Australian Government

Medical Services Advisory Committee

Public Summary Document

Application 1662 – The reduction of mitral regurgitation (MR) through tissue approximation using transvenous / transeptal techniques

Applicant: **Edwards Lifesciences Pty Limited**

Date of MSAC consideration: 83rd MSAC Meeting, 25-26 November 2021

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

1. Purpose of application

An application requesting MBS listing of the Edwards PASCAL Transcatheter Mitral Valve Repair System (TMVr) for the treatment of patients with degenerative mitral regurgitation (DMR) or functional mitral regurgitation (FMR) was received from Edwards Lifesciences by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support amending Medicare Benefits Schedule (MBS) items 38461 and 38463 for transcatheter mitral valve repair (TMVr) by transvenous or transeptal techniques using Mitraclip™ to be device agnostic. MSAC considered that the quality of evidence for TMVr using the PASCAL Transcatheter Valve Repair System™ was low and did not adequately support the claim of clinical non-inferiority. MSAC advised that higher quality evidence would be needed to support the claim of non-inferiority. MSAC also considered that an unmet clinical need for an alternative device was not clearly demonstrated.

Consumer summary
Edwards Lifesciences applied for Medicare Benefits Schedule (MBS) funding for a medical procedure called transcatheter mitral valve repair to manage a condition in which the heart's mitral valve doesn't close tightly. This allows blood to flow backward in the heart (mitral regurgitation). This procedure is already funded on the MBS for another type of device (called MitraClip), and Edwards Lifesciences applied to amend these MBS items to include a device called the PASCAL system. The PASCAL system includes a small device made of clasps, paddles and spacers. The interventional cardiologist or surgeon uses a customised catheter to insert the device

Consumer summary

through a vein in the leg to the heart. The device gently grasps the edges of the faulty valve to help close the valve.

Edwards Lifesciences has applied for the procedure and device to be publicly funded for people with mitral regurgitation who cannot have open heart surgery to repair their mitral valve. Within this group, there are people who have degenerative mitral regurgitation (DMR – caused by problems related to the valve itself) and people who have functional mitral regurgitation (FMR – caused by a condition external to the valve – for example, an issue with abnormal heart muscle structure and/or function).

MSAC noted that the clinical evidence to support the PASCAL system was not as high quality as the evidence that was used to support MitraClip. Because there were no studies to directly compare PASCAL with MitraClip, the application had included a complex analysis called a matching adjusted indirect comparison (MAIC). MSAC considered that it was difficult to check if these results were reliable. This also made it very hard to tell whether the PASCAL system would be good value for money.

MSAC noted that a clinical trial comparing the PASCAL system with MitraClip is currently underway. The results from this trial might help to resolve some of these issues in the future.

MSAC's advice to the Commonwealth Minister for Health

MSAC did not support listing of the PASCAL system on the MBS because there was not enough high-quality clinical evidence to show that the device is safe and effective. MSAC also could not be sure if it would be good value for money.

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

MSAC noted the purpose of the application was to amend the current Medicare Benefits Schedule (MBS) item numbers for Transcatheter Mitral Valve Repair System (TMVr) using the MitraClip™ device (items 38461, 38463, 6082 and 6084) to also include the PASCAL system for reduction of mitral regurgitation (MR) through tissue approximation for the treatment of degenerative mitral regurgitation (DMR) and functional mitral regurgitation (FMR).

MSAC noted that DMR and FMR have different underlying causes. DMR is a disease of the valve itself and correcting the valve can help correct DMR. FMR is caused by left ventricular dilatation and dysfunction that can lead to the mitral valve not sealing properly. As mitral regurgitation is one component of disease in FMR, correcting the valve does not correct the underlying condition.

MSAC noted that this application was based on the ratified PICO for application 1192.3 (MitraClip) and that the populations were the same and the intervention uses a similar technique (although the device is different for application 1662).

MSAC agreed with ESC's preference for updating the existing MBS item to be device-agnostic and retaining the term transcatheter mitral valve repair (TMVr) rather than transcatheter edge-to-edge repair (TEER). This approach was supported by the applicant in the pre-MSAC response.

MSAC noted the proposed clinical management algorithms. MSAC noted the inconsistencies in the algorithms and the proposed MBS items which the applicant clarified was due to the algorithms being based on the 2017 European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines.

The comparator for the proposed medical service is the MitraClip system which MSAC considered appropriate. MSAC noted the applicant's clinical claim that PASCAL is non-inferior in safety and efficacy compared with MitraClip.

The clinical evidence for PASCAL was based on the CLASP study - a small (N=124), prospective, single-arm, observational study that aimed to assess the safety and feasibility of the PASCAL transcatheter valve repair system. The study was conducted at 14 sites in 5 countries, including a small number of patients in Australia. The study reported results after 2 years and included patients with FMR and DMR. MSAC noted that the risk of bias in this study was high, as it was a single-arm feasibility study. Primary endpoints were procedural success, reduction of MR severity ≤ grade 2+, and major adverse events at 30 days.

MSAC noted the evidence for the comparator (MitraClip), which comprised two randomised controlled trials (RCTs) – COAPT (N = 614) and EVEREST-II (N = 279). Both trials had a low risk of bias.

MSAC noted the level of evidence available for PASCAL was lower than that considered by MSAC for MitraClip, where an RCT with 2 years follow-up (COAPT trial) was available for the FMR population and several larger observational studies were considered for the DMR population.

MSAC noted the lack of direct evidence to compare PASCAL and MitraClip. The ADAR instead used a matching-adjusted indirect comparison (MAIC). MSAC noted it has previously considered a small number of applications that used a MAIC and that this methodology has also been applied in several applications considered by the Pharmaceutical Benefits Advisory Committee. MSAC noted that patient-level data are not required for the comparator studies in a MAIC, and aggregate data are used instead. A weight is calculated for each patient in the individual data of the intervention (CLASP), such that the overall mean of the weighted individual data (which is calculable) matches that of the aggregate data for the comparator (COAPT and EVEREST-II). Using the resulting weights, it is then possible to estimate reweighted outcomes of the study in a similar patient group to those in the comparator trials. This effectively means the study data that are available for the TMVr using the PASCAL device (CLASP) are reweighted to better match that of the comparator (COAPT and EVEREST-II).

The applicant consulted three clinicians (blinded to endpoints) to determine which baseline characteristics should be used for matching of studies for the MAIC analysis. For the comparison of the CLASP study and COAPT trial, the analyses in the applicant-developed assessment report (ADAR) matched patients on the following:

- **REDACTED** [1]

For the comparison of the CLASP study and EVEREST-II trial, the ADAR matched patients on the following:

[1] Applicant has not agreed to the publication of the matching variables used in the MAIC presented to MSAC.

- **REDACTED**[2]

MSAC noted the advice from ESC that one of the main limitations of the unanchored (no common comparator arm between trials) MAIC analysis is that it strongly assumes that all treatment effect modifiers and prognostic factors are known and accounted for. This is largely considered very hard to meet and may lead to an unknown amount of bias in the unanchored estimate (Phillipo 2018 [3] and Phillipo 2016 [4]). MSAC noted the factors available for matching differed for the comparisons with the COAPT and EVEREST trials. MSAC noted the commentary highlighted that **REDACTED** and **REDACTED**[5] were not balanced between CLASP (weighted) and COAPT and it is unclear whether these would be treatment effect modifiers or prognostic variables.

