Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1662.1 – The reduction of mitral regurgitation through tissue approximation using transvenous/transeptal techniques

Applicant: **Edwards Lifesciences**

Date of MSAC consideration: **24-25 November 2022**

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

1.   Purpose of application

An application requesting Medicare Benefits Schedule (MBS) for a transcatheter mitral valve repair (TMVr) using PASCAL for treatment of patients with degenerative mitral regurgitation (DMR) or functional mitral regurgitation (FMR) was received from the Edwards Lifesciences by the Department of Health and Aged Care.

2.   MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC 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 limited new evidence presented did not change its previous conclusions from November 2021, that the evidence does not adequately support the claim of non-inferior safety and effectiveness of TMVr using the PASCAL Transcatheter Valve Repair System™ compared to MitraClip and that an unmet clinical need was not clearly demonstrated.

Consumer summary
This is the second application from Edwards Lifesciences requesting Medicare Benefits Schedule (MBS) listing for a medical procedure called transcatheter mitral valve repair (TMVr). The mitral valve is the valve that sits in the left side of the heart. The heart muscle has four sections, called chambers. When everything is working well, blood travelling from the arteries in the lungs enters the heart via the upper left heart chamber. When the heart beats, blood is first squeezed out of this top left chamber, through the one-way mitral valve, into the lower left chamber. The mitral valve is supposed to close tightly again before blood is then squeezed out towards the rest of the body. TMVr is a procedure performed to manage a condition, called mitral regurgitation, in which the mitral valve does not close tightly. This means that, with each heartbeat, some blood can flow backward from the left lower chamber to the left upper chamber again. This condition makes it difficult for the heart to pump blood around the body, which can cause shortness of breath and may cause heart failure in the long-term. TMVr is already funded on the MBS for another type of device (called MitraClip), and Edwards Lifesciences applied to amend these MBS items to include an approach called the PASCAL system.

Consumer summary

The PASCAL system includes a small device made of clasps, paddles and spacers. The interventional cardiologist or surgeon uses a small, customised tube, called a catheter to insert the device through a vein in the leg up to the heart. Inside the heart, the device gently grasps the edges of the faulty valve to help close the valve.

Edwards Lifesciences has applied for public funding for the PASCAL device to be used for the TMVr procedure for people with mitral regurgitation who cannot have open heart surgery to repair their mitral valve. TMVr is currently already funded on the MBS when it is performed using the MitraClip device.

MSAC considered that the clinical evidence to support TMVr using the PASCAL system was not as high quality as the evidence that was used to support TMVr using the MitraClip system. MSAC was also not convinced that the PASCAL system was addressing an unmet need, as TMVr using the MitraClip device is already funded and the MitraClip device has been continuously evolving. MSAC was also not certain that the PASCAL system would be good value for money.

MSAC noted that a clinical trial of TMVr comparing the PASCAL system with MitraClip is currently underway. The short-term results from this trial appear promising, but longer-term results are needed to be certain that the PASCAL system works as well as the MitraClip system over a longer period of time.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support listing the TMVr using 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 was addressing an unmet need or was good value for money.

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

MSAC noted that this application from Edwards Lifesciences requested amendment of the MBS listings for TMVr for treatment of patients with DMR or FMR. The Applicant-Developed Assessment Report (ADAR) requested amendment of the current device specific MBS items for TMVr using the MitraClip system (MBS items 38461 and 38463) to be device agnostic, allowing the PASCAL system to be used as an intervention to reduce MR through tissue approximation.

MSAC noted that this is a resubmission, with the first submission considered by MSAC in November 2021 (MSAC 1662 PSD).

MSAC noted that at its September 2020 out-of-session meeting, MSAC supported listing MitraClip (Abbott Australasia Pty Ltd) for TMVr through tissue approximation (MSAC 1192.3 PSD). This led to the creation of MBS items 38461 and 38463 for DMR and FMR in July 2021. At its November 2021 meeting, MSAC did not support amending these MBS items to make them device agnostic for the PASCAL device (MSAC 1662 PSD). At the time, MSAC considered that the quality of evidence for TMVr using the PASCAL system was low and did not adequately support the claim of clinical non-inferiority for safety and effectiveness. MSAC advised that a future submission should preferably include evidence comparable in quality to the MitraClip randomised control trial (RCT) with two-year follow-up, as well as comparative evidence for DMR alone. Additionally, MSAC considered that the submission had not clearly demonstrated an unmet clinical need for an alternative device for MR.

MSAC noted that public consultation feedback was supportive. However, feedback stated that the item fee of $1,514.10 (the same fee as MBS items 38461 and 38463 for MitraClip) was too low for

the complexity of the procedure and should be payable twice within five years if agreed by the multidisciplinary team.

MSAC noted the clinical management algorithms for both DMR and FMR. MSAC noted that patients must have an unacceptably high risk for surgical valve replacement. MSAC noted that the proposed populations for PASCAL align with the two populations already listed for this procedure on the MBS using the MitraClip system.

MSAC noted that the comparator was TMVr using MitraClip, which MSAC considered to be appropriate. However, MSAC considered that for patients not anatomically suitable for TMVr using MitraClip, the comparator would be best supportive care.

MSAC noted that the applicant considered that TMVr using the PASCAL system to largely be an alternative to TMVr using MitraClip, providing potential technical advantages including improvements in manoeuvrability and implant dimensions that make it more appropriate for patients with complex anatomy. However, MSAC considered that the MitraClip device has continued to evolve, and the recently released fourth generation MitraClip may address some of the drawbacks described in the ADAR. The ADAR did not identify a group of patients with an unmet clinical need who are eligible for TMVr but unable to undergo TMVr using the currently funded MitraClip device. Therefore, MSAC considered the applicant's claim that TMVr using the PASCAL system would address an unmet clinical need requiring an alternative device was not adequately supported in the context of the currently available (fourth generation) MitraClip devices.

MSAC noted that the evidence presented in the ADAR remained largely unchanged from the previous ADAR with respect to the studies presented and data on longer term outcomes. The current ADAR included additional 24-month follow-up data for the mixed FMR/DMR population (CLASP, EVEREST-II) and a revised analysis of the same studies in an unanchored matching-adjusted indirect comparisons (MAIC). MSAC noted that the unanchored MAIC method 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 [1] and Phillipo 2016 [2]).

The primary sources of evidence in the ADAR consisted of two single-arm studies for PASCAL (CLASP and Mauri 2020), the MitraClip arms from two RCTs (COAPT and EVEREST-II) and data from the STS/ACC TVT Registry for MitraClip (Mack 2022). Results of these five observational datasets were presented as naïve comparisons. The pre-ESC response included conference presentations reporting results from the CLASP IID trial (comparing TMVr using PASCAL and MitraClip in DMR) and the PASCAL IID Registry that assessed TMVr using PASCAL in prohibitive surgical risk patients with significant symptomatic DMR and complex mitral valve anatomy. An uncorrected proof was considered by ESC[3]. MSAC noted these results were not provided with the ADAR and not formally evaluated. No results from the CLASP IIF trial were presented. MSAC noted that these are a part of a current clinical trial (Edwards PASCAL CLASP IID/IIF Pivotal Clinical Trial) comparing the safety and effectiveness of PASCAL to MitraClip. There are three arms with a target total of 1,275 participants.

[1] Phillippo DM et al. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. Med Decis Making. 2018;38(2):200-211.

[2] 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/wpcontent/uploads/2018/08/Population-adjustment-TSD-FINAL-ref-rerun.pdf

[3] Lim D, Smith R, Gillam L, et al. Randomized Comparison of Transcatheter Edge-to-Edge Repair for Degenerative Mitral Regurgitation in Prohibitive Surgical Risk Patients. *J Am Coll Cardiol Intv.* Sep 17, 2022 https://doi.org/10.1016/j.jcin.2022.09.005

Two additional non-randomised, comparative clinical studies (Geis 2022 and Haschemi 2022) were included in an appendix of the ADAR, but not the main body. MSAC noted that that the population in the Geis study had baseline differences (e.g. a higher EURSCORE II with MitraClip, $P = 0.05$) and included some patients that would be ineligible for the MBS item (17% had left ventricular ejection fraction of <20%). MSAC also noted that, in the Geis study, PASCAL had three-times more patients lost to follow-up (46% at 1–4 months, 68% at 6–18 months) compared to MitraClip, with insufficient explanation provided. MSAC considered that these additional studies had a low to medium risk of bias and were a higher level of evidence than the MAICs. MSAC considered that the new studies did not address previous MSAC advice (from November 2021) that any future submission should include evidence that is comparable in quality to the MitraClip trial evidence and comparative evidence for the DMR population alone.

MSAC considered the comparative safety outcomes to be reassuring. However, MSAC was concerned about the limited long-term data (beyond 6 months), in particular small numbers and variable or incomplete follow-up for the published comparative studies. MSAC also considered the MAIC and naïve comparisons to be limited by not having a common comparator. MSAC considered these analyses likely affected by confounding due to different participant characteristics, time-varying confounders and different proportions of FMR/DMR for mixed analyses. MSAC considered the pre-post analysis used to measure heart failure hospitalisation was not informative as the method used to identify these patients (e.g. more likely to be identified if recently hospitalised with heart failure) would bias the result and make it difficult to interpret. MSAC considered the overall survival outcomes for FMR from the MAIC lacked face validity as there were ██ ██ ██ ██ ██ ██ ██ ██ ██ according to the Kaplan-Meier curves. However, the Kaplan-Meier estimate of overall survival from the ██ ██ ██ ██ decreased from ██ ██ ██ to ██ ██ ██.

MSAC noted that a pre-specified interim analysis of the CLASP IID cohort ($n = 117$ for PASCAL, $n = 63$ for MitraClip) met the Bayesian predictive probability for trial success. Major adverse events (MAEs) at 30 days were 3.4% for PASCAL vs 4.8% for MitraClip, with the upper bound one-sided confidence interval (CI; 5.1%) within the pre-specified 15% non-inferiority margin. Further, safety persisted to 6 months, with MAEs at 6.1% for PASCAL vs 11.1% for MitraClip. Preliminary (6 month) survival outcomes for cardiovascular mortality were also promising (99.1% for PASCAL, 93.7% for MitraClip; $P = 0.035$). MSAC noted the applicant suggested that this medium-term outcome [six months] is indicative of longer-term response.

MSAC considered the safety profile of PASCAL to be promising (especially MAEs at 30 days), but longer-term comparative safety (including reintervention rates beyond six months) is uncertain.

