Australian Government

Department of Health

Application 1662

The reduction of mitral regurgitation through tissue approximation using transvenous/transeptal techniques

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): Edwards Lifesciences LLC
Corporation name: Edwards Lifesciences LLC
ABN: 77098906873
Business trading name: Edwards Lifesciences

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

2. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

☐ Yes
☒ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

The reduction of mitral regurgitation through tissue approximation using transvenous/transeptal techniques

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Mitral regurgitation (MR), also known as mitral insufficiency, is a condition in which incompetency of the mitral valve causes abnormal backflow of blood from the left ventricle to the left atrium during the systolic phase of the cardiac cycle. There are two types of MR: degenerative and functional. Degenerative mitral regurgitation (DMR), also known as primary MR, refers to regurgitation resulting from the structural abnormality of the mitral valve leaflets and/or valve apparatus. In contrast, functional mitral regurgitation (FMR), also known as secondary MR, occurs when the valve and/or valve apparatus is structurally normal, but dysfunction, distortion, or dilation of the left atrial or ventricular chambers results in tethering of the leaflets and/or mitral annular dilation. Mitral regurgitation (MR) is the most common heart valve disorder worldwide (Dziadzko et al., 2018), with a high prevalence in industrialized nations with aging populations. MR is associated with an increased risk for heart failure and death.

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Edwards has developed a catheter-based technique for the delivery of a permanent implant to the mitral valve via transseptal access. The implant clasps the anterior and posterior leaflets around a spacer, thus creating a double orifice and reducing MR. The Edwards PASCAL Transcatheter Valve Repair System addresses some of the limitations of other devices, including: a larger implant with wider paddles to potentially reduce the number of implants required for adequate MR reduction; independent clasp control to address complex anatomies and regurgitant jets; a spacer in the centre of the implant to act as a filler in the regurgitant orifice for reduction of MR; working length that allows manoeuvrability even with higher septal puncture heights; and ergonomic controls similar to other Edwards transcatheter product lines which are already familiar to many interventional cardiologists.

This Application refers to the proposed medical service as transcatheter mitral valve repair (TMVr).

6. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

N/A

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

i. ☐ An amendment to the way the service is clinically delivered under the existing item(s)
ii. ☐ An amendment to the patient population under the existing item(s)
iii. ☐ An amendment to the schedule fee of the existing item(s)
iv. ☐ An amendment to the time and complexity of an existing item(s)
v. ☐ Access to an existing item(s) by a different health practitioner group
vi. ☐ Minor amendments to the item descriptor that does not affect how the service is delivered

vii. ☐ An amendment to an existing specific single consultation item
viii. ☐ An amendment to an existing global consultation item(s)
ix. ☐ Other (please describe below):

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☒ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

(g) If yes, please advise:

7. What is the type of service:

☒ Therapeutic medical service
☐ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☐ To be used as a screening tool in asymptomatic populations
ii. ☐ Assists in establishing a diagnosis in symptomatic patients
iii. ☐ Provides information about prognosis
iv. ☐ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

☐ Pharmaceutical / Biological
☒ Prosthesis or device
☐ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☐ No

(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☐ No

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

N/A

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

☐ Yes
☒ No

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

☐ Yes
☒ No

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

☒ Yes
☐ No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

Type of therapeutic good: MitraClip Clip Delivery System - Mitral valve clip
Manufacturer's name: Abbott Vascular
Sponsor's name: Abbott Vascular Division of Abbott Australasia Pty Ltd

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: The Edwards PASCAL Transcatheter Valve Repair System components are designed, intended, and distributed for single use only. There are no data to support the sterility, non-pyrogenicity, and functionality of the devices after reprocessing.

Device	Model	Reorder Number
Implant System	10000IS, **REDACTED**	10000ISCE, **REDACTED**
Guide Sheath	10000GS	10000GSCE
Stabilizer	10000ST	10000STCE
Table	10000T	10000TCE

Multi-use consumables: None

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: Edwards PASCAL Transcatheter Valve Repair System – Implant System - Mitral valve clip
Manufacturer's name: Edwards Lifesciences LLC
Sponsor's name: Edwards Lifesciences Pty Ltd

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☒ Class III
☐ AIMD
☐ N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☒ Yes (if yes, please provide details below)
☐ No

The PASCAL which is used to perform the TMVr is registered on the Australian Register of Therapeutic Goods (Table 1). The intended purpose is not restricted by stage of MR.

Table 1 List of ARTGs for PASCAL:

ARTG	Functional Description	Intended Purpose	Manufacturer
342270 Date: 25/08/2020	Edwards Lifesciences Pty Ltd - PASCAL Transcatheter Valve Repair - System Implant System - Mitral valve clip The Implant System consists of the Steerable Catheter (outermost layer), the Implant Catheter (innermost layer), and the PASCAL implant. The Implant System percutaneously delivers the PASCAL implant to the valve via a femoral vein access using a transvenous, transseptal approach. The implant is deployed and secured to the leaflets of the valve, acting as a filler in the regurgitant orifice. The primary components of the Implant are the spacer, paddles, and clasps made from Nitinol.	The Edwards PASCAL valve repair system is indicated for the percutaneous reconstruction of an insufficient mitral valve through tissue approximation. The PASCAL System - Implant System is part of the Edwards PASCAL Transcatheter valve repair system.	Edwards Lifesciences LLC
342271	Edwards Lifesciences Pty Ltd - PASCAL Transcatheter Valve Repair System –	The Edwards PASCAL valve repair system is indicated for the	Edwards Lifesciences LLC

Date: 25/08/2020	Guide Sheath - Catheter, intravascular, guiding The Guide Sheath set includes a steerable Guide Sheath and Introducer. The Guide Sheath provides left atrial access. It has a hydrophilic coating and a rotational control knob which actuates the flexion mechanism to position the Guide Sheath at the target location. The Introducer is compatible with a 0.035 inch (0.89mm) guidewire.	percutaneous reconstruction of an insufficient mitral valve through tissue approximation. The PASCAL System - Guide Sheath is part of the Edwards PASCAL transcatheter valve repair system.	
329680 Date: 10/02/2020	Edwards Lifesciences Pty Ltd - Cardiac implantation catheter holder	The Edwards PASCAL valve repair system is indicated for the percutaneous reconstruction of an insufficient mitral valve through tissue approximation. The PASCAL System - Stabilizer is part of the Edwards PASCAL transcatheter valve repair system.	Edwards Lifesciences LLC
329150 Date: 24/01/2020	Edwards Lifesciences Pty Ltd - Cardiac implantation catheter table	The Edwards PASCAL valve repair system is indicated for the percutaneous reconstruction of an insufficient mitral valve through tissue approximation. The PASCAL System Table is part of the Edwards PASCAL transcatheter valve repair system.	Edwards Lifesciences LLC
REDACTED	**REDACTED**	**REDACTED**	Edwards Lifesciences LLC

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

☒ Yes (please provide details below)
☐ No

Date of submission to TGA: **REDACTED**
Estimated date by which TGA approval can be expected: **REDACTED**
TGA Application ID: **REDACTED**
TGA approved indication(s), if applicable: The Edwards PASCAL valve repair system is indicated for the percutaneous reconstruction of an insufficient mitral valve through tissue approximation. The PASCAL System - PASCAL Ace Implant System is part of the Edwards PASCAL Transcatheter valve repair system.
TGA approved purpose(s), if applicable: The Implant System consists of the Steerable Catheter (outermost layer), the Implant Catheter (innermost layer), and the Implant (implant Model 10000ISM). The Implant

System percutaneously delivers the Implant to the valve via a femoral vein access using a transvenous approach. The implant is deployed and secured to the leaflets of the valve, acting as a filler in the regurgitant orifice. The primary components of the Implant are the spacer, paddles, and clasps made from Nitinol.