MSAC noted it was not possible to independently verify the specific method used or to replicate the results of the MAIC because the ADAR did not provide the statistical codes and methods used for the analysis, or the matching options that were presented to clinicians for matching of baseline characteristics. The pre-ESC response provided some additional information and analyses, but these could not be evaluated. MSAC noted ESC's residual concerns regarding these issues. MSAC therefore advised that the claim of non-inferiority could not be reliably demonstrated with the evidence presented in the ADAR.

Regarding comparative safety, MSAC noted the definition of major adverse events measured in COAPT and EVEREST-II differed to those measured in CLASP. MSAC noted the MAIC analysis suggested the odds of experiencing major adverse events at 30 days in the FMR population were **REDACTED** for PASCAL than for MitraClip, and the rate of major adverse events at 30 days in the mixed FMR and DMR population was **REDACTED** for PASCAL than for MitraClip. MSAC considered it unclear what impact the differences in definitions of major adverse events had on the MAIC findings. No long-term comparative safety data were available. For these reasons, and the limitations in the unanchored MAIC, MSAC considered the claim of non-inferior safety was uncertain.

Regarding comparative effectiveness in the FMR population (CLASP versus COAPT), the MAIC analysis suggested **REDACTED**[6] overall survival was **REDACTED** in patients that were treated with the PASCAL system compared with MitraClip. However, MSAC noted the data presented had some inconsistencies that could not be verified. In particular, MSAC noted the baseline number at risk in the unadjusted analysis of overall survival in the CLASP study differed to the trial publication (Szerlip 2021[7]). MSAC noted the MAIC analysis suggested that patients treated with the PASCAL system had **REDACTED** MR severity scores at 24 months and NYHA classifications at 24 months of follow-up compared with patients treated with the MitraClip system.

In the mixed FMR and DMR population (CLASP versus EVEREST-II), the MAIC analysis suggested that overall survival in the PASCAL population is **REDACTED** the overall

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[2] Applicant has not agreed to publish the matching variables used in the MAIC.
[3] Phillippo DM *et al*. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. *Med Decis Making*. 2018;38(2):200-211. doi:10.1177/0272989X17725740
[4] Phillippo DM *et al*. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. Available from http://nicedsu.org.uk/wp-content/uploads/2018/08/Population-adjustment-TSD-FINAL-ref-rerun.pdf
[5] Applicant has not agreed to publish the clinical factors that were unbalanced in the MAIC.
[6] Applicant has not agreed to publish the outcome variables of the MAIC analysis.
[7] Szerlip M *et al.* 2-Year Outcomes for Transcatheter Repair in Patients With Mitral Regurgitation From the CLASP Study. *JACC Cardiovasc Interv*. 2021;14(14):1538-1548.

survival in the MitraClip population. The MAIC analysis suggested that MR severity scores at 12 months were **REDACTED** for patients treated with the PASCAL system, and NYHA classifications at 12 months were **REDACTED** for patients treated with the PASCAL system compared with MitraClip system. MSAC noted that no comparative evidence was available for the DMR population alone and considered this to be a limitation.

MSAC noted that only a subset of patients in the CLASP study had 24-month data, and the effective sample size was further reduced in the MAIC.

MSAC noted that an RCT comparing PASCAL with MitraClip to treat DMR and FMR (CLASP IID/IIF trial) is actively recruiting, with an estimated primary completion date in 2023 and study completion date in 2028 [8]. However, MSAC noted the estimated dates may be delayed by the COVID-19 pandemic, and the technology may change over this time period.

MSAC noted the economic evaluation presented in the ADAR was a cost-minimisation analysis of PASCAL compared with MitraClip**,** which included the costs of **REDACTED**[9] from the CLASP study were used in the economic analysis. MSAC noted advice from ESC that the time horizon of 30 days was adequate for evaluating the TMVr procedure but introduced additional implicit assumptions when extending conclusions to the intervention over its lifespan. MSAC noted the pre-MSAC response, which stated that the 30-day time horizon covered **REDACTED** within the cost-minimisation analysis and most clinical events, but that no long-term performance data were available.

MSAC noted that uncertainty of the MAIC affected the economic analysis indirectly, through clinical claims of non-inferiority, and directly, through comparative rates of adverse events applied in the cost-minimisation analysis. MSAC noted that translation issues were not presented in the ADAR. MSAC noted ESC's advice that a comparison of the trial population with the Australian population would have been informative, and that extrapolation of outcomes beyond 30 days should have been formally explored. MSAC noted the pre-MSAC response, which stated the data presented reflect real-world challenges.

MSAC noted the sensitivity analyses presented in the commentary for the costs of **REDACTED**[9], and noted that changing these parameters had little effect on the base case outcome. MSAC considered there is a possibility of an incremental cost associated with the use of PASCAL over MitraClip when different rates of **REDACTED**[9] were applied. However, MSAC noted this cost would be relatively small.

MSAC noted the ADAR reported using an **REDACTED** approach to estimate utilisation and financial consequences; however, the results were **REDACTED** to the published utilisation from the MitraClip Public Summary Document, reflecting a **REDACTED** approach with assumed **REDACTED** market share. MSAC noted that 1.5 years had passed since this approach was accepted for MitraClip but considered this was acceptable. MSAC further considered that the basis of the **REDACTED** market share was unclear given that MitraClip was first to market and may have the advantage of familiarity. MSAC considered the addition of PASCAL into the market would be unlikely to drive an overall increase in utilisation.

MSAC noted that no consumer comments were received for this application. Letters of support were received with the application from The Australian & New Zealand Society of

[8] https://clinicaltrials.gov/ct2/show/NCT03706833
[9] Applicant has not agreed to publish the variables in the cost-minimisation analysis

Cardiac & Thoracic Surgeons (ANZSCTS) and the Hearts4Heart group. Both organisations supported the need for TMVr devices for the treatment of severe mitral regurgitation in patients not suitable for surgical interventions. The ANZSCTS considered that PASCAL is comparable to Mitraclip and that ongoing trials will provide data supporting this view.

MSAC did not support amending the MBS items for TMVr by transvenous or transeptal techniques using Mitraclip to be device agnostic or include the PASCAL system. MSAC considered the quality of evidence for TMVr using the PASCAL Transcatheter Valve Repair System™ did not adequately support the clinical claim of non-inferiority. MSAC noted the CLASP study was a small, early feasibility study and did not consider the unadjusted MAIC could reliably demonstrate the claim of non-inferiority. MSAC considered that higher quality evidence would be needed to support the claim of non-inferiority. MSAC advised that any future submission should preferably include evidence that is comparable in quality to the MitraClip trial evidence (RCT with 2 years follow-up) and comparative evidence for the DMR population alone. Longer-term comparative data should also be included. MSAC also considered that an unmet clinical need for an alternative device was not clearly demonstrated.

4. Background

This is the first submission (Applicant Developed Assessment Report [ADAR]) for the treatment of patients with degenerative mitral regurgitation (DMR) or functional mitral regurgitation (FMR) using the Edwards PASCAL Transcatheter Valve Repair System. MSAC has not previously considered an application requesting MBS listing of catheter-based technique with PASCAL system for patients with mitral regurgitation. The application was based on the ratified PICO for application 1192.3 (for MitraClip) and bypassed consideration by the PICO Advisory Subcommittee (PASC).