MSAC noted that the evidence for clinical effectiveness in the published comparative and single-arm studies suggested favourable technical and procedural success, with reductions in MR severity and symptoms. MSAC noted that a naïve comparison across the included studies showed promising results for MR severity at 30-day follow-up. Additionally, the MR grade to 24 months in the CLASP study was maintained out to two years but with very small patient numbers.

MSAC noted that the CLASP IID cohort from the current clinical trial showed similar proportions of patients with MR ≤2+ (mild–moderate) at six months (96.5% for PASCAL vs 96.8% for MitraClip), with the lower bound of the one-sided CI (−6.2%) within the pre-specified non-inferiority margin (−18%). MSAC considered the point estimates to be suggestive of non-inferiority, but MSAC was concerned that these conclusions were based on a wide margin for non-inferiority. MSAC considered that a more stringent margin in the full trial would provide better certainty of non-inferiority.

MSAC had the same concerns with the comparative effectiveness evidence as it did with the comparative safety evidence This included small sample sizes for long-term outcomes, variable or incomplete follow-up for the published comparative studies; limitations with the unanchored MAIC,

and naïve comparisons limited by not having a common comparator. MSAC considered the claim of non-inferior comparative effectiveness was not adequately supported by the evidence.

MSAC noted that the applicant considered the evidence presented in the current ADAR is of a similar standard to that included in MSAC Application No. 1192.3, which presented a series of observational studies to support the listing of TMVr using MitraClip for the DMR population. MSAC considered that for the MitraClip application ([MSAC 1192.3 PSD](#)) the FMR evidence for MitraClip was of a higher quality (RCT, two year follow up including morbidity and mortality) and supported the claim of non-inferior safety and superior effectiveness compared to OMT. In relation to the DMR population, MSAC considered the DMR evidence to be of lower quality but accepted it was reasonable that TMVr with MitraClip was at least non-inferior to OMT in the DMR population, particularly in the context of a serious condition with limited treatment options. MSAC considered that given an unmet need was not adequately demonstrated for the PASCAL system, evidence comparable in quality to the MitraClip randomised control trial (RCT) with two-year follow-up, as well as comparative evidence for DMR alone was required.

MSAC considered the cost-minimisation analysis used for the economic evaluation to be appropriate but was not supported by sufficient clinical evidence supporting the clinical claim of non-inferiority. MSAC noted the inclusion of a limited number of adverse events favoured TMVr using PASCAL and accounted for the small cost saving with TMVr using PASCAL. MSAC noted that, as in the previous submission, a weighted approach was used to determine the overall result of the cost-minimisation analysis.

MSAC noted that some hospitals are being charged costs higher than the Prosthesis List benefit for cardiac devices. This cost may be incurred by the hospital or patient. MSAC noted the applicant confirmed that the proposed Prosthesis List benefit will fully reimburse the price of the PASCAL device, implant system and guide sheath, but did not confirm if there were additional consumable costs that may be charged outside of the standard hospital/insurer arrangements.

MSAC noted that the estimated financial impact used a ▮▮▮ approach. Unchanged from the previous submission, it assumed PASCAL would account for ▮▮▮▮▮▮▮▮▮▮▮▮ ▮▮▮▮▮▮▮▮ TMVr utilisation. Therefore, the total financial impact is estimated to be ▮▮▮. The estimate also assumes that there will be an ▮▮▮ in MitraClip numbers with ▮▮▮ ▮▮▮▮▮▮▮▮▮▮▮▮▮. MSAC considered the utilisation estimates to be uncertain. MSAC noted the ADAR claimed that TMVr using PASCAL will address an unmet clinical need. MSAC considered that this was not adequately addressed in the ADAR. MSAC advised that a claim of unmet clinical need should be addressed in the context of patients who are unable to undergo TMVr using current generation Mitraclip devices. MSAC noted the pre-MSAC response claimed that ▮▮▮% of patients screened for CLASP IID trial were deemed eligible to undergo TMVr using PASCAL only. MSAC considered the financial estimates should calculate the net costs arising from the additional population that will be able to undergo TMVr.

Overall, MSAC considered that its previous concerns (from Application 1662) were not adequately addressed in this new ADAR. MSAC considered that the evidence supporting longer term outcomes (beyond 6 months) was of low quality and did not support the claim of non-inferior safety and clinical effectiveness compared with TMVr using MitraClip.

MSAC considered that any resubmission should include evidence to support the claim of non-inferior safety and clinical effectiveness compared with TMVr using MitraClip. MSAC reaffirmed that evidence comparable in quality to the MitraClip RCTs, as well as comparative evidence for DMR alone was required. MSAC advised that this should include adequately powered, direct comparative evidence reporting:

- o Rates of MAEs including reintervention with at least 12 months follow-up,
- o MR reduction and with at least 12 months follow-up in the FMR and DMR populations,

- o Quality-of-life data,
- o Demonstrate cost neutrality compared with TMVr using MitraClip using a cost-minimisation analysis informed by high-quality clinical evidence, and clearly accounting for costs of devices, consumables, procedures and hospital accommodation.

MSAC considered 2-year outcomes for functional outcomes such as overall survival and NYHA class would also be informative for demonstrating non-inferiority. MSAC considered that non-inferiority should be assessed using a more stringent non-inferiority margin than used in the interim CLASP IID trial results. MSAC advised that a claim of unmet clinical need should be supported by evidence demonstrating that TMVr using PASCAL can be used for people unable to undergo TMVr using the current generation of MitraClip, and the financial implications for this additional population.

4. Background

This is the second application for this technology. It was previously considered at the November 2021 MSAC meeting, MSAC 1662 PSD. A successful application for MBS listing for reduction of mitral regurgitation through tissue approximation, using transvenous/transeptal techniques using the MitraClip device, from Abbott Australasia Pty Ltd, was considered at the MSAC Sept 2020 meeting. (MSAC 1192.3 PSD). As a result of this, there are two MBS items for Transcatheter Mitral Valve Repair System (TMVr), by transvenous or transeptal techniques for DMR and FMR with the MitraClip system (MBS items 38461, 38463). The MSAC 1662 application sought to make these MBS items device agnostic.

In respect of application 1662, MSAC did not support amending MBS items 38461 and 38463 for TMVr by transvenous or transeptal techniques using Mitraclip to be device agnostic. MSAC considered the quality of evidence for TMVr using the PASCAL system to be low and did not adequately support the claim of clinical non-inferiority for safety and effectiveness. 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.

Throughout this document, content that was unchanged from MSAC's previous 2021 consideration is shaded in blue.

Table 1   Summary of key matters of concern

Component	Matter of concern	How the current assessment report addresses it
Clinical need	MSAC considered that an unmet clinical need for an alternative device was not clearly demonstrated (p1 of PSD).	The ADAR provided the following in support of the need for an alternative device: • Anecdotal evidence from unnamed clinicians that there are certain MR anatomies that are better suited for treatment with PASCAL (Sections 1.4 & 1.5); • Patient testimonials (Sections 1.4 & 1.5); and • A study from Moonen et al 2022 of 17 patients treated under compassionate use, all who received the PASCAL system, of which it reported that 9 (53%) had technically difficult or anatomically challenging for TMVr procedure.
Clinical management algorithms	MSAC noted there were inconsistencies in the algorithm and the proposed MBS items (p3 of PSD).	The ADAR has replaced the clinical management algorithms with ones based on those used in the MSAC 1192.3 (MitraClip) application, that aligns with the proposed MBS item descriptor.
Quality of the level of evidence presented	MSAC considered 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 (p1 of PSD). MSAC noted that an RCT comparing PASCAL with MitraClip to treat DMR and FMR (CLASP IID/IIF) is actively recruiting, with an estimated primary completion date in 2023 and study completion date in 2028 (p5 of PSD).	The Applicant suggested that, as in the previous ADAR, the best available evidence for the current ADAR comes from the same small feasibility study, CLASP (Szerlip 2021). Additional supportive evidence was presented including a single-arm real-world study (Mauri 2020). The evidence from single-arm studies was organised into "naïve comparisons" with results from the MitraClip single-arm datasets. The concern has not been addressed. In the absence of results from the ongoing head-to-head RCT (CLASP IID/IIF), the current ADAR continues to rely on the same small-size, single-arm observational study (Szerlip, 2021) that was considered to be of low quality and did not adequately support the claim of clinical non inferiority.
Uncertain clinical claim	The clinical claim could not be fully verified. Evidence to support non-inferiority with the MitraClip system relies on an unanchored MAIC *[matched adjusted indirect comparison]*. The MAIC approach is appropriate given the lack of direct evidence, however a key limitation is the assumption that all covariates and prognostic values are accounted for. The unanchored MAIC therefore carries an unknown risk of bias. In its consideration of the previous ADAR, ESC also considered that the lack of transparency regarding the presented MAIC analysis was a source of additional uncertainty.	The Applicant presented a naïve comparison and MAIC, including a discussion of potential prognostic characteristics or treatment effect modifiers. Sensitivity analyses were also presented. Additional supportive evidence is presented, including real-world evidence (Mauri 2020). On balance, the ADAR proposes that PASCAL is non-inferior to MitraClip. Apart from the newly identified non-randomised comparative studies that were not included in the main body of evidence, the level of evidence was not and could not be improved by inclusion of noncomparative results from studies of different designs, conducted in different settings and in heterogenous populations. The unanchored MAIC analysis was essentially unchanged since the presentation of additional calculations in the pre-ESC response for the previous ADAR, and therefore remains open to the previous concerns. However, some discussion of the key limitations relating to the potential bias due to remaining imbalance in covariates and prognostic variables was provided but failed to eliminate the concerns.

MSAC = Medical Services Advisory Committee; PSD = Public Summary Document; TMVr = transcatheter Mitral Valve Repair

5.   Prerequisites to implementation of any funding advice

Items on the Australian Register of Therapeutic Goods (ARTG) that are relevant to this Application are the PASCAL Transcatheter Valve repair System (ARTG no. 342270, 342271, 329680, 329150) and the PASCAL ACE implant System (ARTG no. 371670).

In addition to their professional practice as an interventional cardiologist and imaging cardiologist, clinicians require accreditation by Edwards Lifesciences to use the PASCAL system. This accreditation includes ███ ██ █ ███ █ ███ ██ ███ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██

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6.   Proposal for public funding

The applicant is seeking amendment of the current MBS items for TMVr using the MitraClip system for DMR and FMR (38461 38463) to a device agnostic listing for TMVr. The proposed amendments are presented in Table 2.

Table 2 Presentation of an existing, amended or newly proposed MBS item

Category 3 - Therapeutic Procedures

MBS item 38461
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
Fee: *$1,514.10 (as per July 2022 MBS Schedule)**

MBS item 38463
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 tolerate 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
a service to which this item, or item 38461, applies has not been provided to the patient in the previous 5 years
Fee: *$1,514.10 (as per July 2022 MBS Schedule)**

*ADAR requested a fee of $1490.25

It is proposed that the 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.