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

N/A

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design	**Title of journal article or research project**	**Short description of research**	**Website link to journal article or research**	**Date of publication**
1.	Prospective, single-arm, observational study Multicentre, international study, 14 sites in 7 countries	CLASP (NCT03170349) Multicentre, prospective, single-arm study of PASCAL Transcatheter Mitral Valve Repair in Patients with Severe Primary and Secondary Mitral Regurgitation (CLASP)	DMR and FMR The study includes both FMR and DMR patients with clinically significant (≥ grade 3+) MR despite OMT, symptomatic NYHA II, III or IV, and who were deemed candidates for TMVr by the local heart team. 109 patients were treated (67% FMR, 33% DMR); mean age 75.5 years, and 57% were NYHA class III or IV. At 1 year, Kaplan-Meier survival was 92% (89% FMR, 96% DMR) with 88% freedom from HF hospitalization (80% FMR, 100% DMR), MR was ≤1+ in 82% of patients (79% FMR, 86% DMR) and ≤2+ in 100% of patients, 88% of patients were NYHA class I or II, and KCCQ score improved by 14 points (p<0.001 for all).	**1-year, 30-day outcomes:** https://www.jacc.org/doi/full/10.1016/j.jcin.2020.06.019 **6-month outcomes:** https://www.tctmd.com/slide/6-month-outcomes-multicenter-prospective-study-novel-pascal-transcatheter-mitral-repair **30-day outcomes:** https://www.jacc.org/doi/full/10.1016/j.jcin.2019.04.034	**30-day outcomes**: n = 62, Lim et al. (2019) n = 109, Webb et al. (2020) **6-month outcomes:** n = 62, Lim (2019) **1-year interim outcomes:** n = 62, Webb et al. (2020) **Estimated primary endpoint date**: December 2019 **Estimated study completion date:** January 2024

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
2.	Compassionate Use Study Observational, single-arm study Worldwide; 7 sites in 5 countries	Compassionate use of the PASCAL TMVr system for patients with severe MR: a multicentre, prospective, observational, first-in-man study	DMR and FMR In this multicentre, prospective, observational, first-in-man study, 23 patients with symptomatic, severe FMR, DMR or mixed etiology deemed at high risk or inoperable were treated using the PASCAL TMVr system for moderate-to-severe (grade 3+) or severe (grade 4+) MR. At baseline, all patients were NYHA class III or IV. In 22 (96%) patients, residual MR was grade 2+ or less. Technical success was achieved in 22 (96%) patients, and device success at 30 days was achieved in 18 (78%) patients. Three patients (13%) died during the 30-day follow-up. 19 (95%) patients were alive 30 days after implantation and were NYHA class I or II.	**6-month outcomes:** https://www.tctmd.com/slide/pascal-system-transcatheter-mitral-leaflet-repair-initial-experience-and-outcomes **30-day outcomes:** https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31600-8/fulltext	**30-day outcomes:** Praz et al (2017) **6-month outcomes:** Fam (2018) **Estimated completion**: TBD
3.	German Registry Study Observational study 3 sites in Germany	Mitral valve leaflet repair with the new PASCAL system: early real-world data from a German multicentre experience	DMR and FMR This study includes the early practical use of the PASCAL TMVr system, a total of 18 consecutive patients with severe, symptomatic MR were included in this German multicentre registry. Six patients with FMR, 2 with DMR and 10 were mixed etiology. The preprocedural severe MR present in all patients was reduced: grade 0 in 4 (22.2%), grade I in 11 (61.1%), grade II in 3 (16.7%). There were no periprocedural complications.	https://link.springer.com/article/10.1007/s00392-019-01538-3	**Discharge outcomes**: Kriechbaum et al. (2020)

Abbreviations: MR, mitral regurgitation; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; TMVr, Transcatheter Mitral Valve repair; HF, heart failure; MC, multicentre; MM, medical management; MN, multinational; NYHA, New York Heart Association; OMT, optimal medical therapy; RCT, randomised controlled trial; SOC, standard of care; RCT, Randomised Controlled Trial; KCCQ, Kansas City Cardiomyopathy Questionnaire; 6MWD, 6 Minute Walk Distance

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

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design	Title of research	Short description of research	Website link to research	Date
1.	Prospective, single-arm, observational study Multicentre, international study, 14 sites in 7 countries	CLASP (NCT03170349) Multicentre, prospective, single-arm study of PASCAL Transcatheter Mitral Valve Repair in Patients with Severe Primary and Secondary Mitral Regurgitation (CLASP)	POPULATION: Patients with clinically significant MR (DMR and FMR) (≥ grade 3+) despite OMT INTERVENTION (N): PASCAL TMVr system N=109 PRIMARY ENDPOINTS: **Coprimary technical endpoints**: 1. Procedural success: At least one device deployed, and delivery system successfully retrieved. 2. MR reduction to ≤ 2+ grade at discharge **Clinical success**: Procedural success with MR reduction to ≤ 2+ grade and without MAEs at 30 days **Safety endpoint**: A composite of MAE rate at 30 days defined as: CV mortality, stroke, MI, new need for renal replacement therapy, severe bleeding. OTHER SECONDARY ENDPOINTS include: Recurrent HF admission, reintervention for treatment of MR, 6MWD, NYHA	**2-Year outcomes:** **N/A**	**2021**

	Type of study design	Title of research	Short description of research	Website link to research	Date
2.	Prospective, multicenter, randomized, open-label, controlled, parallel trial of the PASCAL repair system vs. MitraClip 57 sites in the United States	CLASP IID/IIF (NCT03706833)	POPULATION: Patients with clinically significant MR (≥ grade 3+) despite OMT INTERVENTION (N): Four treatment arms: 1. PASCAL TMVr system in patients with DMR, 2. MitraClip in patients with DMR, 3. PASCAL TMVr system in patients with FMR on GDMT, and 4. MitraClip in patients with FMR on GDMT, N = 1,275 (planned) PRIMARY ENDPOINTS: Coprimary technical endpoints: 1. Proportion of patients with MR severity reduction, 2. Proportion of patients with recurrent HF hospitalizations and all-cause mortality Safety primary endpoint: Composite MAE rate at 30 days, defined as: CV mortality, stroke, MI, new need for renal replacement therapy, severe bleeding SECONDARY ENDPOINTS: Follow-up at 30 days, 6 months, 12 months, and 5 years: 6MWD, KCCQ and SF-36 Safety: Rates of various adverse events at 6 and 12 months: All-cause mortality, HF hospitalization, new onset AF; Rates of AEs at 12 months: Severe MR, worsening MR, Stroke, TIA, MAEs, Renal complications, Residual atrial septal defect by Doppler	**N/A**	Ongoing: 5-year follow-up Estimated primary endpoint completion: December 31, 2023 Estimated study completion: January 31, 2028

	Type of study design	Title of research	Short description of research	Website link to research	Date
3.	Postmarket follow-up safety registry Maximum of 100 sites in Europe	MiCLASP	POPULATION: Patients with clinically significant (≥ grade 2+) MR despite OMT INTERVENTION (N): PASCAL TMVr system. Up to 300 patients. PRIMARY ENDPOINTS: **Primary technical endpoint**: MR severity at discharge **Primary safety endpoint**: Composite MAE rate at 30 days: CV mortality, stroke, MI, new need for renal replacement therapy, severe bleeding SECONDARY ENDPOINTS: Follow-up at 30 days, 6 and 12 months and 5 years: KCCQ and SF-36, 6MWD, NYHA **Procedural success**: Device deployment success with MR reduction to ≤ 2+ grade at discharge and without the need for a surgical or percutaneous intervention before hospital discharge **Clinical success**: Procedural success with reduction of MR to ≤ 2+ grade and without MAEs at 30 days **Safety:** CV mortality, Stroke, MI, MV reintervention; major access site, vascular, and cardiac structural complications; Device embolization; Renal complications requiring unplanned dialysis or renal replacement therapy; severe bleeding	N/A	Ongoing Estimated endpoint completion: TBD Estimated study completion: TBD
4.	Prospective, observational, international registry	PASCAL Registry	POPULATION: Patients with clinically significant MR (≥ grade 2+) despite OMT INTERVENTION (N): PASCAL TMVr system. N = 200 (planned). PRIMARY ENDPOINTS: **Technical endpoint**: MR reduction to ≤ 2+ grade at 30 days and 12 months **Safety endpoint**: Composite of MAEs rate at 30 days, defined as: CV mortality, stroke, MI, new need for renal replacement therapy, severe bleeding SECONDARY ENDPOINTS: Follow-up at 30 days, 6 months, 12 months, and 5 years: 6MWD, NYHA class; KCCQ and EQ-5D-5L at 30 days and 12 months	N/A	Ongoing Estimated endpoint completion: TBD Estimated study completion: TBD