5. Prerequisites to implementation of any funding advice

Items on the ARTG that are relevant to this application are shown in Table 1.

Table 1 Edwards PASCAL Transcatheter Valve Repair System listed on the ARTG

ARTG no.	Product no.	Product description	Product category	Sponsor
342270	Model number (see guidance docs) 10000IS	Edwards Lifesciences Pty Ltd - PASCAL Transcatheter Valve Repair System – Implant System - Mitral valve clip	Medical Device Class III	Edwards Lifesciences LLC
342271	Model number (see guidance docs) 10000GS	Edwards Lifesciences Pty Ltd - PASCAL Transcatheter Valve Repair System – Guide Sheath - Catheter, intravascular, guiding	Medical Device Class III	Edwards Lifesciences LLC
329680	Model number (see guidance docs) 10000ST	Edwards Lifesciences Pty Ltd – PASCAL Stabilizer	Medical Device Class Is	Edwards Lifesciences LLC
329150	Model number (see guidance docs) 10000T	Edwards Lifesciences Pty Ltd – PASCAL Table	Medical Device Class I	Edwards Lifesciences LLC
Application Identifier: DV-2020-DA-31682-1	10000SM	PASCAL Transcatheter Valve Repair System - PASCAL Ace Implant System	Medical Device Class III	Edwards Lifesciences LLC

Source: Therapeutic Goods Administration, Link to TGA.gov.au

In addition to their professional practice as an interventional cardiologist and imaging cardiologist, clinicians interested in utilizing PASCAL for their patients need to receive Edwards product training. The training includes **REDACTED**[10]**.**

6. Proposal for public funding

On 1 July 2021, the MitraClip mitral valve clip and MitraClip G4 system was approved as a new listing on the Prostheses List for a total $26,386 [11]. **REDACTED.** The pre-ESC response requested **REDACTED** Prosthesis List benefit for the PASCAL devices. Simultaneously, the MitraClip implant was listed on the MBS schedule for Transcatheter Mitral Valve repair. There are currently four listed MBS items (added on 1st July 2021) for provision of TMVr using the MitraClip system. The current MitraClip MBS items were listed after the applicant submitted the current assessment and is different to the item descriptor proposed by the applicant in following aspects:

- There are two approved items for the MitraClip system, one for each type of mitral regurgitation.
- Current MitraClip MBS items provide specific criteria for LVEF for each population (FMR and DMR) and specify that only patients with symptoms of mild, moderate, or severe chronic heart failure (New York Heart Association class II, III or IV) are eligible.

The pre-ESC response clarified that it was seeking amendment of the current MBS items to a device agnostic listing for TMVr. The current item descriptor for TMVr, removing references to the MitraClip device are presented in Table 2.The ADAR also proposed replacing the term

[10] Applicant has not agreed to publish details of the PASCAL training program information
[11] https://www.health.gov.au/sites/default/files/documents/2021/06/prostheses-list-part-a-new-prostheses-items.pdf

TMVr (transcatheter mitral valve repair) with mitral valve Transcatheter Edge-to-Edge Repair (TEER). The ADAR considered this would differentiate this procedure from other mechanisms of repair (i.e. annuloplasty) and would align with ESC/EACTS Guidelines and the 2020 ACC/AHA Guidelines.

Table 2 Item descriptors

Category 3 – Therapeutic Procedures
MBS Item 38461 – Transcatheter Mitral Valve Repair (TMVr) using one or more tissue approximation implants for moderate to severe, or severe, symptomatic degenerative (primary) mitral valve regurgitation (grade 3+ or 4+)
TMVr, by transvenous or transeptal techniques, for permanent coaptation of mitral valve leaflets using one or more ~~Mitraclips~~ tissue approximation implants, including intra-operative diagnostic imaging, if: (a) the patient has each of the following risk factors: (i) moderate to severe, or severe, symptomatic degenerative (primary) mitral valve regurgitation (grade 3+ or 4+); (ii) left ventricular ejection fraction of 20% or more; (iii) symptoms of mild, moderate or severe chronic heart failure (New York Heart Association class II, III or IV); and (b) as a result of a TMVr suitability case conference, the patient has been: (i) assessed as having an unacceptably high risk for surgical mitral valve replacement; and (ii) recommended as being suitable for the service; and (c) the service is performed: (i) by a cardiothoracic surgeon, or an interventional cardiologist, accredited by the TMVr Accreditation Committee to perform the service; and (ii) via transfemoral venous delivery, unless transfemoral venous delivery is contraindicated or not feasible; and (iii) in a hospital that is accredited by the TMVr Accreditation Committee as a suitable hospital for the service; and (d) a service to which this item, or item 38463, applies has not been provided to the patient in the previous 5 years (H) (Anaes.) (Assist.) Fee: $1,490.25
Category 3 – Therapeutic Procedures
MBS Item 38463 - Transcatheter Mitral Valve Repair (TMVr) using the one or more tissue approximation implants for moderate to severe, or severe, symptomatic functional (secondary) mitral valve regurgitation (grade 3+ or 4+).
TMVr, by transvenous or transeptal techniques, for permanent coaptation of mitral valve leaflets using one or more ~~Mitraclips~~ tissue approximation implants, including intra-operative diagnostic imaging, if: (a) the patient has each of the following risk factors: (i) moderate to severe, or severe, symptomatic functional (secondary) mitral valve regurgitation (grade 3+ or 4+); (ii) left ventricular ejection fraction of 20% to 50%; (iii) left ventricular end systolic diameter of not more than 70mm; (iv) symptoms of mild, moderate or severe chronic heart failure (New York Heart Association class II, III or IV) that persist despite maximally tolerated guideline directed medical therapy; and (b) as a result of a TMVr suitability case conference, the patient has been: (i) assessed as having an unacceptably high risk for surgical mitral valve replacement; and (ii) recommended as being suitable for the service; and (c) the service is performed: (i) by a cardiothoracic surgeon, or an interventional cardiologist, accredited by the TMVr Accreditation Committee to perform the service; and

(ii) via transfemoral venous delivery, unless transfemoral venous delivery is contraindicated or not feasible; and

(iii) in a hospital that is accredited by the TMVr Accreditation Committee as a suitable hospital for the service; and

(d) a service to which this item, or item 38461, applies has not been provided to the patient in the previous 5 years

(H) (Anaes.) (Assist.)

Fee: $1,490.25

ESC suggested amendments marked up

The proposed PASCAL system would be delivered in the same clinical setting and with the same frequency as the MitraClip system. The current MBS item can be claimed once in a five-year period for each patient. Patient selection should be performed by a multi-disciplinary heart team (MDHT) specialising in the treatment of mitral regurgitation to assess patient risk and anatomical suitability. The delivery of PASCAL system is restricted to be performed only by a cardiothoracic surgeon, or an interventional cardiologist, accredited by the TMVr accreditation committee to perform the service in a hospital accredited to perform the procedure.

7. Summary of public consultation feedback/consumer Issues

No consumer feedback/consumer comments were received for this application. Letters of support were received with the application from The Australian & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS) and the Hearts4Heart group. Both organizations supported the need for TMVr devices for the treatment of severe mitral regurgitation in patients not candidates for surgical interventions. ANZSCTS noted the need for strict criteria and the Heart Team model to ensure appropriate patient selection and suggested as a requirement the use of a National Registry with mandated involvement and data submission for accredited sites and proceduralists.