The PASCAL system is 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. 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 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.

If MSAC had supported this application, and MBS items 38461 and 38463 become device agnostic, then the PASCAL system will also need to be listed on the Prostheses List. The proposed Prosthesis List benefit for PASCAL is $███ ███ ███ ███ ███ ███ ███ ███ ███ ███ Should MBS items 38461 and 38463 become device agnostic, it would allow for all future similar devices to be used as long as the safety, effectiveness and cost effectiveness had been assessed.

The applicant accepts that the procedure may require more than one device and proposes that they will charge the same device fee per procedure, irrespective of the number of devices used.

7.   Population

The proposed population for TMVr using the PASCAL system was unchanged from MSAC's previous 2021 consideration. The proposed populations align with the two populations already listed for this procedure on the MBS using the MitraClip system (items 38461 and 38462):

1. Patients with degenerative mitral valve (DMR):

- Moderate-severe or severe MR (grade 3+ or 4+)
- LVEF ≥20%
- Symptoms of mild, moderate or severe chronic heart failure (NYHA class II, III, or IV)
- Assessed as having unacceptably high risk for surgical valve replacement by a TMVr case conference

2. Patients with functional mitral valve disease (FMR):

- Moderate-severe or severe MR (grade 3+ or 4+)
- LVEF 20-50%
- LVESD of ≤70 mm
- Symptoms of mild, moderate or severe chronic heart failure (NYHA class II, III, or IV) that persist despite guideline-directed medical therapy
- Assessed as having unacceptably high risk for surgical valve replacement by a TMVr case conference

The population are those patients with mitral regurgitation 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. Primary or degenerative mitral regurgitation (DMR) is caused by a structural abnormality of the mitral valve leaflets and/or valve apparatus. In contrast, secondary or functional mitral regurgitation (FMR) 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.

For each of these populations, in the proposed clinical management of patients with symptomatic, chronic degenerative mitral regurgitation or symptomatic, chronic functional mitral regurgitation with the characteristics described above, then TMVr with PASCAL or MitraClip plus continuing medical management will be available to the specialist to treat the condition.

The ADAR stated that the PASCAL system addresses an unmet clinical need for an alternative device that is better suited to treating complex anatomies. However, the ADAR did not identify a subgroup of patients with an unmet clinical need who could undergo TMVr using PASCAL and are unable to undergo TMVr using MitraClip. Instead, it was noted that the ADAR emphasised the technical advantages of the PASCAL system, particularly for patients with complex anatomies. The commentary considered that a technical comparison of the PASCAL and MitraClip systems would have been useful in this patient population.

The PICO confirmation specific to this application was not required as an updated PICO used for MSAC Application 1192 (MitraClip), considered by PASC in April 2012 was used. The main difference, aside from the intervention, is the comparator which for the MitraClip Application (1192) was surgery or medical management, now the comparator is the MitraClip system.

8. Comparator

The appropriate comparator for the proposed medical service is TMVr using the MitraClip system, as accepted by MSAC in its previous consideration.

9. Summary of public consultation input

Consumer feedback was received from three (3) individuals (specialist) and two organisations (Hearts4Hearts and Abbott Medical Australia Pty Ltd). The input was supportive of the need for TMVr devices for the treatment of severe mitral regurgitation in patients not candidates for surgical interventions and noted that PASCAL system may offer better outcomes than MitraClip and provide access to therapy for patients excluded from MitraClip. The availability of an alternative option for treating these patients was noted as an advantage. An individual considered that PASCAL device can be used in more complex mitral valve anatomies, such as commissural mitral regurgitation and may also offer a more durable result than the MitraClip. Another individual considered the PASCAL system is more manoeuvrable and in challenging transeptal and left atrial anatomies, will provide an advantage over the more rigid MitraClip system. In addition, it was considered that having access to the intervention will allow clinicians the choice to use the device best suited to the patient they're treating. One of the organisations considered that the lack of high-quality randomised controlled data for this intervention was the main disadvantage. Feedback was received regarding the item fee and descriptor, stating that the fee was too low for the complexity of the procedure and that the item should be payable twice within 5 years if agreed by MDT that a progressive development of new mitral regurgitation is amenable to repeat clipping. Feedback noted that the time to perform the procedure is for highly experienced operators and will not apply to most Australian proceduralists.

10. Characteristics of the evidence base

In the previous 2021 consideration, MSAC did not support MSAC application 1662 and considered that the quality of evidence was low and did not adequately support the clinical claim of non-inferiority.

The current ADAR sought to address these concerns by presenting the best available evidence in the form of single-arm datasets. The identified non-randomised comparative evidence was not included

in the main body of the current ADAR but was elevated for inclusion by the commentary on the basis of the hierarchy of evidence.

The key features of the studies included in the current ADAR are provided in Table 3.

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

Trial/Study (whether new to the 1662.1ADAR)	N	Design/ Observation timepoints	Risk of bias	Patient population	Key outcome(s)
Single-arm noncomparative datasets included in the main body of evidence					
CLASP (the same study used in MAIC in the previous ADAR)	124	Multicentre, prospective, single-arm, observational study 30 days and 12 and 24 months	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(the MitraClip arm was used in MAIC in the previous ADAR)	614	RCT, MC, MN, OL 30 days and 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	PRIMARY ENDPOINTS: HF hospitalisation freedom from device-related complications; Mortality, Major complications; MR severity, NYHA functional class of I or II; Change in KCCQ score from baseline
EVEREST II (the MitraClip arm was used in MAIC in the previous ADAR)	279	RCT, OL, MC 30 days, 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
Mauri 2020 (identified, but excluded from the previous ADAR)	309	A multicentre, retrospective, single-arm, observational study 30 days,	High	Patients with at least moderate-severe symptomatic MR (≥ grade 3+), at high surgical risk or ineligible for surgical intervention. In a real-world study there were no pre-specified inclusion/exclusion criteria. Characteristics of patients were not reported by DMR/FMR: 48% had LVEF≤50%; mean LVESD = 44mm (SD=13), NYHA functional class was II or greater	PRIMARY ENDPOINTS: Technical success; MR severity at discharge; OTHER ENDPOINTS: MR severity and device success at 30 days, freedom from mortality; clinical success; 6-min walk distance; NYHA functional class SAFETY: MAE (all-cause mortality, stroke, cardiac-structural complication due to access-related issues, acute kidney injury requiring new renal replacement therapy, and severe bleeding) at 30-day follow-up
Mack 2022 (new evidence)	10,460	STS/ACC TVTR – registry 30 days	High	Results from 2019 MitraClip TMVr procedures. Characteristics of patients were not reported by DMR/FMR: LVEF -NR; LVESD- NR, NYHA majority (97%) had II or greater	At 30 days mortality, stroke, mitral valve reintervention, bleeding, acute kidney injury, NYHA functional class, MR severity, and quality of life (12-Item Kansas City Cardiomyopathy Questionnaire (KCCQ-12). Overall survival to 1-year

Trial/Study (whether new to the 1662.1ADAR)	N	Design/ Observation timepoints	Risk of bias	Patient population	Key outcome(s)
Direct non-randomised comparative studies *(added to the main body of evidence by the evaluators)*					
Haschemi 2022 (new evidence)	PASCAL (102); MitraClip (112)	Quasi-randomised Prospective cohort study At discharge 30 days	Low-Medium [a]	Patients with at least moderate-severe symptomatic MR (≥ grade 3+), at high surgical risk or ineligible for surgical intervention. Characteristics of patients were not reported by DMR/FMR: LVEF; LVESD were similar; NYHA functional class was > II in 81% PASCAL and 79% MitraClip patients.	SAFETY: Adverse events EFFICACY: Residual MR, NYHA functional class (30 days), technical success, device success, procedural success
Geis 2022 (new evidence)	PASCAL (41) MitraClip (82)	1:2 Propensity-score matched[c] retrospective cohort study; At discharge At the follow up Short-term (1-4 months) Long-term (6-18 months)	Medium	Patients with at least moderate-severe symptomatic MR (≥ grade 3+), at high surgical risk or ineligible for surgical intervention. In a real-world study there were no pre-specified inclusion/exclusion criteria. Characteristics of patients were not reported by DMR/FMR: 17% in either arm had LVEF<20%; mean LVESD = 44mm; NYHA functional class II or greater was in 88% in both arms	SAFETY: Composite of death, HF rehospitalisation, MV reintervention EFFICACY[b]: Technical success, device success, procedural success, MR severity, NYHA functional class
Additional studies presented in the pre-ESC response *(not evaluated)*					
Lim 2022 (New evidence)	PASCAL (117) MitraClip (63)	Interim results from the CLASP IID RCT. Follow up at discharge, 30 days, 6 months.	Not assessed	Patients with clinically significant symptomatic DMR (≥ grade 3+) deemed ineligible for surgical intervention.	SAFETY: Adverse events at 30 days, 6 months, mortality, HF hospitalisation EFFICACY: MR severity ≤2+ at 30 days, 6 months, NYHA functional class at 6 months, functional capacity and QoL
CLASP IID registry (new evidence)	PASCAL (98)	MC, MN prospective single-arm registry. Follow-up 30 days, 6 months	Not assessed	Age ≥18 years Prohibitive risk for mitral valve surgery Candidate for M-TEER with the PASCAL system but not for MitraClip Degenerative mitral regurgitation (3+ to 4+) Suitable valve and regurgitant jet morphology LVEF ≥20%, LVEDD ≤80 mm	SAFETY: Adverse events at 30 days, 6 months, mortality, HF hospitalisation EFFICACY: MR severity ≤2+ at 30 days, 6 months, NYHA functional class at 6 months, functional capacity and QoL

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; STS/ACC TVTR= The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry;; NYHA=New York Heart Association; 6MWD= Six-Minute Walk Distance

[a] Independently assessed by evaluators using the Cochrane Risk of Bias In Non-Randomised Studies- of Interventions (ROBINS-I) tool; There were insufficient details in the "research correspondence" to assign low level of bias with confidence

[b] Technical, procedural and clinical success all defined by Mitral Valve Academic Research Consortium (MVARC) criteria in Stone et al. (2015)

[c] Matching was performed using a statistical algorithm and was based on age, gender, NYHA class, LVEF, MR aetiology, flail width, flail gap, posterior leaflet length, coaptation length and depth, MV mean pressure gradient (MPG), medical history (diabetes, hypertension, and coronary artery disease), and some laboratory findings

Content that was unchanged from MSAC's previous 2021 consideration is shaded in blue.