	Type of study design	Title of research	Short description of research	Website link to research	Date
5.	Retrospective, observational, international registry	EURO-SMR DRKS00017428	POPULATION: Severe secondary symptomatic MR. Moderate FMR if repeat hospitalizations for HF were necessary in the past due to worsening of MR INTERVENTION (N): PASCAL TMVr system, MitraClip, Cardioband, Carillon PRIMARY ENDPOINTS: All-cause death OTHER SECONDARY ENDPOINTS: Hospitalization for HF, NYHA, MR grade	N/A	Ongoing Estimated endpoint completion: not reported Estimated study completion: not reported

Abbreviations: MR, mitral regurgitation; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; MV, mitral valve; TMVr, Transcatheter Mitral Valve repair; HF, heart failure; MM, medical management; MN, multinational; NYHA, New York Heart Association; OMT, optimal medical therapy; GDMT, Goal Directed Medical Therapy; RCT, randomised controlled trial; KCCQ, Kansas City Cardiomyopathy Questionnaire; SF-36, Short-Form 36 Questionnaire; 6MWD, 6 Minute Walk Distance; TIA, Transient ischemic attack; MI, Myocardial infarction; AE, adverse events; MAE, Major adverse events; AF, atrial fibrillation,

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. **List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

    Cardiac Society of Australian and New Zealand (CSANZ)

    Australia and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS)

20. **List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

    Cardiac Society of Australian and New Zealand

    Australian & New Zealand Society of Cardiac & Thoracic Surgeons

21. **List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

    Consumer Health Forum of Australia

    Hearts4Hearts

22. **List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

    Abbott (MitraClip™ Transcatheter Mitral Valve Repair)

23. **Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

    Name of expert 1: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED**

    Name of expert 2: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED**

    Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease in terms of both morbidity and mortality:

Mitral regurgitation (MR), also known as mitral insufficiency, is a condition in which incompetency of the mitral valve causes abnormal backflow of blood from the left ventricle to the left atrium during the systolic phase of the cardiac cycle.

There are two types of MR (see Table 1, below): degenerative and functional. Degenerative mitral regurgitation (DMR), also known as primary MR, refers to regurgitation resulting from the structural abnormality of the mitral valve leaflets and/or valve apparatus. In contrast, functional mitral regurgitation (FMR), also known as secondary MR, occurs when the valve and/or valve apparatus is structurally normal, but dysfunction, distortion, or dilation of the left atrial or ventricular chambers results in tethering of the leaflets and/or mitral annular dilation.

Table 1. Overview of MR Classification (contents of table described below)

The information presented in **Table 1** summarises the points on MR Classification that can be found in Chapter 23 'Mitral Valve Malformations', including Table 23-2, from (Carpentier et al. (2010)) Carpentier A, Adams DH, Filsoufi F. Carpentier's reconstructive valve surgery: from valve analysis to valve reconstruction. Philadelphia, PA: Saunders; 2010.

MR is nearly two separate diseases with different definitions, different therapies, and different outcomes (Carabello et al., 2014) (El Sabbagh et al., 2018) (Figure 1). Primary regurgitation involves structural alteration of the valvular apparatus; secondary regurgitation occurs when cardiac chamber remodeling affecting a structurally normal valve, leading to insufficient coaptation (Zoghbi et al.,2003). For both primary and secondary MR, the restoration of mitral competence with mitral repair improves patients' LV function and survival (Sarano et al.,1995) (Chikwe et al., 2011). It is important to distinguish primary MR from secondary MR, as therapeutic approaches and outcomes differ.

Figure 1. Classification of the Etiology of Primary and Secondary MR

Figure 1 shows the classification of the etiology of Primary and Secondary MR is reproduced from the Central Illustration 'Classification of the Etiology of MR' from (El Sabbagh et al. (2018)) A. El Sabbagh, Y.N.V. Reddy, R.A. Nishimura. Mitral valve regurgitation in the contemporary era: insights into diagnosis, management, and future directions. J Am Coll Cardiol Img, 11 (2018), pp. 628-643.

Mitral regurgitation (MR) considered to be one of the most common heart valve disorders internationally (Dzaidzko et al., 2018), with a particularly high prevalence in the aging populations of industrialized nations. Mitral valve disease diagnosis increases with age, and disease progression commonly leads to more severe, symptomatic MR.

In a prospective study of 79,043 patients who were referred to a community open-access echocardiography service between 2001 and 2011 for suspected heart failure, the prevalence of MR was 12.5% and was the most common left-sided valve pathology (Marciniak et al., 2017). The Euro Heart Survey on valvular heart disease that included 5001 patients from 92 centres in 25 European countries reported that valvular intervention was indicated in 48.7% of the patients with severe symptomatic MR (Lung et al., 2003). Severe symptomatic patients presented with heart failure symptoms due to MR persist even after revascularization and optimization of medical therapy, and exhibit decreased exercise tolerance and exertional dyspnea (Nishimura et al, 2017).

At a 10-year follow-up, 90% of patients with severe MR will have died or undergone surgical repair because of developing and progressing MR symptoms (Ling et al., 1997) (Tribouilloy et al., 2009). Annual mortality rates in patients with moderate-to-severe MR who were medically managed due to their high surgical risk (New York Heart Association [NYHA] class III/IV) have been found to range from 26.2% (Velazquez et al., 2015) (in a sample in which most patients had secondary MR) to 34.0% (in a sample of patients with primary MR) (El Sabbagh et al.,2018).

Even in communities with well-equipped medical facilities and good access to treatment, the vast majority of patients with moderate-to-severe isolated MR are not referred for surgical treatment (Dziadzko et al., 2018). Given the high incidence of heart failure associated with MR, poor outcomes, and severe excess mortality across all subgroups (including patients with moderate MR), Dziadzko et al. (2018) strongly suggested that their data represented a "call for action" to expand MR treatment options in all subsets of patients.

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of 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 service:

The proposed population is patients with moderate-severe or severe MR as determined by echocardiography and objective and subjective measures (i.e. MR grading of 3+ [moderate-severe] or 4+ [severe]), who are symptomatic (NYHA functional class II or greater). Patient selection should be performed by a multi-disciplinary heart team (MDHT) specializing in the treatment of mitral regurgitation to assess patient risk and anatomical suitability.

Rationale:
The proposed population for MR is consistent with that in MSAC Application 1192.3 for DMR and FMR. As acknowledged in that application, "MSAC has recognised that "there is a clinical need in a small patient population identified as being eligible for the intervention" (MSAC Application 1192.2 public summary document [PSD])".

Australian clinician feedback confirmed that there is an unmet clinical need in mitral repair therapeutic options for the proposed MR population, which is consistent with the treatment population proposed in MSAC Application 1192.3 and that of the CLASP (Edwards PASCAL Transcatheter Mitral Valve Repair System Study) trial. Australian clinician feedback also anticipates the consensus/position statement from the Australian Clinical society to provide a set of guidelines to be used by the MDHT in identifying patients.

Mitral Regurgitation Pathology:

A patient will generally be referred by a general practitioner to a cardiologist if the presence of MR is suspected, who in turn refers the patient to either an interventional cardiologist or a cardiothoracic surgeon.

The first step after MR has been detected is to perform an assessment of the anatomy to determine the mechanism of regurgitation, FMR or DMR. In DMR there is leaflet abnormally whereas in FMR there is ventricular remodeling (Figure 4, Table 2) (Zhogbi et al 2017).

Table 2. Etiology of Primary and Secondary MR (contents of table described below)

The information presented in **Table 2** is reproduced from Table 5 ' Etiology of primary and secondary MR' from (Zoghbi et al. (2017)) Zoghbi W.A., Adams D., Bonow R.O. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017;30:303–371.