8. Proposed intervention's place in clinical management

Description of Medical Service

A catheter-based technique for the delivery of a permanent implant to the mitral valve via transeptal access. The PASCAL system consists of the Implant System, Guide Sheath as well as the optional Stabiliser and cardiac implantation catheter table. The implant clasps the anterior and posterior leaflets around a spacer, thus creating a double orifice and reducing mitral regurgitation (MR). The Implant System consists of the Steerable Catheter (outermost layer), the Implant Catheter (innermost layer), and the implant. The Implant System percutaneously delivers the implant to the valve via a femoral vein access using a transvenous, transeptal 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. This application refers to the proposed medical service as transcatheter mitral valve repair. The PASCAL Ace, a smaller size version of the original size PASCAL is also listed on the ARTG (Table 1).

Description of Medical Condition

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, 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, 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. MR is associated with an increased risk for heart failure and death.

Two proposed clinical management algorithms are presented in the ADAR, one for FMR (Figure 1) and one for DMR (Figure 2). The commentary highlighted discrepancies between the clinical management algorithms and the current MBS listing. The pre-ESC response clarified that the intended treatment population is consistent with the current MBS listing. The algorithms were based on 2017 European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines and not fully consistent with the proposed population for TMVr.

Figure 1 Clinical management algorithm for the Edwards PASCAL valve repair system/Transcatheter Edge-to-Edge Repair (TEER) for Symptomatic Primary (Degenerative) MR (REDACTED at applicant request. A comparable algorithm is available in Figure 4 of the 2017 ESC and EACTS Guidelines)

AF = atrial fibrillation; HF = heart failure; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SPAP = systolic pulmonary arterial pressure.

[a] When there is a high likelihood of durable valve repair at a low risk, valve repair should be considered (IIa C) in patients with LVESD ≥ 40 mm and one of the following is present: flail leaflet or left atrial volume ≥ 60 mL/m^2 body surface area at sinus rhythm.

[b] Extended heart failure management includes cardiac resynchronization therapy, ventricular assist devices, cardiac restraint devices, and heart transplantation.

Source: ADAR

Figure 2 Clinical management algorithm for the Edwards PASCAL valve repair system/Transcatheter Edge-to-Edge Repair (TEER) for Symptomatic Secondary (Functional) MR (REDACTED at applicant request. A comparable algorithm is available in the Figure 2 of MSAC PSD for application 1192.3)

GDMT = guideline-directed medical therapy; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MDHT = multidisciplinary heart team; NYHA = New York Heart Association; TMVr = transcatheter mitral valve repair.

[a] Symptomatic = NYHA functional class II or greater.

[b] Patients considered ineligible for surgery as determined by a multidisciplinary heart team, combining surgical risk assessment, frailty, major organ system dysfunction, and procedure-specific impediments.

[c] Medical management refers to maximally tolerated GDMT.

[d] Extended heart failure management includes cardiac resynchronization therapy, ventricular assist devices, cardiac restraint devices, and heart transplant.

Source: ADAR

9. Comparator

The comparator for the proposed medical service is the MitraClip system from Abbott Vascular which is listed on the MBS as the only transcatheter mitral valve repair device that has obtained successful listing.

10. Comparative safety

The safety outcomes included in the ADAR were overall survival, major adverse events (MAEs), stroke and myocardial infarction (MI) observed by 30 days. The primary source of evidence used was matched adjusted indirect comparison (MAIC) analysis between a single arm study of the PASCAL TMVr (CLASP)[12] and the MitraClip arms of two comparative

[12] Szerlip, M., Lim, D. S., Fam, N., Webb, J., Schaefer, U., & O'Neill, W. (2021). 2-year outcomes from the multicenter, prospective CLASP study with the PASCAL transcatheter repair system in patients with mitral regurgitation [Accepted]. JACC Cardiovasc Interv.
Szerlip, M., Spargias, K. S., Makkar, R., Kar, S., Kipperman, R. M., O'Neill, W. W., . . . Lim, D. S. (2021). 2-Year Outcomes for Transcatheter Repair in Patients With Mitral Regurgitation From the CLASP Study. JACC Cardiovasc Interv

trials (COAPT[13] and EVEREST-II[14]). Details of the studies are presented in Table 3. Unanchored MAIC analyses of overall survival and MAEs were presented separately for the two comparisons CLASP vs COAPT (FMR population only) and CLASP vs EVEREST-II (mixed population) and included both the results of the base-case and sensitivity matching.

Table 3 Key features of the included evidence for the PASCAL and MitraClip studies

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)
CLASP	124	Multicentre, prospective, single-arm, observational study	High; early feasibility study	Patients with clinically significant MR (DMR and FMR) (≥ grade 3+) despite OMT	PRIMARY ENDPOINTS: **Coprimary technical endpoints:** 1. Procedural success: 2. MR reduction to ≤ 2+ grade (discharge) **Safety endpoint**: MAE rate at 30 days defined as: composite of CV mortality, stroke, MI, new need for renal replacement therapy, severe bleeding. SECONDARY ENDPOINTS include: Recurrent HF admission, reintervention for treatment of MR, 6MWD, NYHA
COAPT	614	RCT, MC, MN, OL 24 months	Low	Patients with moderate-severe or severe FMR (MR 3+ or 4+), who have LVEF 20–50% and LVESD ≤ 70mm, ineligible for surgical intervention, and whose symptoms (NYHA functional class II or greater) persist despite maximally tolerated GDMT	Mortality, HF hospitalisation Major complications
EVEREST II	279	RCT, OL, MC 12 months	Low	Grade 3+ to 4+ MR If symptomatic were required to have LVEF ≥ 25% and LVESD ≤ 55 mm. If asymptomatic were required to have at least one of the following: an LVEF of 25 to 60 LVESD of 40 mm to 55 mm, new atrial fibrillation, or pulmonary hypertension	Freedom from death, from surgery for mitral- valve dysfunction, and from grade 3+ or 4+ mitral regurgitation MAEs

Abbreviations: GDMT=guideline directed medical therapy; MC=multicentre; OL=open label (unblinded); RCT=randomised controlled trial; LVEF= left ventricular ejection fraction; FMR=functional mitral regurgitation; LVESD=left ventricular end systolic dimension; HF=heart failure; MAE=major adverse event; MN=multinational; OL=open label (unblinded); DMR=degenerative mitral regurgitation; MI=myocardial infarction; NYHA=New York Heart Association; 6MWD= Six-Minute Walk Distance
Source: ADAR commentary

[13] Stone, G. W., Lindenfeld, J., Abraham, W. T., Kar, S., Lim, D. S., Mishell, J. M., . . . Investigators, C. (2018). Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med, 379(24), 2307-2318
[14] Feldman, T., Foster, E., Glower, D. D., Kar, S., Rinaldi, M. J., Fail, P. S., . . . Engeron, E. (2011). Percutaneous repair or surgery for mitral regurgitation. New England Journal of Medicine, 364(15), 1395-1406.