The matched adjusted indirect comparison (MAIC) of the outcomes from a single-arm study of PASCAL TMVr (CLASP) and the MitraClip arms of two comparative trials (COAPT and EVEREST-II) that formed the core evidence in the previous ADAR was replicated in the current ADAR. The same patient characteristics were used for matching and results were mostly unchanged from the previous ADAR.

The current ADAR reformatted the same evidence already utilised in the MAIC and complemented it with additional observational data. The primary sources of evidence presented in the current ADAR consisted of two single-arm studies for PASCAL (CLASP and Mauri 2020), the MitraClip arms from two RCTs (COAPT and EVEREST-II) and data from the STS/ACC TVT Registry for MitraClip (Mack 2022). Results of these five observational datasets were presented in the form of "naïve comparisons".

The commentary considered that it is not clear why non-comparative evidence was given a higher priority than the evidence from the direct, albeit non-randomised comparative clinical studies (Geis 2022, Haschemi, 2022) that were presented in Appendix D of the ADAR. The commentary conducted an independent quality assessment of these comparative clinical studies and assessed results from the two studies as having a low to medium level of bias (Geis 2022, Haschemi, 2022).

Assessment of comparative analyses of PASCAL and MitraClip TMVr systems

Non-randomised comparative studies

Clinical endpoints used in the comparative studies were defined according to the Mitral Valve Academic Research Consortium[4] (MVARC) and assumed to be comparable across the studies. The commentary considered there was insufficient data to decide whether technical, procedural or device success was measured according to the same criteria. Procedural success was measured at discharge in both studies, in Geis (2022), device success was also assessed at discharge, and it is not clear at which timepoint the device success was assessed in Haschemi (2022). The follow-up appointments in Geis (2022) were frequently performed by the referring specialist in private practice. The time frame for a short follow-up was between 30 days and 4 months and a long follow-up between 6 and 18 months after device implantation. Pooling clinical results of interest for a meta-analysis was prevented by the variation in the timeframe for assessment of the outcomes. None of the studies declared non-inferiority as a null hypothesis, nor estimated a sample size that would be sufficient to demonstrate it. However, the design of both studies included controlling for baseline differences in the intervention and comparator arms. Geis (2022) used propensity score matching, while allocation of patients to the TMVr device in Haschemi (2022) was considered quasi-random, since each patient was assigned to the next available implantation date with weekly alternating time slots for PASCAL and MitraClip and treating physicians had no influence on scheduling or system selection.

In the mixed DMR/FMR population in the study by Haschemi (2022) the 4th quarter of the interquartile range of left ventricular ejection fraction and left ventricular end systolic diameter exceeded the limits indicated in the MBS Item 38463 (for the secondary/FMR subgroup) but not the limits indicated in the MBS Item 38461 (for the primary/DMR subgroup). These parameters are not reported separately for each of the DMR and FMR subgroups, so it is not certain whether the entire population enrolled in the study meets the MBS item eligibility criteria.

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[4] Stone GW, et al. (2015). Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: A consensus document from the Mitral Valve Academic Research Consortium. *European Heart Journal,* 36(29): 1878-1891.

In the Geis (2022) study 17% of patients in either arm had LVEF<20% thus not meeting eligibility criteria for the MBS items 38461 and 38463. There were significantly more patients presenting with previous cardiac surgery in the MitraClip group and significantly more patients suffering from malignancies in the PASCAL group at baseline. Assessed with EuroSCORE II, the patients in the MitraClip arm had a more serious surgical risk (borderline p value of 0.0502). In addition, the PASCAL group had a slightly larger MV area and mitral annulus AP diameter.

Another concern about the Geis (2022) study highlighted in the commentary was the large proportion of patients lost to follow-up (other than dying or having left ventricular assist device implantations or MV re-interventions), which was three times the rate in the PASCAL arm compared to the MitraClip arm and not explained further. 46% (19/41) were lost to follow up in the PASCAL arm by the time of the first follow-up (that took place over the various time intervals ranging from one to four months) and 68% (28/41) by the second follow-up (6-18 months since the procedure). In the MitraClip arm, loss to the follow-up was 13% (11/82) by the first follow-up reaching 23% (19/82). Within-group variability in the number of days passed until the first and the second follow-up makes the interpretation of comparative outcomes problematic (due to time-varying confounding). Notably, the difference in the number of days passed until the first follow-up was borderline statistically significant (p=0.0533).

The matched adjusted indirect comparison (MAIC)

Individual patient level data (PLD) were available for CLASP, while only aggregate data were available for the comparator studies (COAPT and EVEREST-II). A MAIC was considered as an appropriate method of analysis for comparisons of the outcomes. To minimise a potential bias, the MAIC used an algorithm to calculate weights to apply to the CLASP PLD in ▮▮ patients (▮▮ (▮▮%) with FMR and ▮▮ (▮▮%) with DMR) in order to match the characteristics of the FMR population from the MitraClip arm of COAPT (N=302) and the mixed DMR/FMR population from EVEREST-II (N=184).

The same baseline characteristics were used for matching in the previous and current ADARs. For

the FMR population, in the base-case analysis these were MI, COPD, CVA/TIA, NYHA class, and LVEF for the comparison of the CLASP (PASCAL) to COAPT (MitraClip). STS scores were added to the list in the sensitivity analysis.

For the mixed population in the base-case analysis baseline characteristics for matching were FMR, Diabetes, MI, COPD, NYHA class, and LVEF for the comparison of CLASP (PASCAL) to EVEREST-II (MitraClip). A single parameter of FMR was used in the sensitivity analysis.

Given the similarity in the approach to the MAIC in the previous and current ADARs, the commentary considered the following limitations remained:

1. The absence of a common comparator arm was an important limitation of the unanchored MAIC because validation of the matching is not possible compared with an anchored MAIC where outcomes from common comparator arms (e.g., placebo) can be used to validate the matching process (Signorovitch, 2010). The matching of baseline characteristics for MAIC in the ADAR relied on the input from clinicians who rated the importance of different baseline characteristics for which data was available from both studies. This does not necessarily mean that the characteristics chosen for matching are considered effect modifiers or prognostic factors. It is also unclear how any remaining differences in the unmatched baseline characteristics would affect outcomes.

2. The MAIC approach was 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 meet except in a well-controlled RCT and the unanchored MAIC estimate therefore carries and unknown amount of bias.

In particular, in the base-case MAIC, MR severity and STS scores were not balanced between the CLASP (weighted) population and the population from COAPT. This equally applies to the current ADAR. It was suggested that one or both of these parameters could be treatment effect modifiers or prognostic variables and needed to be controlled for in statistical analyses.

The current ADAR stated that since sensitivity analyses included STS score in the match, the imbalance in STS baseline characteristic is addressed. This, however, reduced an effective sample size [ESS] to 45.2.

The ADAR also referred to clinical experts who did not include ▇▇ ▇▇ in the list of key characteristics for matching. The ADAR argues that ▇▇ ▇▇ at baseline was "similar" between the two study populations (▇▇ ▇▇ ▇▇ ▇▇ ▇▇ ▇▇ ▇▇ ▇▇ ▇▇ ▇▇ ▇▇ ▇▇). There was no evidence to support this opinion and it could be equally argued that the difference of ▇▇ ▇▇ ▇▇ ▇▇ ▇▇ ▇▇ that favours PASCAL may bias the MAIC results, especially if ▇▇ ▇▇ could be a treatment effect modifier.

To deal with this concern, the current ADAR conducted a statistical test of association between ▇▇ ▇▇ and major adverse events using two alternative values for MAEs, with and without occurrences of ▇▇ ▇▇. In the FMR population, the degree of association (Cramér's V) reduced from "moderate" (0.3-0.5) to little (0.084) when a comparable MAE definition was used. However, in the mixed population, a moderate degree of association remained Cramér's V = 0.31.

One additional MAIC identified in the current ADAR was also undertaken in the context of addressing the persistent baseline imbalances. The current ADAR made a modification to the data by "pragmatically pooling the efficacy results for MR severity to include ▇▇ ▇▇ ▇▇ ▇▇ as a single group". The commentary considered that it is not clear how this change would address the baseline differences as no patients had a ▇▇ ▇▇ ▇▇ ▇▇ ▇▇ ▇▇ at baseline. However, reducing the number of categories would affect the correlation coefficient, potentially bringing it to the desired "little or no association".

11. Comparative safety

Unchanged from the previous ADAR, the current ADAR reaffirmed the clinical claim that the PASCAL system is non-inferior in safety and efficacy compared with the MitraClip system. For this purpose, the current ADAR provided some new evidence, and altered, to some degree, the presentation of the evidence considered in the previous ADAR. The structure of the results in the ESC report are organised, firstly, by study design according to the hierarchy of evidence, starting with the recently published direct comparative evidence, followed by the MAIC results (essentially the same as in the previous ADAR) and concluding with "naïve comparisons" of the outcomes extracted from the single-arm studies. Secondly, for each study design, the evidence is presented by the type of MR (where possible). To facilitate navigation through the multiple pieces of evidence, Table 4 was designed to serve as a "road map" for the results. Nevertheless, navigation through the numerous outcomes collected at the different observational timepoints with respect to two population subgroups and subjected to the different methods of analysis and result presentation add complexity.