Doppler echocardiography (transthoracic echocardiography [TTE]) is the primary imaging used to determine the severity for MR. However, no single Doppler and echocardiographic parameter is sufficiently precise for MR to be quantified in an individual patient (Zoghbi et al., 2017). An integrated approach to determining the severity of MR is suggested by the American Society of Echocardiography (ASE).

Table 3. Grading of the severity of chronic MR by echocardiography (ASE) (contents of table described below)

The information presented in **Table 3** is reproduced from Table 8 'Grading the severity of chronic MR by echocardiography' from (Zoghbi et al. (2017)) Zoghbi W.A., Adams D., Bonow R.O. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017;30:303–371.

As shown in Table 4, there is substantial overlap between the ESC/EACTS and AHA/ACC guidelines regarding recommendations for intervention in patients with primary MR.

Table 4. Overview of Recommendations for Intervention in Patients with Primary MR, by Guideline (contents of table described below)

The information presented in **Table 4** outlines recommendations for intervention in patients with Primary MR from the ESC/EACTS and AHA/ACC guidelines. Recommendations from the ESC/EACTS Guidelines are reproduced from Section 6.1.2 in (Baumgartner et al. (2017)), p. 2760 'Indications for Intervention'. Recommendations from the AHA/ACC Guidelines are reproduced from (Nishimural et al. (2017)) Section 7.3.3 and Nishimura et al. (2014), Table 17, Section 7.3.3.

- (Baumgartner et al. (2017)) Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep;38(36):2739-91.
- (Nishimural et al. (2017)) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al.2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.Circ.2017;135:e1159-e1195.
- (Nishimura et al. (2014)) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2014 Jul;148(1):e1-e132.

As shown in Table 5, there is some overlap between the ESC/EACTS and AHA/ACC guidelines regarding recommendations for intervention in patients with secondary MR and minimal overlap of these recommendations with the AATS guidelines.

Table 5. Overview of Recommendations for Intervention in Patients with Secondary MR (contents of table described below)

The information presented in **Table 5** outlines recommendations for intervention in patients with Secondary MR from the ESC/EACTS, AHA/ACC, and AATS guidelines. Recommendations from the ESC/EACTS Guidelines are reproduced from Section 6.2.2 in (Baumgartner et al. (2017)), p. 2761 'Indications for Intervention' . Recommendations from the AHA/ACC Guidelines are reproduced from (Nishimura et al. (2017)) Section 7.4.3 and Nishimura et al. (2014), Table 18, Section 7.4.3. Recommendations from the AATS are reproduced from (Kron et al. (2017)) Sections IV-VI.

- (Baumgartner et al. (2017)) Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep;38(36):2739-91.
- (Nishimura et al. (2014)) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2014 Jul;148(1):e1-e132.
- (Nishimura et al. (2017)) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al.2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.Circ.2017;135:e1159-e1195.

- (Kron et al. (2017)) Kron IL, LaPar DJ, Acker MA, Adams DH, Ailawadi G, Bolling SF, et al. 2016 update to the American Association for Thoracic Surgery (AATS) consensus guidelines: ischemic mitral valve regurgitation. J Thorac Cardiovasc Surg. 2017 May;153(5):e97-e114.

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

A search of the literature identified no Australian specific clinical management pathways for patients with mitral regurgitation. The ESC/EACTS (2017) and the AHA/ACC (2017) guidelines were summarised regarding indications for surgical intervention above in response to question 25 for this Application.

The ESC/EACTS guidelines and AHA/ACC guidelines are fairly consistent in their recommendations regarding medical therapy for patients with primary MR (Table 6). The ESC/EACTS guidelines note that medical therapy should be considered for patients with chronic primary MR after the development of heart failure who are not suitable for surgery or when symptoms persist following surgery. Similarly, the AHA/ACC guidelines note that medical therapy for systolic dysfunction is reasonable in symptomatic patients with chronic primary MR and LVEF < 60% in whom surgery is not being considered (class IIa; level of evidence [LOE] B). The ESC/EACTS guidelines and AHA/ACC guidelines also both recommend against the use of vasodilators in certain patients with primary MR.

There are some differences between European guidelines and American guidelines on the specific cut-offs with respect to the quantitative parameters used to determine severity of MR. The European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACT) guidelines for the management of heart valve disease (2017) specifies a lower EROA and regurgitant volume cut-offs for severe secondary MR (Table 3) than the ASE guidelines. In the ASE guidelines, severe FMR is defined as EROA ≥ 0.40 cm2 and regurgitant volume ≥ 60 mL/beat. However, the ESC/EACT guidelines specify significantly lower cut-offs (EROA ≥ 0.20 cm2 and regurgitant volume ≥ 30 mL/beat). For classification of severe DMR, the ACC/AHA (2017) and ES/EACT (2017) guidelines are consistent regarding EROA and regurgitant volume (> 0.40 cm2 and ≥ 60 mL/beat). ESC/EACT (2019) guidelines provide different cut-offs for DMR and FMR, but the ASE guidelines do not differentiate between etiology in the classification of severity of MR.

Table 6. Comparison of ESC/EACTS and AHA/ACC Recommended Medical Therapy in Patients with Primary MR (contents of table described below)

The information presented in **Table 6** contains recommendations for medical therapy in patients with Primary MR from the ESC/EACTS and AHA/ACC guidelines. Recommendations from the ESC/EACTS Guidelines are reproduced from Section 6.1.3 in (Baumgartner et al. (2017)). Recommendations from the AHA/ACC Guidelines are reproduced from (Nishimura et al. (2014)), Section 7.1.2.

- (Baumgartner et al. (2017)) Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep;38(36):2739-91.
- (Nishimura et al. (2014)) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2014 Jul;148(1):e1-e132.

As shown in Table 7, the ESC/EACTS, AHA/ACC, and AATS guidelines are fairly consistent in their recommendations regarding medical therapy for patients with secondary MR.

Table 7. Comparison of ESC/EACTS, AHA/ACC, and AATS Recommended Medical Therapy in Patients with Secondary MR (contents of table described below)

The information presented in **Table 7** contains recommendations for medical therapy in patients with Secondary MR from the ESC/EACTS, AHA/ACC, and AATS guidelines. Recommendations from the ESC/EACTS Guidelines are reproduced from Section 6.2.3 in (Baumgartner et al. (2017)). Recommendations from the AHA/ACC Guidelines are reproduced from (Nishimura et al. (2017)) Table 2, Section 7.2 and (Nishimura et al. (2014)), Section 7.1.2. Recommendations from the AATS are reproduced from (Kron et al. (2017)), Section IV and Section VI.

- (Baumgartner et al. (2017)) Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep;38(36):2739-91.
- (Nishimura et al. (2014)) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2014 Jul;148(1):e1-e132.
- (Nishimura et al. (2017)) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al.2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.Circ.2017;135:e1159-e1195.
- (Kron et al. (2017)) Kron IL, LaPar DJ, Acker MA, Adams DH, Ailawadi G, Bolling SF, et al. 2016 update to the American Association for Thoracic Surgery (AATS) consensus guidelines: ischemic mitral valve regurgitation. J Thorac Cardiovasc Surg. 2017 May;153(5):e97-e114.

Neither the ESC/EACTS guidelines nor the AHA/ACC guidelines provide specific recommendations regarding the use of CRT in patients with primary MR.

The ESC/EACTS guidelines note that indications for CRT should be evaluated in accordance with guidelines for the management of heart failure; accordingly, recommendations from the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure are presented below. Recommendations regarding the use of CRT in patients with secondary MR from AHA/ACC, and AATS are also shown in Table 8, as there is some consistency across these guidelines regarding the use of CRT for patients with secondary MR.

Table 8. Overview of Recommendations for Cardiac Resynchronization Therapy in Patients with Secondary MR, by Guideline (contents of table described below)

The information presented in **Table 8** contains recommendations for cardiac resynchronization therapy in patients with Secondary MR from the ESC/EACTS, AHA/ACC, and AATS guidelines. Recommendations from the ESC/EACTS Guidelines are reproduced from Section 6.2.2 in (Baumgartner et al. (2017)). Recommendations from the AHA/ACC Guidelines are reproduced from (Nishimura et al. (2017)) Figure 2, Section 7.4.3 and (Nishimura et al. (2014)), Section 7.3.2, sub-bullet 3. Recommendations from the AATS are reproduced from (Kron et al. (2017)), Section IV.