Overall survival

Results presented in the ADAR suggest that in the FMR population (CLASP vs COAPT) those treated with PASCAL system had **REDACTED** overall survival compared with the MitraClip population, which was **REDACTED** (Table 3). In the mixed population (CLASP vs EVEREST-II[15]) there may be a **REDACTED** in survival between the two treatments in the base case analysis but there were **REDACTED** in the sensitivity analysis in which populations were matched on FMR only (**Table 4**).

Table 4 Hazard ratios with 95% CI's for the comparison of overall survival

MAIC	Matching	Method	Hazard ratio (95% CI)
CLASP vs COAPT	Base case	Unadjusted Cox model	**REDACTED**
		Weighted Cox model	**REDACTED**
	Sensitivity analysis	Unadjusted Cox model	**REDACTED**
		Weighted Cox model	**REDACTED**
CLASP vs EVEREST-II	Base case	Unadjusted Cox model	**REDACTED**
		Weighted Cox model	**REDACTED**
	Sensitivity analysis	Unadjusted Cox model	**REDACTED**
		Weighted Cox model	**REDACTED**

MAIC=matched adjusted indirect comparison; CI=confidence interval
Source: ADAR

The commentary noted discrepancies in the **REDACTED[16].** The commentary considered this discrepancy added uncertainty to the hazard ratio values (Table 3). The pre-ESC response addressed the discrepancy **REDACTED.** The effective sample size (ESS) is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. The number of patients at the start of the Kaplan-Meier plot in the weighted population is equivalent to the sum of the weights. This will be different to the ESS.

Major Adverse Events

The commentary noted that differences in the MAE definitions for each of the studies (CLASP, COAPT and EVEREST-II) may make it difficult to draw conclusions about the comparative MAE rates. The key differences in MAE definitions are summarised in Table 5. Stroke and myocardial infarction were also compared separately in the ADAR with **REDACTION** found between treatments, although low event rates were observed in each of the three studies. With low event rates for some of the common components of the MAEs (death, stroke, MI) it may be difficult to draw conclusions about the comparative MAE rates.

In the EVEREST MitraClip population transfusions comprised the largest single component of the major adverse events at 30 days,[17] with other events occurring at 5%, **REDACTED** to the rate reported for the weighted CLASP population. The commentary noted it may not be reasonable to compare the MAE rates between the CLASP and EVEREST MitraClip populations.

[16] Applicant has not agreed to publish information pertaining to the results of the MAIC analysis

[17] Feldman, T., Foster, E., Glower, D. D., Kar, S., Rinaldi, M. J., Fail, P. S., . . . Engeron, E. (2011). Percutaneous repair or surgery for mitral regurgitation. New England Journal of Medicine, 364(15), 1395-1406.

Table 5 Comparison of MAE definitions for each study

CLASP	COAPT	EVEREST-II
Cardiovascular mortality	-	-
-	Death from any cause	Death
Stroke	Stroke	Stroke
Myocardial infarction	Myocardial infarction	Myocardial infarction
New need for renal replacement therapy	-	Renal failure
Severe bleeding (major, extensive, life-threatening, or fatal)	-	
Reintervention for study device-related complications	Nonelective cardiovascular surgery for study device-related complications	Reoperation for failed mitral valve surgery Nonelective cardiovascular surgery for adverse events
-	-	Deep wound infection
-	-	Mechanical ventilation for more than 48 hours
-	-	Gastrointestinal complications requiring surgery
-	-	New-onset permanent atrial fibrillation
-	-	Septicaemia
		Transfusion of 2 units or more of blood

Source: ADAR commentary

Table 6 Odds ratios and 95% CI's for the comparison of MAE by 30 days of follow-up for CLASP (PASCAL) vs COAPT (MitraClip)

Matching	Method	Odds ratio (95% CI)
Base case	Unadjusted regression model	**REDACTED**
	Weighted regression model	**REDACTED**
Sensitivity analysis	Unadjusted regression model	**REDACTED**
	Weighted regression model	**REDACTED**
Pre-ESC response - Base case [a]	*Weighted regression model*	**REDACTED**
Pre-ESC response - Sensitivity analysis [a]	*Weighted regression model*	**REDACTED**

a Supplementary analysis by applicant following commentary *in italics*. Reconstructed CLASP MAE definition: **REDACTED** compared against the secondary end-point from the COAPT study: death from any cause, stroke, myocardial infarction, and nonelective cardiovascular surgery for a device-related complication
Source: ADAR commentary

Table 7 Odds ratios and 95% CI's for the comparison of MAE by 30 days of follow-up for CLASP (PASCAL) vs EVEREST-II (MitraClip)

Matching	Method	Odds ratio (95% CI)
Base case	Unadjusted regression model	**REDACTED**
	Weighted regression model	**REDACTED**
Sensitivity analysis	Unadjusted regression model	**REDACTED**
	Weighted regression model	**REDACTED**
Pre-ESC response - Base case [a]	*Weighted regression model*	**REDACTED**
Pre-ESC response - Sensitivity analysis [a]	*Weighted regression model*	**REDACTED**

a Supplementary analysis in the pre-ESC response, excluding **REDACTED**
Source: ADAR commentary, *pre-ESC response*

In response to the differences in MAE definitions noted by the commentary, the pre-ESC response performed an additional analysis suggested by the commentary in the MAIC using a "reconstructed" CLASP MAE, defined as: **REDACTED**[18]. The MAE variables from the CLASP data (Table 5), were compared against the secondary end-point from the COAPT study: death from any cause, stroke, myocardial infarction, and nonelective cardiovascular surgery for a device-related complication**.** The percentage of patients with an MAE by 30 days of follow up using the ADAR definition of MAE and the reconstructed MAE rate are shown in Table 8. In the FMR population there were **REDACTED** between PASCAL and MitraClip using the reconstructed MAE rates (Table 6).

Table 8 Percentage of patients with an MAE by 30 days of follow-up

MAIC	Matching	CLASP (PASCAL) weighted, %	MitraClip, %
CLASP vs COAPT	Base-case analysis	**REDACTED** [19]	2.98 3.07 (9/293) [a]
	Sensitivity analysis	**REDACTED**	*NR*
	Pre-ESC response [b]	**REDACTED**	*2.98*
	Pre-ESC response [b] *(Sensitivity analysis)*	**REDACTED**	*2.98*
CLASP vs EVEREST-II	Base-case analysis	**REDACTED**	15.00
	Sensitivity analysis	**REDACTED**	15.00
	Pre-ESC response [c]	**REDACTED**	*5.00*
	Pre-ESC response [c] *(Sensitivity analysis)*	**REDACTED**	*5.00*

MAE = major adverse event; MAIC=matched adjusted indirect comparison; NR=not reported
a Commentary corrections to calculations
b Reconstructed MAE rate from CLASP study, defined as **REDACTED** [18]The MAE variables from the CLASP data, listed above, were compared against the secondary end-point from the COAPT study: death from any cause, stroke, myocardial infarction, and nonelective cardiovascular surgery for a device-related complication.
c Reconstructed MAE rate between CLASP and EVEREST-II study excluding **REDACTED**
Source: ADAR commentary =*and the pre-ESC response*.