Table 4   Structure of the evidence presentation

Study design/type of analysis	Whether new to MSAC1662.1	New evidence included in the 1662.1 ADAR	Evidence assessed and included in ES	Comments
Non-randomised comparative trials in the mixed DMR/FMR subgroup	Yes	Two full-text studies (Geis 2022, Gerçek 2021) and a research letter (Haschemi, 2022)[1] were newly presented in the current ADAR	Evaluators conducted an independent quality assessment[2] and excluded Gerçek (2021) as associated with severe degree of bias	Includes only mixed DMR/FMR subgroup
MAIC (base-case and sensitivity analyses). All outcomes essentially remained as in the previous ADAR	No [3]	None. The current ADAR relied on the same small-size, single-arm feasibility study (Szerlip, 2021) and the unanchored MAIC that carries an unknown risk of bias	MAIC safety and effectiveness results from the previous ADAR were replicated in the current ADAR. There were non-essential variations in aggregating the categories of MR severity	FMR and DMR/FMR subgroups
MAIC (base-case) MR severity	Yes	MR severity in grades 0 and 1+ were pooled in a single (0-1+) MR severity category. Results of logistic regression analyses comparing CLASP (weighted) with COAPT have lost statistical significance, which appears to be the only objective of the additional MAIC exercise.	Pooling grades 0 and 1+ in a single (0-1+) MR severity category was meant to address a potential bias from the persistent baseline imbalances in MR severity and STS risk scores in the CLASP (weighted) and COAPT populations.	Only a base-case analysis was conducted and only in relation to FMR subgroup
MAIC (base-case) NYHA class I or II aggregated in a single category	Yes	In the previous ADAR only 12 month NYHA class outcomes were reported for DMR/FMR subgroup. These were replaced with 24 month outcomes in the current ADAR.	Additional MAIC analyses were undertaken for the 24 month NYHA class I and II in DMR/FMR subgroup. For FMR subgroup MAIC for 24 months was also added for the current ADAR (see NYHA results)	FMR and DMR/FMR subgroups Only base-case analyses were undertaken
Naïve comparisons of outcomes observed in single-arm datasets	Yes	Study by Mauri (2020) was previously identified, but excluded from the previous ADAR. 2019 data from the MitraClip STS/ACC TVT registry (Mack 2022) is the newly identified evidence	A naïve comparison of single-arm results from PASCAL (CLASP and Mauri 2020) and MitraClip arms in COAPT and EVEREST-II RCTs that were complemented with the data from the MitraClip STS/ACC TVT registry (Mack 2022)	FMR and DMR/FMR subgroups

ES=Executive Summary; DMR/FMR=Degenerative/Functional mitral regurgitation; MR=mitral regurgitation; STS=Society of Thoracic Surgeons
[1]These studies were included in Appendix D of the 1662.1 ADAR; the decision to elevate the comparative studies was made by the evaluators
[2]Two evaluators independently conducted a bias assessment using the Cochrane ROBINS-I tool for non-randomised studies;
[3]The inputs (patients' characteristics used for matching) did not change since the additional results were presented in the pre-ESC response
Content that was unchanged from MSAC's previous 2021 consideration is shaded in blue.

Comparative studies in the mixed DMR/FMR population

Table 5 shows the safety results (ITT analysis) from included non-randomised studies of Geis (2022), and Haschemi (2022).

Table 5 Safety results (ITT analysis) from the comparative studies

Study	Endpoint	Time point	PASCAL	MitraClip	p-value
Haschemi 2022	Single leaflet device attachment	at discharge	1% (1/102)	0.9% (1/112)	0.94*
	Stroke		1% (1/102)	0%	0.2899*
	Pericardial tamponade after transseptal puncture		0%	0.9% (1/112)	0.3380*
	Mortality	In-hospital	0.9%	0.9%	0.947
		30-day	2%	2%	0.947
Geis 2022	In-hospital mortality	at discharge	0% (0/41)	6.1% (5/82)	0.1682
	Cerebrovascular accident		0% (0/41)	2.44% (2/82)	0.5519
	Severe bleeding**		0% (0/41)	2.44% (2/82)	0.5519
	Death, HF rehospitalisation, mitral valve reintervention	1-4 months (median 50-58 days)	14.63% (6/41)	23.17% (19/82)	0.3447
	Mortality		7.32% (3/41)	8.54% (7/82)	1.00
	HF hospitalisation		9.76% (4/41)	15.85% (13/82)	0.4188
	Mitral valve reintervention		0% (0/41)	3.66% (3/82)	0.5501
	Death, HF rehospitalisation, mitral valve reintervention	6-18 months (median 360 days)	34.15% (14/41)	42.68% (35/82)	0.4361
	Mortality		19.51% (8/41)	15.85% (13/82)	0.6189
	HF hospitalisation		14.63% (6/41)	30.49% (25/82)	0.0774
	Mitral valve reintervention		2.44% (1/41)	6.1% (5/82)	0.6625

HF= heart failure;
*   Calculated by evaluators;
**   Major, extensive, life-threatening, or fatal bleeding;
Source: Haschemi (2022); Geis (2022);

Notwithstanding insufficient reporting in Haschemi (2022) that precluded detailed assessment of allocation of patients to PASCAL or MitraClip devices, no statistically significant differences in any of the safety outcomes were observed between PASCAL and MitraClip. Both single leaflet attachments were fixed with a second device and there was no difference in either in-hospital or the 30-day mortality that was 0.9% and 2% respectively in both groups (P=0.947). In the Geis (2022) retrospectively matched cohort study, five out of 82 patients (6.1%) in the MitraClip group died before hospital discharge. This included a death during the procedure. In the PASCAL group, no patients died during hospital stay. The difference in in-hospital mortality was not statistically significant (P = 0.1682), but since neither a non-inferiority margin nor the corresponding sample size estimation were provided, it is not clear how reliable this statistic is and to what degree it could be attributed to the baseline differences between the groups.

Randomised trials in the DMR population (not evaluated)

At the time of the ADAR submission there was one ongoing RCT comparing PASCAL and MitraClip in DMR patients, the CLASP IID study. The CLASP IID study is a randomised, open label study comparing the PASCAL system with the MitraClip system in patients with DMR. Patients with DMR severity 3+ or 4+ who had prohibitive surgical risk were randomised 2:1 and treated with either PASCAL or MitraClip. In their pre-ESC response, the applicant presented preliminary results from a

pre-specified interim analysis of 180 patients[5]. The primary safety endpoint is a composite MAE comprising of cardiovascular mortality, stroke, myocardial infarction, need for new renal replacement therapy, severe bleeding, and non-elective mitral valve re-intervention (either percutaneous or surgical). Composite and component MAE at 30 days are shown in Table 6. These are the same MAEs used for the CLASP study. For the difference in composite MAE, the upper bound of the 95% CI for the point estimate of difference was within the prespecified noninferiority margin of 15%. A summary of survival outcomes at 30 days and 6 months is Shown in Table 7. No statistically significant differences in survival outcomes between PASCAL and MitraClip were found at 6 months except for cardiovascular mortality.

Major adverse events at 30 days in the DMR population (not evaluated)

Table 6 Major adverse events at 30 days in the DMR population (CLASP IID)

Outcome	PASCAL, % (n) N=117#	MitraClip, % (n) N=63	Difference, % (95%CI)
Cardiovascular mortality	0.9 (1)	1.6 (1)	NR
Stroke	0.0 (0)	0.0 (0)	NR
Myocardial Infarction	0.0 (0)	0.0 (0)	NR
New need for renal replacement therapy	0.0 (0)	0.0 (0)	NR
Non-elective mitral valve re-intervention (percutaneous or surgical)	0.9 (1)	0.0 (0)	NR
Severe bleeding	2.6 (3)	3.2 (2)	NR
Composite MAE at 30-days	3.4 (4)	4.8 (3)	-1.3 (5.1)^

#One patient withdrew prior to 30-day follow-up without an MAE.
^ one-sided 95% CI upper bound limit

Overall survival in the DMR population (not evaluated)

Table 7 Summary of survival outcomes in CLASP IID (DMR population, CLASP IID)

	PASCAL (N=117) mean (±SE)			MitraClip (N=63)			Difference	P-value
Freedom from:	30-day	6-month	mean change (SD)	30-day	6-month	mean change (SD)	Mean difference (95% CI)	6-month intergroup
All-cause mortality	98.3 (1.2)	94.9 (2.0)	NR	98.4 (1.6)	93.7 (3.1)	NR	NR	0.737
HFH	100 (0.0)	98.3 (1.2)	NR	98.4 (1.6)	96.8 (2.2)	NR	NR	0.524
Cardiovascular mortality	99.1 (0.9)	99.1 (0.9)	NR	98.4 (1.6)	93.7 (3.1)	NR	NR	**0.035**
MAE	96.6 (1.7)	93.9 (2.2)	NR	95.2 (2.7)	88.9 (4.0)	NR	NR	0.231

NR: Not Reported, HFH: Heart Failure Hospitalization. Source: Pre-ESC response by Applicant, Lim (2022)

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[5] Lim D, Smith R, Gillam L, et al. Randomized Comparison of Transcatheter Edge-to-Edge Repair for Degenerative Mitral Regurgitation in Prohibitive Surgical Risk Patients. *J Am Coll Cardiol Intv.* Sep 17, 2022 https://doi.org/10.1016/j.jcin.2022.09.005

MAIC of the safety outcomes

Safety outcomes used in the MAIC analyses included overall survival (OS) and MAEs at 30 days. Unanchored MAIC analyses of overall survival and MAEs included both the results of the base-case and sensitivity matching. In the pre-ESC response, the results presented in the previous ADAR were updated according to the "reconstructed" definition of MAE in the CLASP study. Only these MAE results are included below.

Overall survival in the FMR population (CLASP vs COAPT)

The Kaplan-Meier (K-M) curves for overall survival (OS) to 24 months in the CLASP and COAPT studies remain unchanged from the previous ADAR and are presented in Figure 1 and Figure 2.

The MAIC estimated that overall survival at 24 months for TMVr using PASCAL (CLASP and CLASP weighted) at approximately 90%. This was much higher than the reported overall survival of 72.3% for the FMR subpopulation in the CLASP study. Although it is reasonable to expect that population matching would impact on the survival estimate, the difference of survival improving by almost 18% is a substantial change that should be explained. Additionally, although the number of patients at risk for CLASP at zero months was consistent with the FMR subpopulation (n=85), the numbers of patients at risk 12 (n=57 vs n=64) and 24 months (n=20 vs n=29) differed from the FMR subpopulation (Figure 2). Additionally, the K-M curves for CLASP (Figure 1) remains fixed at just under 90% from the 12th month through the 24th month and beyond in the MAIC. However, the number of patients at risk in the first (coloured in red) decline from 57 at 12th month to 20 at the 24th month.