- (Nishimura et al. (2014)) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2014 Jul;148(1):e1-e132.
- (Nishimura et al. (2017)) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al.2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.Circ.2017;135:e1159-e1195.
- (Kron et al. (2017)) Kron IL, LaPar DJ, Acker MA, Adams DH, Ailawadi G, Bolling SF, et al. 2016 update to the American Association for Thoracic Surgery (AATS) consensus guidelines: ischemic mitral valve regurgitation. J Thorac Cardiovasc Surg. 2017 May;153(5):e97-e114.
- (Baumgartner et al. (2017)) Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep;38(36):2739-91.

Australian clinician feedback was queried to establish the unmet need for MR patients that TMVr would meet, the clinical efficacy of the PASCAL Transcatheter Repair System, and the appropriate clinical pathway for utilization within the Australian symptomatic, severe MR patient population; their letters of support are attached to this application.

The comparator medical service is the dominant transcatheter mitral valve repair device system and clip component in the TMVr landscape at present, and as TMVr is accepted as a much-needed therapeutic options for symptomatic, severe MR patients, guidelines that reflect treatment pathways will adapt, however, that time has not come.

The PASCAL Transcatheter Mitral Valve Repair System's objective of the proposed medical service (TMVr) is to repair the mitral valve. Therefore, if placement of one PASCAL implant does not result in acceptable reduction in MR, a second PASCAL implant may be placed. This is in line with our comparator, MitraClip.

Therefore, our current clinical management pathway up until procedure mirrors that which MSAC application 1192.3 from Abbott Vascular iterates. Per Abbott's MSAC application 1192.3's answer to question number 26 in relation to the clinical management pathway in DMR, "The clinical algorithm evaluated by MSAC in Application 1192.2 in 2016 was reviewed by four KOLs in January 2019. The resultant adapted clinical management algorithm for patients with severe DMR is provided in Figure 5. The standard treatment of patients with severe DMR (grade 3+ or 4+) is surgical repair (or replacement if repair is not feasible). However, in patients that are considered by the MDHT to be high risk surgical candidates, but considered suitable for MitraClip, TMVr provides a treatment option. The alternate treatment option in these patients is medical management."

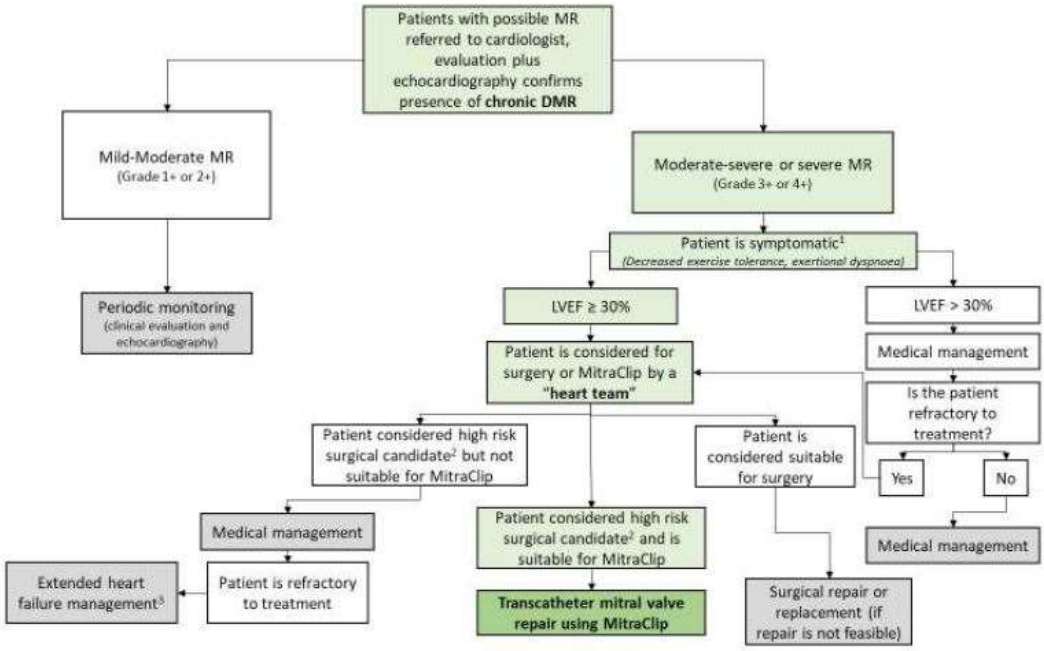

Figure 5 Clinical management algorithm for DMR

DMR, degenerative mitral regurgitation; MR, mitral regurgitation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.
[1] Symptomatic = NYHA functional class II or greater
[2] Patients considered 'high risk surgical candidate' for surgery as determined by a multidisciplinary heart team, combining surgical risk assessment, frailty, major organ system dysfunction, and procedure-specific impediments.
[3]. Extended heart failure management includes cardiac resynchronisation therapy, ventricular assist devices, cardiac restraint devices and heart transplant

Per MSAC application 1192.3 from Abbott Vascular, their answer to question number 26 in relation to the clinical management pathway in FMR also applies to PASCAL: "Based on discussion with four Australian KOLs, a consensus on the current clinical management algorithm for patients with severe FMR was provided (Figure 6). Severe FMR results in volume overload to a decompensated left ventricle which in turn leads to worsening the prognosis of the patient. In contrast to the DMR population, there is only scant evidence to indicate that correcting the MR in these patients with FMR results in increased survival or extended symptom improvement.

Hence in this population, there is much less focus on surgical repair and the mainstay treatment is medical management. Given the less invasive nature of the TMVr compared with standard surgical approaches, this treatment option provides patients and clinicians with an alternate to medical management. Given the superiority of TMVr over optimal medial management (Stone et al., 2018), there is a high clinical need for this to be reimbursed on the MBS in Australia."

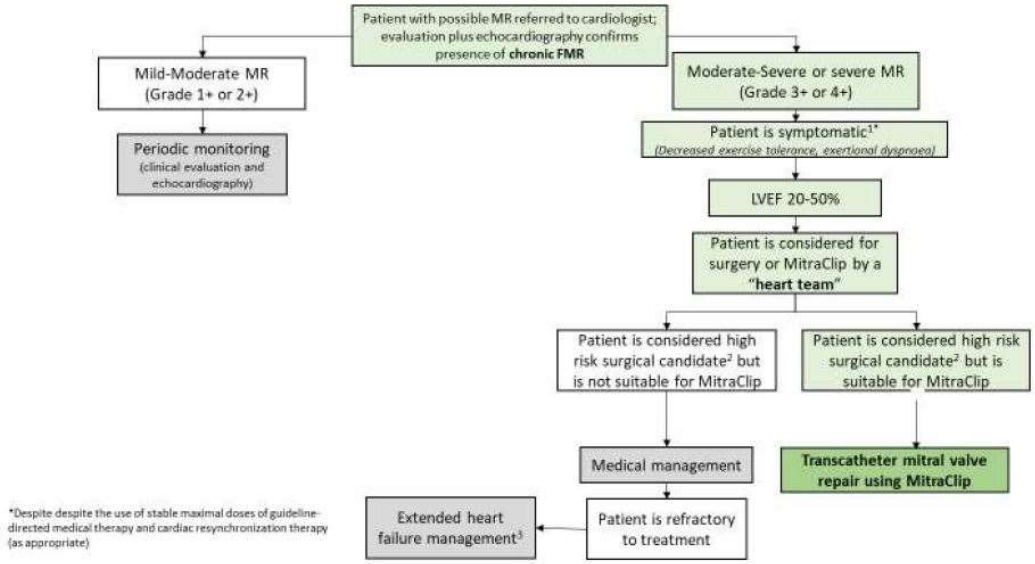

Figure 6 Clinical management algorithm for FMR

FMR, functional mitral regurgitation; MR, mitral regurgitation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.
[1] Symptomatic = NYHA functional class II or greater
[2] Patients considered 'high risk surgical candidate' for surgery as determined by a multidisciplinary heart team, combining surgical risk assessment, frailty, major organ system dysfunction, and procedure-specific impediments.
[3] Extended heart failure management includes cardiac resynchronisation therapy, ventricular assist devices, cardiac restraint devices and heart transplant