[18] Applicant has not agreed to publication of variables in the MAIC analysis
[19] Applicant has not agreed to publication of the results of the MAIC analysis

Due to the differences noted by the commentary between the CLASP and EVEREST-II MAE definitions, the applicant performed an additional analysis in the MAIC, excluding **REDACTED** for the EVEREST II definition. With **REDACTED** excluded, there were **REDACTED** differences in the odds of MAEs at 30 days for PASCAL vs MitraClip in the mixed DMR/FMR population (Table 7), either in the base case or the sensitivity analysis (matching on FMR status only).

11. Comparative effectiveness

MR severity

The ADAR commentary presented distribution of MR severity dichotomised to MR Severity grade 2+ or lower at 24 months and 12 months of follow-up for the respective MR populations (Table 9). Values for the unweighted CLASP (PASCAL) FMR population are added in for comparison (Table 9).

Table 9 Percentage of patients with MR grade 2+ or lower

MAIC	Matching	Follow-up	*CLASP (PASCAL) unweighted, %*	CLASP (PASCAL) weighted, %	MitraClip, %
CLASP vs COAPT	Base-case	24 months	95 (n=19)*	**REDACTED**	99.13
	Sensitivity analysis			**REDACTED**	99.13
CLASP vs EVEREST-II	Base-case	12 months	100 (n=36)#	**REDACTED**	100
	Sensitivity analysis			**REDACTED**	100

*FMR population only
#Overall population
Source: ADAR Commentary

The results of the MAIC analysis suggested that at 24 months follow-up, in the FMR population a **REDACTED** proportion of patients achieved MR grade 2+ or lower in the two populations (CLASP vs COAPT) (Table 9). In the mixed population, at 12 months follow-up, **%redacted** of patients in the CLASP and EVEREST-II populations achieved MR grade 2+ (Table 9).

NYHA class

Table 10 Percentage of patients with NYHA class I or II

MAIC	Matching	Follow-up	*CLASP (PASCAL) unweighted, %*	CLASP (PASCAL) weighted, %	MitraClip, %
CLASP vs COAPT	Base-case	24 months	88 (n=24)*	**REDACTED**	66.67
	Sensitivity analysis			**REDACTED**	66.67
CLASP vs EVEREST-II	Base-case	12 months	11 (n=92)#	**REDACTED**	98
	Sensitivity analysis			**REDACTED**	98

*FMR population only
#Overall population
Source: ADAR Commentary

The results of the MAIC analysis presented in the ADAR suggested that at 24 months follow-up, in the FMR population a **REDACTED** proportion of patients achieved NYHA class 1 or II in the CLASP population (Table 10). In the mixed population, at 12 months follow-up, proportion of patients achieved NYHA class 1 or II in the CLASP population appeared **REDACTED** than in MitraClip arm (Table 10).

12. Economic evaluation

The economic evaluation is summarised in Table 11. A cost-minimisation analysis was presented on the basis that PASCAL is non-inferior in safety and efficacy compared with MitraClip.

Table 11 Summary of the economic evaluation

Perspective	Australian Healthcare System
Comparator	MitraClip
Type of economic evaluation	Cost-minimisation
Sources of evidence	MAIC, identified literature (refer section B)
Time horizon	30 days
Outcomes	**REDACTED**
Methods used to generate results	**REDACTED**
Discount rate	Not applicable
Software packages used	Microsoft Excel 365

MI=mitral regurgitation; MAE=major adverse event; MAIC=matched adjusted indirect comparison
Source: ADAR

The ADAR reported the costs of the procedure including prosthesis, revision surgery costs and adverse event costs. The cost minimisation considered that the cost of procedure including prosthesis would be **REDACTED** for PASCAL and MitraClip. The expected costs of revision surgery and adverse events had the potential to be **REDACTED**, as determined from the MAIC using rates of adverse events at 30 days. The ADAR then used a weighted approach to determine the overall cost-minimised result, using a **%redacted** FMR to **%redacted** DMR split.

Table 12 and Table 13 present the results of the cost-minimisation analyses presented in the ADAR and the commentary, respectively. The ADAR presented different results in the main body (presented in Table 12) and the cost-minimisation spreadsheet based commentary results (Table 13).

Table 12 Total weighted cost-minimised cost across both FMR and DMR populations from the ADAR

	PASCAL	MitraClip
Total cost FMR	**$redacted**	**$redacted**
Total cost DMR	**$redacted**	**$redacted**
Total cost all MR – weighted [a]	**$redacted**	**$redacted**
Total incremental cost of PASCAL	**$redacted**	

a Weighting **REDACTED**
Source: ADAR

Table 13 Cost-minimised results as reported in the ADAR commentary

	PASCAL		MitraClip	
	FMR	DMR	FMR	DMR
Redacted	$redacted	$redacted	$redacted	$redacted
Redacted	$redacted	$redacted	$redacted	$redacted
Redacted	$redacted	$redacted	$redacted	$redacted
Redacted	$redacted	$redacted	$redacted	$redacted
Total cost	$redacted	$redacted	$redacted	$redacted
Total costs (FMR + DMR weighted)	$redacted		$redacted	
Incremental cost of PASCAL	$redacted			
Redacted	$redacted	$redacted	$redacted	$redacted
*Total costs including m*Redacted *(FMR + DMR weighted)*	$redacted		$redacted	
Incremental cost of PASCAL (including Redacted*)*	$redacted			

Source: ADAR commentary

The total weighted cost for all MR (FMR and DMR) for PASCAL and MitraClip are **$redacted** and **$redacted** (Table 12). The total incremental cost of PASCAL to MitraClip using the weighted populations of all MRs as presented in the main body of the ADAR is **$redacted**. The corresponding value reported in the ADAR commentary's cost-minimisation spreadsheet was **$redacted** (Table 13). The cost-minimisation spreadsheet did not include the cost of **REDACTED[20].** Accounting for this cost (**$redacted)** resulted in an incremental cost of **$redacted.** The remaining difference in cost-minimisation results between the ADAR and the model spreadsheet appears to be driven by the different costs of **REDACTED[20]** attributed to PASCAL when used for DMR.

The ADAR and commentary both noted the potential for double counting costs when including **REDACTED [20]** as well as separate costs for **REDACTED**. The commentary tested the impact of these parameters by setting the **REDACTED** to 0%, thus removing them from the analysis. This resulted in the weighted cost of PASCAL compared with MitraClip increasing from **$redacted** to **$redacted** (Table 14). Additionally, removing the **REDACTED**[20] to prevent double counting resulted in a **REDACTED** of **$redacted** with PASCAL compared with MitraClip (Table 14). The maximum additional cost for PASCAL compared with MitraClip in any scenario changing the value of the parameters was **$redacted** (Table 14).