Figure 1 K-M overall survival in CLASP original numbers at risk; weighted numbers for MAIC and COAPT original numbers at risk (base case)
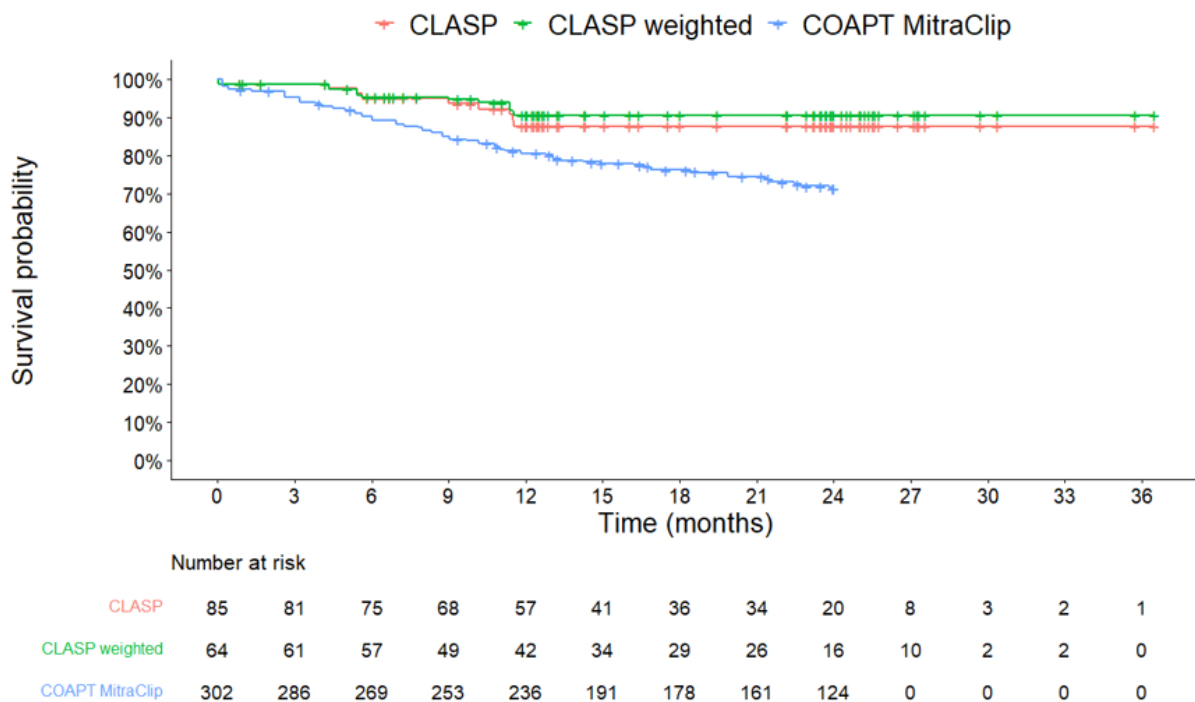
Source: ADAR

Figure 2 Kaplan-Meier curve of overall survival to 24 months in the CLASP study

Redacted[6]

Table 8 replicates the hazard ratios as reported in the previous ADAR, indicating that those treated with the PASCAL system had better overall survival compared with the MitraClip population, which was statistically significant based on the 95% CI values.

Table 8 OS hazard ratios with 95% CI's for the comparison of CLASP (PASCAL) with COAPT (MitraClip)

Matching	Method	Hazard ratio (95% CI) *As in the previous ADAR*
Base case (MI, COPD, CVA/TIA, NYHA class, and LVEF)	Unadjusted Cox model	0.44 (0.22 to 0.88)
	Weighted Cox model	0.33 (0.15 to 0.76)
Sensitivity analysis (as above + STS score)	Unadjusted Cox model	0.44 (0.22 to 0.88)
	Weighted Cox model	0.40 (0.16 to 0.98)

CI=confidence interval; OS=overall survival
Source: Table 2-29 and Table 2-30 of the 1662.1 ADAR; Table 4 PSD
Cells shaded in blue represent results previously considered by MSAC

Major adverse events (MAEs) at 30 days in the FMR population (CLASP vs COAPT)

Table 9 shows 30-day MAE rates and results of logistic regression analyses in the FMR population matched by the selected baseline characteristics. Both base-case and sensitivity analyses were using the reconstructed MAE outcomes. These results remain unchanged from the previous ADAR.

Table 9 MAIC of reconstructed MAEs* in CLASP and COAPT at 30-days

Outcome	CLASP (weighted)	COAPT	OR (95% CI)
MAE at 30-days (base case)	2.91%	2.98%	0.98 (0.20, 4.87)
MAE at 30-days (sensitivity)	3.54%	2.98%	1.19 (0.22, 6.43)

CI=confidence interval; MAE=major adverse event; MAIC, matching adjusted indirect comparison; OR, odds ratio
Source: Table 2-24; Attachment 2.4 – Additional MAIC analyses; Table 6 PSD
*"reconstructed" MAE outcome in CLASP included all-cause mortality, stroke, myocardial infarction, and reintervention for study device-related complications and was compared against the secondary endpoint from the COAPT study: "death from any cause, stroke, myocardial infarction, and nonelective cardiovascular surgery for a device-related complication".
Cells shaded in blue represent results previously considered by MSAC

PASCAL patients had slightly lower odds of experiencing an MAE at 30 days in the base-case (2.91% vs 2.98% in MitraClip), however the difference was not significant (OR, 0.98; 95% CI, 0.20 – 4.87). In contrast, in the sensitivity analysis, where STS scores were included in the match, the odds of experiencing an MAE at 30 days were higher in PASCAL patients but the difference remained non-significant (OR, 1.19; 95% CI, 0.22 – 6.43). Change of direction likely confirms the assumption that STS score is likely to be a covariate that needs to be controlled for.

Overall survival in the mixed population (CLASP vs EVEREST-II)

The Kaplan-Meier (K-M) curves for overall survival to 36 months in the CLASP and EVEREST-II remain unchanged from the previous ADAR and are presented in Figure 3. The difference between the

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[6] Figure 2 adapted from Szerlip *et al.,* 2-Year Outcomes for Transcatheter Repair in Patients With Mitral Regurgitation From the CLASP Study. JACC Cardiovasc Interv. 2021 Jul 26;14(14):1538-1548. doi: 10.1016/j.jcin.2021.04.001

survival curves in the base-case and sensitivity analyses were minor and unlikely to change decision-making on the graphs, so the K-M for the sensitivity analysis is not replicated here.

Figure 3 K-M overall survival in CLASP original numbers at risk; weighted numbers for MAIC; EVEREST-II original numbers at risk (base case)
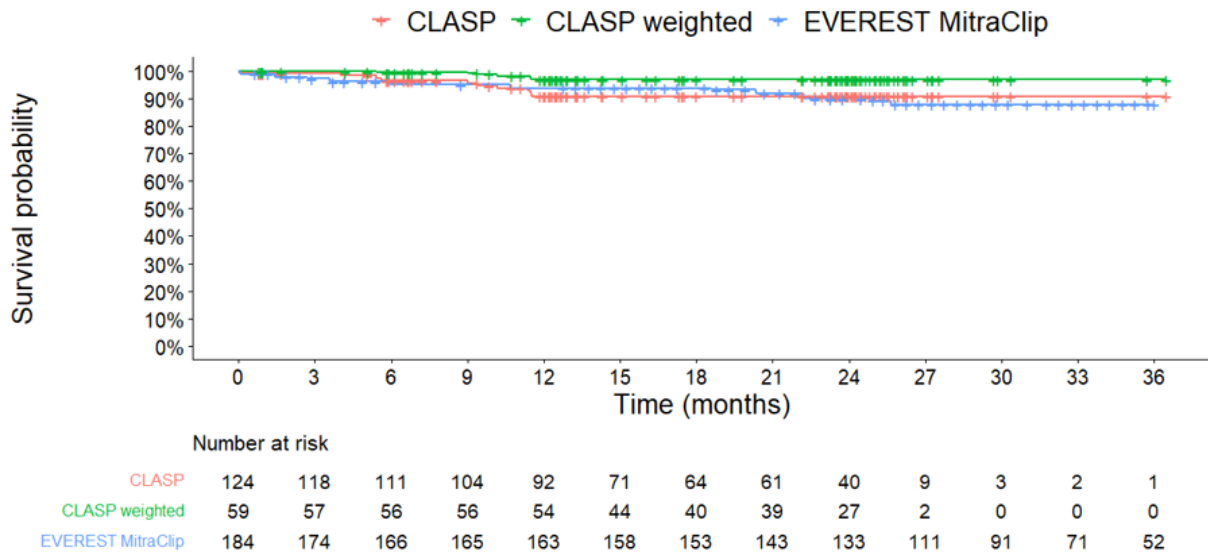
Source: ADAR

The same concern, as in relation to the FMR population (Figure 1), applies to the mixed population. A simple visual examination of the above graph demonstrates that the K-M curve for CLASP remain fixed at just under 90% from the 12th month through the 24th month and beyond. This despite the first row of CLASP numbers at risk (unadjusted numbers) that decline from 92 at the 12th month to 40 at the 24th month. However, unlike in the FMR population where "a clear separation of the survival curves evident in the graph", the EVEREST-II survival curves are very similar to both the adjusted or unadjusted survival curves in CLASP.

Table 10 presents the hazard ratios for overall survival in the mixed FMR/DMR population (unchanged from the previous ADAR). The results suggest that while there is a statistically significant difference in survival between the two treatments in the base-case analysis, it disappears in the sensitivity analysis in which populations were matched on FMR only. Removing the Diabetes, MI, COPD, NYHA class, LVEF produced a different conclusion. This suggests the importance of FMR/DMR split in the population, may also indicate that one or more of the baseline characteristics selected for matching is a prognostic variable. Unlike conventional statistical modelling, MAIC by its very nature does not extend to examination of the interaction between the parameters to explore this hypothesis.

Table 10 OS hazard ratios with 95% CI's for the comparison of CLASP (PASCAL) with MitraClip (EVEREST-II)

Matching	Method	Hazard ratio (95% CI) *As in the original ADAR*
Base case (FMR, Diabetes, MI, COPD, NYHA class,LVEF)	Unadjusted Cox model	0.94 (0.43 to 2.02)
	Weighted Cox model	0.31 (0.11 to 0.85)
Sensitivity analysis (FMR only)	Unadjusted Cox model	0.94 (0.43 to 2.02)
	Weighted Cox model	0.52 (0.20 to 1.38)

CI=confidence interval; FMR=functional mitral regurgitation;
Source: Table 2-31 and Table 2-32 of the 1662.1 ADAR; Table 4 in PSD
Cells shaded in blue represent results previously considered by MSAC

The commentary to the previous ADAR noted the inconsistency in the approach to sensitivity analyses across the populations. When discussing the sensitivity analysis of overall survival, the ADAR referred to this as 'adjusting the CLASP population to better match the EVEREST-II (MitraClip) population' but [the mixed] population is matched on FMR status only so many more characteristics become dissimilar than in the base case scenario.

Unchanged from the previous ADAR, the survival analyses data presented had some inconsistencies which could not be checked and, in the absence of a common comparator, the results could not be validated. In addition, in relation to the EVEREST-II study, the baseline characteristics and outcomes were not reported separately by the type of MR. This affected the applicability of the MAIC results to the MBS items 38461 and 38463 eligibility criteria.

Major adverse events at 30 days in the DMR/FMR population (CLASP vs EVEREST-II)

The observed MAE rate in CLASP and EVEREST-II studies were 8.1% and 15% respectively. This is largely because of the incomparability in the MAE definitions between the studies. Unchanged from the previous 2021 MSAC consideration, the reconstructed EVEREST II MAE definition excluded transfusions for the purposes of comparing results in DMR/FMR mixed population. This makes the MAE outcomes from the MAIC result incomparable with results of the naïve comparisons. Notably, transfusions comprised the largest single component of the MAEs at 30 days in the EVEREST-II MitraClip population.