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

Patients are screened and assessed for anatomical feasibility for device implantation by transthoracic echocardiography (TTE) and TEE. The TTEs are performed according to specific core laboratory protocols and previously published guidelines defined by the American Society of Echocardiography (ASE) for assessment of valve, ventricular function, and core laboratory measurements (Baumgartner et al., 2017) (Zoghbi et al., 2017). The MR severity is assessed using two-dimensional Doppler echocardiography and graded using the MR severity scale recommended by ASE (Zoghbi et al., 2017). The grading includes none/trace (0), mild (1+), mild-moderate (2+), moderate-severe (3+), and severe regurgitation (4+). Additionally, three-dimensional (3D) images allowing reconstruction of the mitral valve area at baseline and after device implantation are acquired. For assessment of the valve area, multiplanar reconstruction is performed as previously described (Biaggi et al., 2013) (ALtiok et al., 2012). All procedures are guided by TEE.

The procedure is performed under general anaesthesia with hemodynamic monitoring in an operating room or in a hybrid operating room with fluoroscopic and echocardiographic (2D and 3D) imaging capabilities, on the beating heart via a femoral venous approach. The transvenous procedure begins by accessing the femoral vein using conventional percutaneous puncture methods. A guidewire is inserted in the left atrium via transseptal access, and the guide sheath with introducer is inserted over the guidewire across the septum. The implant system is inserted into the guide sheath using a loader and advanced until the flex section exits the guide sheath. The steerable catheter is maneuvered until the implant is centred in the target leaflet zone and appropriately aligned with the mitral annular plane using transesophageal

echocardiography (TEE) guidance. The implant position is confirmed and adjusted as necessary to achieve the desired outcome, and then released.

The treatment is carried out by a multidisciplinary heart team including an interventional cardiologist, an echocardiograph, and an anaesthesiologist. The implantation can be done either by the cardiologist or the cardiac surgeon.

28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

Edwards, Edwards Lifesciences, the stylized E logo, and PASCAL are trademarks or service marks of Edwards Lifesciences Corporation. All other trademarks are the property of their respective owners.

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

The proposed medical service includes a device component as part of the procedure, the implantation of PASCAL implant(s). The proposed patient populations are currently managed with medical management and once the MitraClip device from Abbott Vascular receives an MBS code, will also be treated with this device. As such, the proposed medical service currently involves a new approach towards the management of the proposed populations currently receiving medical management and, once approved, the implantation of MitraClip(s).

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

The PASCAL system is contraindicated in patients with:

- Patient in whom a TEE is contraindicated or screening TEE is unsuccessful
- Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
- Contraindication to transseptal catheterization
- Presence of an occluded or thrombosed IVC filter that would interfere with the delivery catheter, or ipsilateral deep vein thrombosis is present
- Known hypersensitivity to nitinol or contraindication to procedural medications which cannot be adequately managed medically
- History of bleeding diathesis or coagulopathy or patient who refuses blood transfusions

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

Healthcare resources (TMVr):

Proposed resources to identify eligible population: TTE, TOE, anaesthesiology for TOE, electrocardiography, chest x-ray, cardiac catheterisation, cardiology consultation, surgical consultation, anaesthetic consultation, heart team consultation.

Resources to deliver proposed intervention: Edwards PASCAL Transcatheter Valve Repair System procedure (including two operators), surgical assistant, PASCAL implant and implant system, TOE, anaesthesiology, catheterisation/hybrid lab, theatres, intensive care unit, coronary care unit, TTE, cardiology consultation, pharmaceuticals.

Table 9 presents the associated medical services that are needed to perform the TMVr procedure, this includes any clinic or hospital related costs.

Table 9 Medical services included in the PASCAL procedure

Resource	Reference
Pre-procedural heart team assessment	Based on MBS Item 6080
	Based on MBS Item 6081
PASCAL MR implantation fee	Proposed MBS fee
Anaesthesia	MBS Item 21936
Intra-operative transoesophageal echocardiography	MBS Item 55135, 55126, 55129, 55127,55134
Flouroscopy	MBS Item 61109
REDACTED	**REDACTED**
Post-procedural/Pre-discharge transoesophageal echocardiography	MBS Item 55126, 55129, 55127, 55134

32. If applicable, advise which health professionals will primarily deliver the proposed service:

The treatment is carried out by a multidisciplinary heart team including an interventional cardiologist, an imaging cardiologist who is trained on TOE imaging, and an anaesthesiologist. The implantation can be done either by the cardiologist or the cardiac surgeon. Edwards Lifesciences procedure clinical specialist for device referral. Edwards Lifesciences imaging clinical specialist for 2D/3D echo referral.

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

N/A

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

In addition to their professional practice as an interventional cardiologist and imaging cardiologist, they need to receive Edwards product training. **REDACTED**

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

Physicians and relevant hospital staff (scrub nurse, radiographers, echo technicians) must be accredited by qualified Edwards personnel before involvement in a PASCAL TMVr procedure.

REDACTED

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

- ☒ Inpatient private hospital (admitted patient)
- ☒ Inpatient public hospital (admitted patient)
- ☐ Private outpatient clinic
- ☐ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☐ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☐ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☐ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☐ Laboratory
- ☐ Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

The procedure is performed in the in-hospital setting with patients admitted.

37. Is the proposed medical service intended to be entirely rendered in Australia?

- ☒ Yes
- ☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. 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 (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

While not yet issued a MBS code, the appropriate comparator for the PASCAL Transcatheter Valve Repair System is the MitraClip Clip Delivery System from Abbott Vascular, as the MitraClip device has already established superiority to guideline directed medical therapy (GDMT) as a result of their COAPT trial (Stone et al., 2018) for the FMR treatment population that also applies to the treatment population of the PASCAL Transcatheter Valve Repair System, and TMVr is superior to surgery in the DMR treatment population (Feldman et al., 2011) that mirrors the treatment population of the PASCAL Transcatheter Valve Repair System, as outlined in the PSD for Application 1192.3.

MitraClip has successfully made the case for TMVr in the moderate to severe treatment population, and therefore is the PASCAL Transcatheter Valve Repair System's comparator.

Recommendations on the clinical and cost-effectiveness of treatments for MR (Table 10) are included in published health technology assessments (HTAs) from Europe (EUnetHTA); England, Wales, and Northern Ireland (NICE); Scotland (Health Improvement Scotland); France (HAS); Italy; Canada; and the US.

In Canada, as of May 2015, the Ontario Health Technology Advisory Committee (OHTAC) recommends that the mitral valve clip procedure be funded by Cardiac Care Network (CCN)–identified excellence centres, and all patients should be enrolled if they are receiving this MR procedure. A review by CADTH in June 2020 showed that compared with pre-procedure, MitraClip for the treatment of TR and/or MR had significantly improved TR grade, NYHA functional class, edema, and ascites at follow-up. The percentage of patients with procedural success ranged from 92% to 97% for the four studies that reported these data.

In the US on March 2019, the FDA expanded the MitraClip indications for use to now include secondary or functional MR. The distinction is that use is now acceptable for MR caused by a dysfunctional LV as opposed to only degenerative MR. At the end of June 2020, the Centers for Medicare & Medicaid Services (CMS) proposed to update its national coverage policy for the transcatheter edge-to-edge repair (TEER) procedure of the mitral valve to now include patients with functional MR. The proposal aligns with the FDA's recent 2019 expansion of approved indications for MitraClip. CMS also proposes to remove the coverage with evidence requirement and proposes local Medicare Administrative Contractor (MAC) discretion for coverage of TEER of the mitral valve for patients with degenerative MR, meaning providers would no longer need a registry or clinical study participation to offer the procedure to Medicare patients.