[20] Applicant has not agreed to publish variables in the cost-minimisation analysis

Table 14 Independent assessment of costing parameters: removing REDACTED [21] or REDACTED from the analysis [a]

	FMR			DMR			Weighted Difference
	PASCAL	MitraClip	Difference	PASCAL	MitraClip	Difference	
Base case	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted
Removing REDACTED	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted
Only including REDACTED	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted
Revision of MitraClip cost	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted
Revision of risk of REDACTION (PASCAL; FMR)	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted
Revision of risk of REDACTED (MitraClip; FMR)	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted
Revision of risk of REDACTED (MitraClip; FMR & DMR)	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted	$Redacted

a Excludes the cost of **REDACTED**
Source: ADAR commentary

MitraClip was not listed on the Prostheses List at the time of submission and has since been listed at a price of $26,386. Following the commentary report, the applicant performed an additional cost-minimisation analysis using the **REDACTED[21]** and the cost of MitraClip and PASCAL as listed on the Prostheses List to inform the revised base case for this submission. The base case with these two amendments results in an incremental cost of PASCAL of **$redacted** (Table 15), when considering **REDACTED[21].**

Table 15 Results of the cost-minimisation analysis using the REDACTED and published price of MitraClip

	PASCAL	MitraClip
Total cost FMR	**$redacted**	**$redacted**
Total cost DMR	**$redacted**	**$redacted**
Total cost all MR – weighted	**$redacted**	**$redacted**
Total incremental cost of PASCAL	**$redacted**	

Source: Pre-ESC response

13. Financial/budgetary impacts

The ADAR stated an **REDACTED** approach was used to estimate utilisation and financial consequences, however the results were **REDACTED** to the published numbers from the MitraClip Public Summary Document, making it **REDACTED** approach**.** The ADAR assumed PASCAL would take a %**redacted** share of MitraClip. The commentary considered this to be reasonable and conservative but noted that this assumption may underestimate the

[21] Applicant has not agreed to publication of variables in the cost-minimisation analysis

effect of clinician preference for and familiarity with MitraClip due to it being first to market. This could result in the market share of PASCAL to be **REDACTED.**

The commentary considered that it is unlikely that the introduction of PASCAL would increase the overall utilisation of mitral valve repair, and that any patient receiving PASCAL under the proposed restriction would have otherwise received MitraClip if PASCAL was not available. Therefore, the commentary considered the overall costs of MitraClip and PASCAL are **REDACTED.** The estimated cost of PASCAL to the MBS is expected to be **REDACTED** each year for the first five years (Table 16).

Table 16 Total costs to the MBS associated with PASCAL

-	2015-16	2016-17	2017-18	2018-19	2019-20
PASCAL	-	-	-	-	-
Number of services	redacted	redacted	redacted	redacted	redacted
Sub-total cost	$redacted	$redacted	$redacted	$redacted	$redacted
Current Prices: Full Benefit [a]: 75% Benefit [a]	$redacted	$redacted	$redacted	$redacted	$redacted

a 3x MBS Items 6081 included
Source: ADAR

The commentary revised hospital and prosthesis costs based on the **REDACTED** share with MitraClip over five years is shown in Table 17.

Table 17 Hospital and prosthesis costs over 5 years based on REDACTED share with MitraClip

	Year 1	Year 2	Year 3	Year 4	Year 5
Total combined					
- In-hospital resource use	$redacted	$redacted	$redacted	$redacted	$redacted
- Prosthesis	$redacted	$redacted	$redacted	$redacted	$redacted
Total combined	$redacted	$redacted	$redacted	$redacted	$redacted

Source: ADAR commentary

14. Key issues from ESC to MSAC

ESC key issue	ESC advice to MSAC
MBS item descriptor	ESC expressed a preference for updating the existing MBS item to be device-agnostic and retaining the term transcatheter mitral valve repair (TMVr) rather than transcatheter edge-to-edge repair (TEER).
Level of evidence	Clinical data are from a small observational study (a feasibility study) with high risk of bias. The overall evidence quality is lower than the evidence used for the MitraClip assessment in application 1192.3, where evidence for the FMR population was available from an RCT with 2 years follow-up.
Uncertain clinical claim of non-inferiority	The clinical claim could not be fully verified. The clinical data for TMVr using the PASCAL system was from a single-arm observational study. The evidence to support non-inferiority with the MitraClip system relies on an unanchored Matched Adjusted Indirect Comparison (MAIC), which is used when there is no common comparator arm in each trial being compared. The MAIC approach is appropriate given the lack of direct comparative evidence. However, a key limitation of the unanchored MAIC approach is the strong assumption that all covariates and prognostic factors are accounted for. This is considered impossible to

ESC key issue	ESC advice to MSAC
	meet except in a well-controlled RCT and the unanchored MAIC estimate therefore carries and unknown amount of bias. ESC also considered that the lack of transparency regarding the presented MAIC analysis was a source of additional uncertainty in this application.
Uncertainty of clinical claim affects economic evaluation	The clinical claim is uncertain due to limitations of evidence, both in terms of the quality of individual studies and their indirect comparison. This also affects the economic evaluation directly through comparative rates of adverse events, although sensitivity analyses exploring this issue have been provided.
Cost-minimisation analysis	The 30-day time horizon is appropriate for capturing typical revision surgery but implicitly assumes identical long-term performance which has no data to support it. While the proposed intervention has some potential to be cost-increasing, ESC considered that this is likely to be immaterial and have a very small financial impact. As such, the primary considerations are those of clinical need and merit.

ESC discussion

ESC noted the purpose of the application was to amend the current Medicare Benefits Schedule (MBS) item numbers for Transcatheter Mitral Valve Repair System (TMVr) using the MitraClip device (items 38461, 38463, 6082 and 6084) to also include the PASCAL system to reduction of mitral regurgitation through tissue approximation using Edwards PASCAL for the treatment of degenerative mitral regurgitation (DMR) and functional mitral regurgitation (FMR).

ESC noted that this application used substantially the same ratified PICO as used for application 1192.3 (for MitraClip, which resulted in the MBS item numbers listed above). Application 1662 had therefore bypassed PASC. ESC noted that the populations were the same, the intervention uses the same technique (although the device is different for application 1662) and the comparator for application 1662 was specified as MitraClip.

ESC noted the applicant's clinical claim that PASCAL is non-inferior in safety and efficacy compared with MitraClip.

ESC noted there were no consultation submissions relating to this application from consumers or organisations.

ESC noted that the current MitraClip MBS item descriptors were listed after the applicant submitted application 1662. The current item descriptors therefore differ to those proposed in the applicant-developed assessment report (ADAR) in the following ways:

- There are two currently approved MBS items for the MitraClip procedure, one for DMR (38461) and one for FMR (38463). ESC considered that maintaining two items would be appropriate to facilitate monitoring of utilisation for each condition.
- Current MitraClip MBS items provide specific criteria for left ventricular ejection fraction (LVEF) for each population and specify that patients are symptomatic (rather than specifying that patients have New York Heart Association [NYHA] class II, II or IV). ESC considered that the currently specified LVEF of >20% for the DMR population should be retained, rather than amending the LVEF to >30% as per the applicant's clinical management algorithm. The pre-ESC response clarified that it did not intend to align with the clinical management algorithm presented in the ADAR.

ESC noted that the proposed new MBS item descriptor would not specify MitraClip and would instead be technology-agnostic as to the type of TMVr used. ESC noted that this aligns with MSAC's general preference for technology-agnostic MBS items. However, ESC noted that technologies continue to evolve over time, and that it is important that the evidence for an application indicates that there is not a substantial difference between the technologies included in an agnostic item descriptor. This would also allow use of the PASCAL ACE device.

ESC noted the ADAR requested replacing the term TMVr with transcatheter edge-to-edge repair (TEER). ESC also considered that it would be preferable to retain the terminology of TMVr rather than changing it to mitral valve for consistency with other items for mitral valve interventions. ESC also noted that TMVr Hospital, TMVr Practitioner and TMVr Patient are specified in the item descriptor (with definitions in the notes), and that this approach is well regulated and appropriate. ESC expressed a preference for amending the existing MBS item descriptors to be device agnostic. ESC considered that it would be unlikely that a technology-agnostic item descriptor would have an impact on the population accessing the service under the MBS or other flow-on impacts to the MBS.