Both studies included serious bleeding in the MAEs, which is defined as major, extensive or life-threatening bleeding, according to the MVARC. However, in the CLASP study the least severe of these categories (major bleeding) was defined as either a drop in haemoglobin level of ≥3 g/dL or requiring transfusion of ≥3 units of whole blood or packed red blood cells and does not meet criteria of extensive or life-threatening bleeding. In comparison, the EVEREST-II definition of bleeding includes all patients who required a transfusion of ≥2 units of blood. The difference in criteria for major bleeding biases the MAE outcome in favour of CLASP. In the pre-ESC response to the previous ADAR, the applicant performed additional MAIC analyses with the transfusion events excluded from the MAE count in the EVEREST-II population. Events of severe bleeding observed in the CLASP study were retained, which may bias the MAE outcome in favour of MitraClip. Results of the MAIC using the reconstructed definition of MAE are presented in Table 11, which corresponds to Table 7 and Table 8 in the MSAC 1662 PSD.

Table 11 MAIC of reconstructed MAEs between CLASP and EVEREST-II at 30-days

Outcome	CLASP (weighted)	EVEREST-II	OR (95% CI)
MAE at 30-days (base case)	4.38%	5%	0.87 (0.21, 3.58)
MAE at 30-days (sensitivity)	4.73%	5%	0.94 (0.28, 3.13)

CI=confidence interval; MAE=major adverse event; MAIC=matching adjusted indirect comparison; OR=odds ratio
Source: Table 2-27, Attachment 2.4 – Additional MAIC analyses
Cells shaded in blue represent results previously considered by MSAC

With reconstructed MAE definition, the difference in MAE rates between PASCAL and MitraClip patients was no longer statistically significant.

Single-arm studies (Naïve comparisons)

The current ADAR complimented the MAIC analyses with a naïve single-arm comparison of results for PASCAL (CLASP and Mauri 2020) and MitraClip (the TMVr arms in COAPT and EVEREST-II trials). The MitraClip results from the registry (Mack 2022) were also included. The Mauri (2020) and Mack (2022) studies were not assessed for quality, and although the baseline patient characteristics were extracted (Appendix B) there was no attempt to assess the eligibility of the study populations for the MBS items 38461 or 38463 or to compare their populations with the populations from other trials in the main body of the evidence. Nevertheless, the single-arm results (rather than results of non-randomised comparative studies) appear to be the main basis for the clinical claim of noninferiority of PASCAL in terms of both safety and efficacy to the MitraClip device.

CLASP study results were presented for the entire study population and also separately by the FMR and DMR subgroups. The FMR subgroup of the CLASP trial could be compared with the COAPT population that included only FMR patients. The results for the mixed FMR and DMR population in EVEREST-II, Mauri, (2020) and Mack, (2022) were not disaggregated making any meaningful comparison difficult. Regardless of insufficient reporting, the informative value of naïve comparisons for decision making is limited because of the degree of potential bias associated with outcomes assembled across heterogenous populations, settings and study designs. Given inherent uncertainties of non-comparative results only selected summary tables are presented.

Overall survival

As in the previous ADAR, the safety outcomes included in the current ADAR were overall survival, major adverse events (MAEs), stroke and myocardial infarction (MI) observed by 30 days.

A naïve comparison of overall survival in the CLASP, COAPT and EVEREST-II studies is presented in Table 12 (FMR) and Table 13 (mixed populations). At 12 months, PASCAL patients from the FMR subgroup in CLASP had a higher rate of overall survival than patients treated with MitraClip in COAPT; the survival rates between PASCAL and MitraClip were similar at 24 months. The naïve comparison does not explain to what degree the overall survival difference in favour of PASCAL at 12 months can be explained by the baseline differences in patient characteristics (i.e. MitraClip patients being of poorer health).

Table 12 Naïve comparison of overall survival in PASCAL and MitraClip studies (FMR population)

Safety event	CLASP (PASCAL) FMR (N=85)	COAPT (MitraClip) FMR (N=302)
Overall survival at 12 months	89.4%	80.9%
Overall survival at 24 months	72.3%	70.9%

DMR=degenerative mitral regurgitation; FMR=functional mitral regurgitation; NR=not reported
Notes: a For procedures reported in 2018
Cells shaded in blue represent results previously considered by MSAC

At 12 months, the mixed patient population in CLASP had a higher rate of overall survival than patients from the MitraClip registry (Mack 2022) but a similar rate to the MitraClip patients from EVEREST-II. At 24 months, however, patients in the EVEREST-II study, had a higher rate of overall survival compared to CLASP.

Table 13 Naïve comparison of overall survival in PASCAL and MitraClip studies (mixed population)

Safety event	CLASP (PASCAL)	EVEREST-II (MitraClip)	Mack 2022 (MitraClip)
	N=124	N=184	N=6,958 [a]
Overall survival at 12 months	91.9%	89%	78.1%
Overall survival at 24 months	80.3%	89%	NR

DMR=degenerative mitral regurgitation; FMR=functional mitral regurgitation; NR=not reported
[a]   For procedures reported in 2018
Cells shaded in blue represent results previously considered by MSAC

A meaningful comparison of OS rates in the mixed population is complicated by the differences in the split of FMR to DMR subgroups across the studies. The CLASP trial enrolled predominantly FMR population (69%), while the EVEREST-II trial enrolled 73% of DMR patients which is close to 68.3% of DMR patients from the MitraClip registry (Mack 2022).

Major adverse events

MAE results reported in the single-arm studies are presented in Table 14 (FMR) and Table 15 (mixed population).

Table 14 Naïve comparison of MAEs reported in the included single-arm studies (FMR population)

Safety event, n (%)	CLASP (PASCAL)	COAPT (MitraClip)	CLASP (PASCAL)	COAPT (MitraClip)
	(N=85)	(N=302)	(N=85)	(N=302)
	30 days		24 months	
Any MAE	9 (10.6)	NR (3.07^)	17 (20.0)	NR
Mortality (all cause)	1 (1.2)	7 (2.3#)	*17 (20.0)*	*80 (29.1)*
Cardiovascular mortality	1 (1.2)	NR	10 (11.8)	61 (23.5)
Stroke	1 (1.2)	2 (0.7#)	3 (3.5)	11 (4.4)
Myocardial infarction	0	3 (1.0#)	1 (1.2)	12 (4.7)
Need for new renal replacement therapy	1 (1.2)	NR	1 (1.2)	NR
Severe bleeding	8 (9.4)	NR	7 (8.2)	NR
Reintervention for study device-related complications	1 (1.2)	3 (1.0)a	3 (3.5)	10 (4.0)a

FMR=functional mitral regurgitation; MAE=major adverse event; NR=not reported
*Results were recalculated using the reconstructed definition of MAE;
^Safety population
#Intention-to-treat population
a Defined as unplanned mitral valve intervention.

In the FMR population at 30 days post procedure, the rate of MAEs for PASCAL was three times higher than the rate of MAEs for MitraClip, however there were significant differences in MAE definitions between the studies. The applicant did not report the MAE counts (only percentages of MAEs adjusted for MAIC purposes) according to the "reconstructed" CLASP MAE definition, therefore no meaningful comparison of rates of MAEs was possible. At 30 days post procedure one PASCAL patient (1.2%) experienced stroke vs two MitraClip patients (0.7%); there were no myocardial infarction events in the CLASP trial and 3 (1.0%) in the much larger COAPT trial. At 24 months the difference in the proportion of patients experiencing stroke was in favour of PASCAL (3.5%) vs MitraClip (4.4%). Similarly, 1.2% of the CLASP patients had a myocardial infarction vs 4.7% of the COAPT patients. It is not clear to what degree the difference in the baseline characteristics is explained by the COAPT patients being of poorer health, as evident by the higher proportions for most comorbidities, the higher Society of Thoracis Surgeons (STS) risk score, and lower left ventricular ejection fraction (LVEF). Both CLASP and COAPT trials observed low rates of strokes and MIs, making a comparison of the difference in rare events uncertain. The rates of reintervention for study device-related complications remained similar between PASCAL and MitraClip patients at both observation points.

Table 15 Naïve comparison of MAEs reported in the included single-arm studies (mixed FMR/DMR)

Safety event, n (%)	CLASP (PASCAL) N=124 69% FMR 31% DMR	Mauri 2020 (PASCAL) N=309 51.5% FMR 32.7% DMR 15.9% both	EVEREST-II (MitraClip) N=184 27% FMR 73% DMR	Mack 2022 (MitraClip) N=10,460 15.07% FMR 68.3% DMR 11.2% both 4.% none	CLASP (PASCAL) N=124	EVEREST-II (MitraClip) N=184
	30 days				12 months	
Any MAE	10 (8.1)	12 (4.1)	27 (15)/ 9(5)^	NR	23 (18.5)	39 (21.2)
Mortality	1 (0.8)	5 (2.0)	2 (1)	429 (4.2)	*10 (8.1)*	NR
Cardiovascular mortality	1 (0.8)	4 (1.4)	NR	NR	*7 (5.6)*	NR
Stroke	1 (0.8)	0	2 (1) [c]	115 (1.1)	*2 (1.6)*	NR
Myocardial infarction	0	NR	0	NR	*2 (1.6)*	NR
Need for new renal replacement therapy	1 (0.8)	2 (0.7)	1 (<1) [b]	96 (1.0)	*1 (0.8)*	NR
Severe bleeding	9 (7.3)	7 (2.4)	24 (13) [d]	464 (4.5)	*14 (11.3)*	NR
Reintervention for study device-related complications	1 (0.8)[a]	1 (0.3)	0	123 (1.2)	*2 (1.6)*	NR

MAE=major adverse event; NR=not reported
^Any MAE excluding transfusion
[a] Defined as unplanned mitral valve intervention.
[b] Defined as renal failure.
[c] One stroke occurred in a patient who underwent randomisation but was not treated.
[d] Defined as transfusion of ≥2 units of blood.

As above, a meaningful comparison of MAE rates in the mixed population is further complicated by the differences in the split of FMR to DMR subgroups across the studies.

As in the FMR population, low rates of MAEs (with exception of bleeding), were observed across the studies at 30 days. There were no reinterventions for MitraClip related complications in EVEREST-II trial, and a single patient in each the CLASP and Mauri (2020) studies (0.8% and 0.3% respectively) required a reintervention for PASCAL-related complications. In comparison to PASCAL studies, the MitraClip related rates of complications (1.2%) as reported in the STS/ACC TVTR registry were higher, however, the rate of severe bleeding, was observed in 4.5% of all MitraClip cases in the registry in comparison to 7.3% of such instances observed in the CLASP study. It is not clear whether the collection and interpretation of the outcomes obtained for the registry purposes (Mack, 2022), is identical the outcomes in the core evidence (EVEREST-II). Some of the sites that provided data for the registry might still be having an early experience with the device.