Table 10. Published Health Technology Assessments of Treatments for Mitral Valve Disease in Europe (contents of table described below)

The information presented in **Table 10** reports on the health technology assessments made or in process for transcatheter mitral valve repair (TMVR) in European health technology appraisals.

- EUnetHTA
    - EUnetHTA. Transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation. 2015. Available at: https://www.eunethta.eu/wp-content/uploads/2018/01/Transcatheter-Implantable-Devices-for-mitral-valve-repair-in-adults-with-chronic-mitral-valve-regurgitation_Rapid-REA_Final_Sep-2015_0.pdf. Accessed April 19, 2021.
- UK NICE (2010)
    - NICE. Interventional procedures guidance 352 (IPG352). Percutaneous mitral valve annuloplasty. National Institute for Health and Care Excellence; 2010. Available at: https://www.nice.org.uk/guidance/ipg352. Accessed April 15, 2021.
- UK NICE (2014)
    - NICE. Clinical guideline 187. Acute heart failure: diagnosis and management. National Institute for Health and Care Excellence; 2014. Available at: https://www.nice.org.uk/guidance/cg187. Accessed April 15, 2021.
- UK NICE (2019)
    - NICE. Interventional procedures guidance. Percutaneous mitral valve leaflet repair for mitral regurgitation. National Institute for Health and Care Excellence; 2019. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ipg10088. Accessed April 15, 2021.
- FRANCE HAS (2015)
    - HAS. Assessment of an edge-to-edge mitral valve repair clip and its implantation. Haute Autorité de Santé; 2015. Available at: https://www.has-sante.fr/portail/jcms/c_2050051/fr/assessment-of-mitraclip-summary. Accessed April 19, 2021.
- ITALY: Rapid HTA Report (2015)
    - Migliore A, Corio M, Perrini MR, Rivoiro C, Jefferson T. Transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation: rapid HTA report. 2015. Available at: http://www.salute.gov.it/imgs/C_17_ReportDispositivi_14_documentoInglese_inglese_itemName_0_documentoENG.pdf. Accessed April 19, 2021.

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☐ Yes (please list all relevant MBS item numbers below)
☒ No

MitraClip/TMVr MBS item number is not approved or published yet and is not yet in the public domain.

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

The comparator medical service is the dominant transcatheter mitral valve repair device system and clip component in the TMVr landscape at present, and as TMVr is accepted as a much-needed therapeutic options for symptomatic, severe MR patients, guidelines that reflect treatment pathways will adapt, however, that time has not come.

The main comparator's (MitraClip) objective of the proposed medical service (TMVr) is to repair the mitral valve. Therefore, if placement of one MitraClip device does not result in acceptable reduction in MR, a second MitraClip device may be placed using the same Steerable Guide Catheter intraprocedurally. After clip deployment, the Delivery System and Catheter are withdrawn, and the venous puncture site is closed.

Per MSAC application 1192.3 from Abbott Vascular, answer to question number 26 in relation to the clinical management pathway in DMR, "The clinical algorithm evaluated by MSAC in Application 1192.2 in 2016 was reviewed by four KOLs in January 2019. The resultant adapted clinical management algorithm for patients with severe DMR is provided in Figure 5. The standard treatment of patients with severe DMR (grade 3+ or 4+) is surgical repair (or replacement if repair is not feasible). However, in patients that are considered by the MDHT to be high risk surgical candidates, but considered suitable for MitraClip, TMVr provides a treatment option. The alternate treatment option in these patients is medical management."

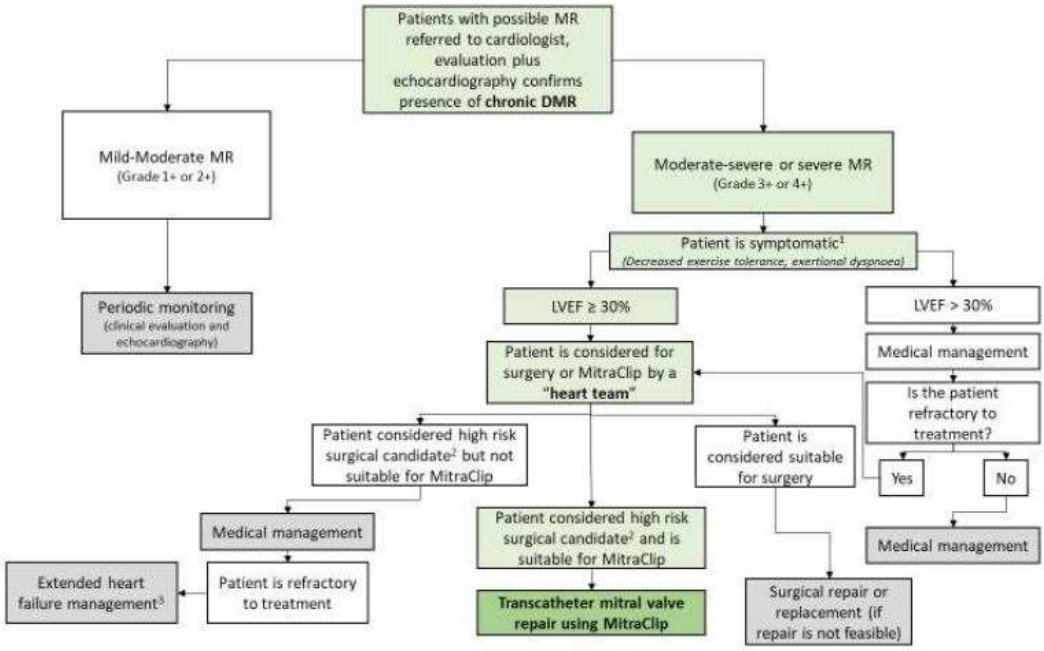

Figure 5 Clinical management algorithm for DMR

DMR, degenerative mitral regurgitation; MR, mitral regurgitation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.
[1] Symptomatic = NYHA functional class II or greater
[2] Patients considered 'high risk surgical candidate' for surgery as determined by a multidisciplinary heart team, combining surgical risk assessment, frailty, major organ system dysfunction, and procedure-specific impediments.
[3]. Extended heart failure management includes cardiac resynchronisation therapy, ventricular assist devices, cardiac restraint devices and heart transplant

Per MSAC application 1192.3 from Abbott Vascular, answer to question number 26 in relation to the clinical management pathway in FMR, "Based on discussion with four Australian KOLs, a consensus on the current clinical management algorithm for patients with severe FMR was provided (Figure 6). Severe FMR results in volume overload to a decompensated left ventricle which in turn leads to worsening the prognosis of the patient. In contrast to the DMR population, there is only scant evidence to indicate that correcting the MR in these patients with FMR results in increased survival or extended symptom

improvement. Hence in this population, there is much less focus on surgical repair and the mainstay treatment is medical management. Given the less invasive nature of the TMVr compared with standard surgical approaches, this treatment option provides patients and clinicians with an alternate to medical management. Given the superiority of TMVr over optimal medial management (Stone et al., 2018), there is a high clinical need for this to be reimbursed on the MBS in Australia."

