) (RR [95% CI]=0.78 [0.47-1.30] p=0.35).	https://academic.oup.com/icvts/article/34/1/137/6352551	2022
5	R, MN, MC cohort study with PSM analyses (Germany, Italy, U.S. & France)	**Schrage 2020** Left Ventricular Unloading Is Associated With Lower Mortality in Patients With Cardiogenic Shock Treated With Venoarterial Extracorporeal Membrane Oxygenation Results From an International, Multicenter Cohort Study	Population: Any CS (excl. post-cardiotomy shock) Comparison: ECPELLA (VA-ECMO plus IMPELLA 2.5/CP/5.0) vs. VA-ECMO The study included 349 patients in the VA-ECMO group and 227 in the ECPELLA group. After PSM, there were 255 patients in each treatment group. In the matched cohort, IMPELLA was associated with lower 30-day mortality (HR [95% CI]= 0.79 [0.63–0.98]; p=0.03).	https://pubmed.ncbi.nlm.nih.gov/33032450/	2020

Abbreviations: aHR, adjusted hazard ratio; AMI, acute myocardial infarction; CA, cardiac arrest; CI, confidence interval; CS, cardiogenic shock; ECLS, extracorporeal life support; ECPELLA, IMPELLA plus VA-ECMO; HR, hazard ratio; IPTW, inverse probability treatment weighting; MC, multicentre; MN, multinational; NS, not specified; OHCA, out of hospital cardiac arrest; OR, odds ratio; PCI, percutaneous coronary intervention; PSM, propensity score matched; pVAD, percutaneous ventricular assist device; R, retrospective; RR, relative risk; SAVE, Survival after VA-ECMO; SC, single centre; STEMI, ST-elevation myocardial infarction; U.S., United States; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

*** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your Application).

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	RCT, P, MC, OL (U.S.)	**NCT05506449** **RECOVER IV** Early IMPELLA® Support in Patients With ST-Segment Elevation Myocardial Infarction Complicated by Cardiogenic Shock: The RECOVER IV Trial	Population: CS with onset ≤12 hours after STEMI and prior to index PCI Comparison: IMPELLA CP vs SOC (may include inotropes and/or vasopressors. IABP may or may not be used according to local practice and the specific condition of each individual patient) 30-day all-cause mortality will be the primary outcome	https://clinicaltrials.gov/ct2/show/NCT05506449	Study start date: 1 October 2023 Estimated study completion date: 30 December 2027
2.	RCT, P, MC, single blind (U.S.)	**NCT03431467** **REVERSE** A Prospective Randomised Trial of Early LV Venting Using IMPELLA CP for Recovery in Patients With Cardiogenic Shock Managed With VA-ECMO	Population: Any CS (excl. post-cardiotomy CS) Comparison: ECPELLA (IMPELLA CP plus VA-ECMO) vs. VA-ECMO Recovery from CS at 30-days will be the primary outcome. Survival to hospital discharge will be the secondary outcome	https://clinicaltrials.gov/ct2/show/NCT03431467	Study start date: 19 March 2018 Estimated study completion date: 1 January 2025
3.	RCT, P, MC, single blind (Germany)	**NCT05577195** **UNLOAD ECMO** UNLOAD ECMO - Left Ventricular Unloading to Improve Outcome in Cardiogenic Shock Patients on VA-ECMO - a Prospective, Randomised, Controlled, Multicenter Trial	Population: Severe CS due to severe left ventricular dysfunction Comparison: ECPELLA (IMPELLA [device NS] plus VA-ECMO) vs. VA-ECMO Time to death from any cause within 30-days of randomisation will be the primary endpoint. Death from any cause at 6 and 12 months will be a secondary endpoint	https://clinicaltrials.gov/ct2/show/NCT05577195	Study start date: 17 November 2022 Estimated study completion date: 1 December 2025
4.	RCT, MN, MC, OL (U.K, Germany, Denmark)	**NCT01633502** **DanShock / DanGer Shock** Effects of Advanced Mechanical Circulatory Support in Patients With ST-Segment Elevation Myocardial Infarction Complicated by Cardiogenic Shock. The Danish Cardiogenic Shock Trial	Population: AMI-CS undergoing primary percutaneous coronary intervention (PCI) for STEMI. Comparison: IMPELLA CP vs. guideline driven therapy Death from all causes up to 6 months will be the primary endpoint. Note: The treatment algorithms in the Protocol indicate patients on Impella may upgrade to biventricular support, ECPELLA, Impella 5 or LVAD if hemodynamically unstable whereas the control arm may be escalated to VA-ECMO or LVAD. To this end, the resultant comparison is likely confounded by cross over, and will not provide a clear comparison of Impella vs medical therapy.	https://clinicaltrials.gov/ct2/show/NCT01633502 Protocol: Udesen (2019): https://pubmed.ncbi.nlm.nih.gov/31176289/	Study start date: December 2012 Estimated study completion date: January 2024

Abbreviations: AMI-CS; acute myocardial infarction complicating cardiogenic shock; CS, cardiogenic shock; ECPELLA, IMPELLA plus VA-ECMO; LVEF, left ventricular ejection fraction; MC, multicentre; MN, multinational; NS, not specified; OL, open label; RCT, randomised controlled trial; STEMI, ST-elevation myocardial infarction; U.K., United Kingdom; U.S., United States; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

*** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).