ESC noted the limited clinical data for this application. The CLASP study was a prospective, single-arm, observational study of the PASCAL system, with results reported for 124 patients after 2 years. The study was conducted at 14 sites in 7 countries, including a small number of patients in Australia. ESC noted that the risk of bias in this study was high, as it was an early feasibility study. Primary endpoints were procedural success, MR reduction to ≤grade 2, and major adverse events at 30 days. Revision rates from the CLASP study were used in the economic analysis.

ESC noted the clinical trial data for the comparator (MitraClip), which comprised two randomised controlled trials (RCTs) – COAPT (N = 614) and EVEREST-II (N = 279). Both trials had a low risk of bias. ESC noted that the level of evidence for PASCAL was lower than considered by MSAC for MitraClip.

ESC noted the lack of direct evidence to compare PASCAL and MitraClip. The applicant instead used a matching-adjusted indirect comparison (MAIC). ESC noted that MSAC has not considered many applications that used a MAIC, although 24 applications have been considered by the Pharmaceutical Benefits Advisory Committee that used a MAIC. ESC noted that patient-level data are not required for the comparator studies in a MAIC, and aggregate data are used instead. A weight is calculated for each patient in the individual data of the intervention (CLASP), such that the overall mean of the weighted individual data (which is calculable) matches that of the aggregate data for the comparator (COAPT and EVEREST-II). Using the resulting weights, it is then possible to estimate reweighted outcomes of the study in a similar patient group to that where the outcomes of the control arm were obtained. This effectively means the data that are available (CLASP) are reweighted to match that of the comparator (COAPT and EVEREST-II). The applicant consulted three clinicians (blinded to endpoints) to determine which baseline characteristics should be used for matching of studies for the MAIC analysis. ESC noted additional details on this process was provided in the pre-ESC response.

ESC noted that one of the main limitations of the unanchored MAIC analysis is that it strongly assumes that all effect modifiers and prognostic factors are accounted for. This is considered impossible to meet and may lead to an unknown amount of bias in the unanchored estimate.

ESC noted that it was not possible to verify or replicate the results of the MAIC because the ADAR did not provide patient-level data, the statistical codes used for the analysis, or the matching options that were presented to clinicians for matching of baseline characteristics. ESC noted the applicant's pre-ESC response, which stated that the applicant does not disclose individual patient-level data. ESC considered that this lack of transparency was a key limitation of the ADAR. However, these data help ensure transparency in the MAIC and allow the MAIC to be verified and replicated. ESC did not consider that the pre-ESC response alleviated any concerns about transparency or fully resolved any uncertainties.

Regarding comparative safety, ESC noted that some of the major adverse events measured in COAPT and EVEREST-II were different to those measured in CLASP. ESC noted that the MAIC analysis suggested that the odds of experiencing major adverse events at 30 days in the FMR population were **REDACTED** for PASCAL than for MitraClip, and the rate of major adverse events at 30 days in the mixed FMR and DMR population was **REDACTED** for PASCAL than for MitraClip. However, ESC considered that it was unclear what impact the differences in definitions of major adverse events had on the MAIC findings. No long-term comparative safety data were available.

Regarding comparative effectiveness in the FMR population (CLASP versus COAPT), the MAIC analysis suggested that overall survival was **REDACTED** in patients that were treated with the PASCAL system compared with MitraClip. ESC noted the DMR population had **REDACTED** survival than the FMR population which had face validity as FMR is due to an underlying condition which itself increases mortality. The MAIC analysis also suggested that patients treated with the PASCAL system had **REDACTED** MR severity scores at 24 months and NYHA classifications at 24 months of follow-up compared with patients treated with MitraClip system. In the mixed FMR and DMR population (CLASP versus EVEREST-II), the MAIC analysis suggested that overall survival in the PASCAL population is **REDACTED** the overall survival in the MitraClip population. The MAIC analysis suggested that MR severity scores at 12 months were **REDACTED** for patients treated with the PASCAL system, and NYHA classifications at 12 months were **REDACTED** for patients treated with the PASCAL system compared with MitraClip system.

The pre-ESC response addressed the discrepancy between the **REDACTED**. The effective sample size (ESS) is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. The number of patients at the start of the Kaplan-Meier plot in the weighted population is equivalent to the sum of the weights. This will be different to the ESS

ESC noted that no comparative evidence was available for the DMR population alone.

ESC noted that an RCT comparing PASCAL with MitraClip is actively recruiting, with an estimated primary completion date in 2023 and study completion date in 2028. However, ESC noted that the estimated dates may be delayed by the COVID-19 pandemic.

ESC noted that the economic evaluation presented in the ADAR was a cost-minimisation analysis of PASCAL compared with MitraClip, which included the costs of **REDACTED** over 30 days. ESC considered that the time horizon of 30 days was adequate for evaluating the TMVr procedure but introduced additional implicit assumptions when extending conclusions to the intervention over its lifespan.

ESC noted that uncertainty of the MAIC affected the economic analysis indirectly, through clinical claims of non-inferiority, and directly, through comparative rates of adverse events

applied in the cost-minimisation analysis. ESC noted that translation issues were not presented in the ADAR. ESC considered that a comparison of the trial population with the Australian population would have been informative, and that extrapolation of outcomes beyond 30 days should have been formally explored.

ESC noted that the costs for **REDACTED** were missing from the results of the cost-minimisation in the commentary and asked for clarification on whether this was a simple omission from the results table. ESC also noted the commentary's identification of double-counting of adverse events, for which the applicant provided new cost considerations in the pre-ESC response. ESC also noted the sensitivity analyses presented in the commentary for the costs of **REDACTED** and noted that changing these parameters had little effect on the base case outcome. ESC considered that, although there is a possibility of a **REDACTED** cost associated with the use of PASCAL over MitraClip, this cost would be **REDACTED.**

ESC noted the ADAR declared using an **REDACTED** approach to estimate utilisation and financial consequences, however the results were **REDACTED** to the published numbers from the MitraClip Public Summary Document, making it effectively a **REDACTED** approach with assumed **%redacted** market share. ESC queried whether this was appropriate given that 18 months have elapsed since this approach was accepted for MitraClip. ESC further considered that the basis of the **REDACTED** approach was unclear given that MitraClip was first to market and may have the advantage of familiarity, making it the preferred first choice in some situations. In conclusion, ESC considered that PASCAL represents an alternative device with no substantial financial impact.

15. Other significant factors

Nil

16. Applicant comments on MSAC's Public Summary Document

The totality of evidence regarding PASCAL therapy has demonstrated its efficacy and consistent improvement across multiple outcomes in patients considered to be too high risk for surgery due to comorbid conditions and other risk factors. These outcomes benefits include reduction of MR, left ventricular reverse remodelling, improvements in NYHA functional class and quality of life, and reductions in heart failure hospitalizations. Patients identified as too high risk for surgery via a qualified heart team assessment represent a group of patients who need access to PASCAL. Edwards Lifesciences look forward to addressing areas of concern outlined by MSAC to ensure patients can have access to PASCAL.

17. Further information on MSAC

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