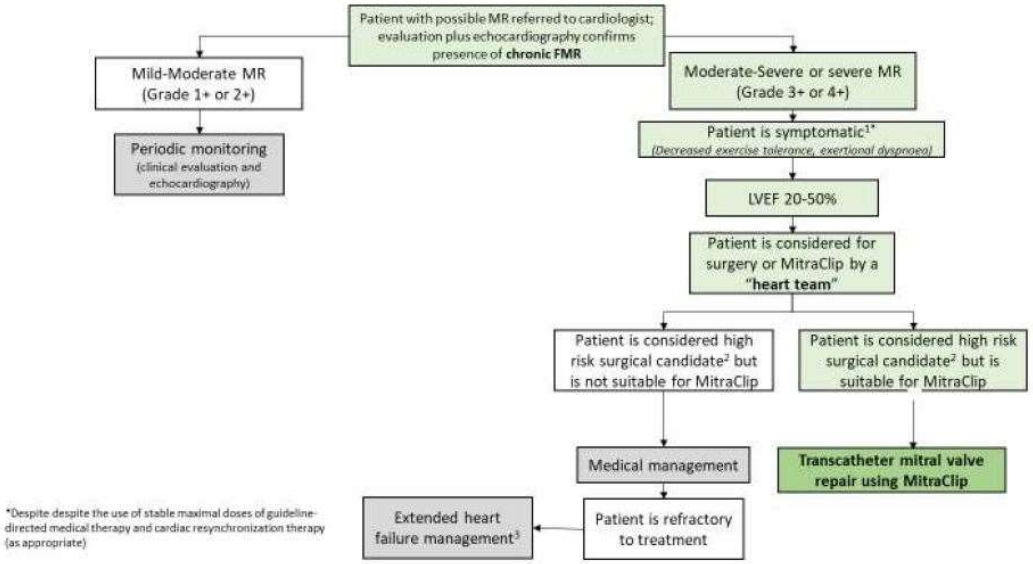

Figure 6 Clinical management algorithm for FMR

FMR, functional mitral regurgitation; MR, mitral regurgitation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.
[1] Symptomatic = NYHA functional class II or greater
[2] Patients considered 'high risk surgical candidate' for surgery as determined by a multidisciplinary heart team, combining surgical risk assessment, frailty, major organ system dysfunction, and procedure-specific impediments.
[3] Extended heart failure management includes cardiac resynchronisation therapy, ventricular assist devices, cardiac restraint devices and heart transplant

41.

(a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

☐ In addition to (i.e. it is an add-on service)
☒ Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

We expect some substitution with our comparator; **REDACTED.**

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

A patient deemed ineligible for surgery (due to feasibility and safety concerns such as multiple comorbidities, advanced age, etc.) the option of receiving the TMVr procedure may be considered as a direct substitute to continued medical management. It is expected that the introduction of the TMVr procedure using TMVr relative to continued use of medical management will result in reduced use of health care resources. Indeed, as noted in Q.40 the COAPT study showed a significantly lower annualized rate of hospitalisation due to heart failure in those who received TMVr versus those on medical management over 24 months (35.8 vs 67.9 events per patient-years; p< 0.0001). Furthermore, COAPT reported significantly lower rate of implantation of a left ventricular assist device (LVAD) or heart transplantation following TMVr compared with optimal medical management (4.4% versus 9.5%; p=0.01; Stone et al 2018).

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

In the 1-Year Outcomes for Transcatheter Repair in Patients With Mitral Regurgitation From the CLASP Study, John Webb et al concluded that The PASCAL transcatheter valve repair system demonstrated a low complication rate and high survival, with robust sustained MR reduction accompanied by significant improvements in functional status and quality of life at 1 year.

The results with the PASCAL repair system in the CLASP study demonstrate favourable clinical and echocardiographic results in a heterogeneous population of patients with FMR and DMR. MAE rates were low at 30 days and 1 year, and MR was reduced to ≤2+ in 96% and 100% of patients, and ≤1+ in 80% and 82%, respectively. There was a significant reduction in all echocardiographic MR indexes and resultant LV reverse remodelling with a significant reduction in both LV end-diastolic diameter and volume. One-year mortality was 8%, and heart failure hospitalizations at 1 year were only 12%. Functional status and quality-of-life indexes were also significantly improved. These results compare favourably with experience with other transcatheter mitral valve repair devices.

The COAPT trial examined the use of the MitraClip system in patients with severe FMR. Although the 2 studies cannot be compared directly because of different trial designs and populations, two-thirds of CLASP patients were treated for FMR. At 1 year, the reduction in MR grade to ≤2+ and ≤1+ was seen in 100% and 79% of CLASP patients with FMR (n = 73) versus 95% and 69% reported in COAPT (n = 273). The reduction in NYHA functional class to I or II at 1 year was seen in 83% of CLASP patients with FMR versus 72% in COAPT patients.

The EXPAND (n = 422) and EVEREST (n = 82) studies reported the use of the MitraClip system in patients with DMR at 30 days and 1 year, respectively. At 30 days, the reduction in MR grade to ≤2+ was seen in 97% and NYHA functional class I or II in 88% of CLASP patients with DMR (n = 36), similar to EXPAND, which reported 97% of patients with MR grade ≤2+ and 84% in NYHA functional class I or II. One-year outcomes in the CLASP patients with DMR (n = 24) continued to be favourable, with 100% of patients achieving MR grade ≤2+ and 95% in NYHA functional class I or II compared with EVEREST, which reported 83% patients with MR grade ≤2+ and 87% in NYHA functional class I or II. (Webb et al.2020)

TMVr is superior to medical management with respect to effectiveness in patients with DMR and FMR.

44. Please advise if the overall clinical claim is for:

☐ Superiority
☒ Non-inferiority

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes: Patient mortality (procedural), clinical adverse events, procedure-specific adverse events (implant embolism, chordal rupture, implant detachment, vascular complication needing reintervention)

Clinical Effectiveness Outcomes: Survival, freedom from MR grade 3+ or 4+, clinical measures of benefit (NYHA functional class, quality of life, LVEF function, rehospitalisation for CHF)

Healthcare resources (TMVr):

Proposed resources to identify eligible population**:** TTE, TOE, anaesthesiology for TOE, electrocardiography, chest x-ray, cardiac catheterisation, cardiology consultation, surgical consultation, anaesthetic consultation, heart team consultation.

Resources to deliver proposed intervention: Edwards PASCAL Transcatheter Valve Repair System procedure (incl. two operators), surgical assistant, PASCAL implant and implant system, TOE, anaesthesiology, catheterisation/hybrid lab, theatres, intensive care unit, coronary care unit, TTE, cardiology consultation, pharmaceuticals.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

The Australian population size data from is from 31010do002_202003 National, state and territory population, Mar 2020Released at 11:30 am (Canberra time) Thu 24 Sep 2020.

The most direct estimate of moderate-to-severe MR utilizes the prevalence from Dziadzko (2018, US); 0.59% of the adult population (18+)-->~114,600 Australians (as MR highly corresponds to age).

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

The proposed medical service is intended to be delivered once only.

At 1-year follow-up in 62 patients, there were 2 additional cardiovascular deaths between 30 days and 1 year, resulting in a 1-year cardiovascular mortality rate of 6.5%. No late stroke, reintervention, or new need for renal replacement therapy occurred. (Webb et al.2020)

48. How many years would the proposed medical service(s) be required for the patient?

The proposed medical service is to be a once off service.

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

REDACTED

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

Year 1: **REDACTED**

Year 2: **REDACTED**

Year 3: **REDACTED**

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

REDACTED

52. Specify how long the proposed medical service typically takes to perform:

The median procedure time from skin incision to femoral vein access closure with the PASCAL repair system in the CLASP study was 127 min. (Lim et al., 2019)

53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Category 3 – Therapeutic Procedures
MBS Item Descriptor per application: Transvenous/transeptal techniques for permanent coaptation of mitral valve leaflets using 1 or more PASCAL tissue approximation devices in patients with moderate-severe or severe symptomatic mitral regurgitation (Grade 3+, 4+) who have been determined by a multi-disciplinary heart team (MDHT) to be at high risk of complications with surgical intervention, in a transcatheter mitral valve repair (TMVr) Hospital, on a TMVr Patient by a TMVr Practitioner – includes all intraoperative diagnostic imaging that the TMVr Practitioner performs upon the TMVr Patient. (Not payable more than once per patient in a five-year period) Fee: **REDACTED**

Given advice from Australian clinical experts, the proposed MBS item descriptor for TMVr is modelled on the transcatheter aortic valve implantation (TAVI) descriptor (MBS item 38495). The proposed MBS item is provided below. The proposed fee of **REDATED** will be justified in the ADAR submission-based assessment. Consistent with TAVI, it is proposed that the following additional items be listed for coordination of the TMVr procedure:

1. Coordination of a TMVr Case Conference by a TMVr practitioner where the TMVr Case Conference has a duration of 10 minutes or more (MBS item 6080)
2. Attendance at a TMVr Case Conference by a specialist or consultant physician who does not also perform the service described in the item above for the same case conference where the TMVr Case Conference has a duration of 10 minutes or more.
3. It is also expected that explanatory notes, like those for item 38495, be included for the TMVr item.

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