The commentary to the 1662 ADAR noted the absence of assessment of the long-term safety outcomes, in particular device-related complications. An Appendix to the current ADAR included a naïve comparison of the PASCAL safety, procedural and clinical efficacy outcomes reported in the small sample-size single-arm studies (Besler 2020, Barth 2020, Praz 2017 and Moonen 2022) identified in the literature review but not included in the main body of the current ADAR. The studies were not assessed for quality, and baseline characteristics of the population were not compared either with the core evidence or with MBS item eligibility criteria. The sample sizes for these studies ranged from 17 to 50 and the period of follow up ranged from 30 days and 24 months. Therefore, it does not appear that the long-term safety outcomes for treatment with PASCAL are reported in the literature.

12. Comparative effectiveness

Comparative studies in the mixed DMR/FMR population

Table 16 shows technical, device, procedural success and clinical efficacy outcomes from the included comparative, non-randomised studies of Geis (2022) and Haschemi (2022).

Table 16 Rates of technical, device, procedural success, and clinical efficacy outcomes

Study	Endpoint	Time point	PASCAL	MitraClip	p-value
Haschemi 2022	Technical success	Immediately post-procedure	97%	98%	0.576
	Procedural success	Discharge	88%	92%	0.836
	MR ≤1	Discharge	70%	73%	0.6294*
	MR ≤2	Discharge	94%	95%	0.7498*
	MR ≤1	30 days	69%	70%	0.8742*
	MR ≤2	30 days	92%	93%	0.975
	NYHA functional class I-II	30 days	78%	86%	0.131*
	NYHA functional class III-IV	30 days	22%	14%	0.112
Geis 2022	Technical success	Immediately post-procedure	90.24% (37/41)	95.12% (78/82)	0.4388
	Device success	Discharge	90.24% (37/41)	89.02% (72/83)	1.000
	Procedural success	Discharge	87.8% (36/41)	80.49% (66/82)	0.4465
	MR ≤1	Discharge	56.1% (23/41)	65.85% (54/82)	0.3265
	MR ≤2	Discharge	90.24% (37/41)	91.46% (75/82)	1.000
	MR ≤1	At short follow-up (1-4 months)	50% (13/26)	57.9% (33/57)	0.5044*
	MR ≤2		92.3% (24/26)	89.5% (51/57)	0.6901*
	MR ≤1	At long (6-18 months) follow-up	61.9% (13/21)	55.1% (27/49)	0.6009*
	MR ≤2		95.2% (20/21)	93.9% (46/49)	0.8311*
	NYHA functional class ≤ 2	At short follow-up (1-4 months)	50% (13/26)	61.02% (36/59)	0.3538
	NYHA functional class ≤ 2	At long (6-18 months) follow-up	57.14% (12/21)	64.82% (35/54)	0.5998

NYHA=New York Heart Association; MR=mitral regurgitation;
*calculated by evaluators

In the Haschemi (2022) study, there were no statistically significant differences between the PASCAL and MitraClip groups with respect to technical or procedural success; and also with respect to the proportion of patients with MR severity either at discharge, or at the 30 days observation point. More patients from MitraClip group achieved a higher NYHA functional class at 30 days, but the difference did not reach statistical significance.

Likewise, in the Geis (2022) study, there were no statistically significant differences between the PASCAL and MitraClip groups with respect to technical or procedural success and MR severity at discharge. However the authors claimed that, while at follow-up no statistical difference regarding mild, moderate, or severe MR grades was apparent, the number of patients with no or trace residual MR was significantly higher among patients in the PASCAL intention-to-treat group at either follow-up

time point (First follow-up: P = 0.0081; Second follow-up: P = 0.0017). Given the small size of the sample, significant loss to follow-up and time-varying confounding, the validity of these results is uncertain.

In Geis (2022) there was no statistically significant difference between PASCAL and MitraClip patients (ITT sample) in either a composite endpoint (death, hospitalisation due to heart failure, and MV re-intervention) or its individual components. Geis (2022) also conducted a Cox hazard model for the composite endpoint and a set of analyses in propensity score matched subgroups (univariate and multivariate logistic regressions) in relation to both the composite endpoint and its individual endpoints: death, hospitalisation due to heart failure, and MV re-intervention. In addition, the difference in proportions of stroke and the degree of absolute MR reduction were investigated. Statistically, there was no significant difference in any of the clinical outcomes between MitraClip-treated and PASCAL-treated groups. Neither of the parameters for sex, age, EuroSCORE II, nor the TMVr system was found statistically significant in the Cox hazard model.

Randomised trials in the DMR population (not evaluated)

MR severity at 6 months in the DMR population

Table 17 shows results from the CLASP IID of patients with MR severity ≤2+ at 6 months. PASCAL patients had a slightly greater reduction with a difference of -0.3% however the lower bound of the one-sided confidence interval (6.2%) was within the pre-specified non-inferiority margin of 18%.

A subset sample of core laboratory evaluated echocardiograms was analysed to show MR reduction ≤1+ at effectiveness endpoints up to 6 months (Table 18). The same subset was used to present results for Functional outcomes (assessed by NYHA class) (Table 19).

In the PASCAL arm, no statistically significant differences in the proportion of patients with MR severity ≤1+ were found between discharge and 30-days (p=0.096) and from 30-days to 6-months (p=0.317). However, in the MitraClip arm significant reductions were found in the proportion of patients with MR severity ≤1+ at 30-days from discharge (p=0.014) and between 6-months and 30-days (p=0.003). Differences in sustained reduction of MR severity between arms were not tested.

Table 17 MR severity ≤ 2+ at 6 months in the DMR population (CLASP IID)

MR Severity	Follow-up	PASCAL, % (n/N)	MitraClip, % (n/N)	Difference, % (95% LCB)
≤2+	6 months	96.5 (110/114)	96.8 (60/62)	-0.3 (-6.2)

LCB= one-sided 95% lower confidence band
Source: Pre-ESC response by Applicant, Lim (2022)

Table 18 MR reduction in DMR population (core lab# sample)

MR severity	PASCAL, % (N=86)				MitraClip, % (N=52)			
	Baseline	Discharge	30-day	6-month	Baseline	Discharge	30-day	6-month
None/trace or mild (0-1+)	0	87.2	81.4	83.7	0.0	88.5	76.9	71.2
≥2+	100.0	12.8	18.6	16.3	100.0	11.5	23.1	28.9

Echocardiographic core lab.

Table 19 NHYA functional class improvement in DMR population (core lab# sample)

NYHA functional class	PASCAL, % (N=101)		MitraClip, % (N=56)	
	Baseline	6-month	Baseline	6-month
Class I	0.0	43.6	0.0	44.6
Class II	38.6	42.6	37.5	50.0
Class III	56.4	12.9	53.6	5.4
Class IV	4.0	1.0	8.9	0.0

Echocardiographic core lab.

MAIC of the efficacy outcomes

The effectiveness outcomes subjected to the MAIC analysis included MR severity and NYHA functional class. MR severity results presented below were derived from the MAIC produced specifically for the current ADAR. The new MAIC output for the aggregated MR severity categories was meant to address the persistent imbalances in the baseline characteristic of the CLASP (weighted) and COAPT populations. In previous 2021 consideration, MSAC noted (PSD, p.4) that MR severity and STS scores were not balanced between CLASP (weighted) and COAPT and it is unclear whether these would be treatment effect modifiers or prognostic variables. The new MAIC output was inconsistent with the objective of achieving MR Severity grade 2+ as indicated in PSD (Table 9, p.18). Equally, the PSD Table 10 (p.18) shows the objective of achieving NYHA functional class of I or II. Both tables, that combine results for both FMR and DMR/FMR populations were updated and reproduced below.

MR severity at 24 months in the FMR population

Table 20 shows MR severity results observed at 24 months in the CLASP and COAPT FMR populations. The results are unchanged from the previous consideration.

Table 20 MAIC of MR severity at 24 months in FMR population (base case)

MR severity	CLASP (weighted)	COAPT
None/trace or mild (0-1+)	77.96%	77.20%
None/trace (0)	25.51%	0.88%
Mild (1+)	52.45%	76.32%
Mild-moderate (2+)	13.14%	21.93%
Moderate-severe or severe (3+ or 4+)	8.90%	0.88%
Moderate-severe (3+)	8.90%	0%
Severe (4+)	0%	0.88%

MAIC=matching adjusted indirect comparison; MR=mitral regurgitation

Cells shaded in blue represent results previously considered by MSAC

The proportion of PASCAL patients no longer experiencing MR (or just traces, grade 0+) was much higher than proportion of MitraClip patients (26% and 0.88% respectively).

Both unadjusted and weighted logistic regression results indicated that the odds of PASCAL patients achieving MR severity 0+ after 24 months were much higher and these results were statistically significant (Table 21). However, the odds of PASCAL patients achieving MR severity in the next severity category (1+) were not statistically different from MitraClip patients. In the current ADAR, the 24-month MR severity in grades 0 and 1+ were pooled in a single category. The recalculated

weighted logistic regression results indicated that the odds of PASCAL patients achieving MR severity in the aggregated 0-1+ category were no longer significantly higher in comparison to MitraClip patients (OR=1.045; 95% CI 0.287-3.800). However, a more informative analysis that would be in line with presentation of results in the MSAC 1662 PSD (Table 9, p.18) with respect to the MR grade 2+ or lower was not undertaken. Results of the sensitivity analysis (i.e. adding STS scores to the list of the parameters for matching) using the pooled (0-1+) MR severity category were not reported.

Table 21 Hazard ratios with 95% CI's for the comparison of MR severity at 24 months (CLASP vs COAPT)

MAIC	Matching	Method	Hazard ratio (95% CI)
MR severity 0+	Base case	Unadjusted Cox model	52.73 (6.06, 458.8)
		Weighted Cox model	38.70 (3.95, 379.17)
	Bootstrap median HR	95% percentile CI	37.33 (8.65, 103.57)
		95% BCa CI	37.33 (12.02, 120.25)
MR severity 0-1+	Base case	Weighted logistic regression	1.05 (0.29, 3.80)

MAIC=matched adjusted indirect comparison; CI=confidence interval;
Cells shaded in blue represent results previously considered by MSAC

The current ADAR reasonably justified this approach as being aligned with the MVARC criteria for mitral valve repair endpoints where reduction of MR severity to 0-1+ is considered optimal. At the same time, the ADAR stated that "This adjustment seeks to negate the impact of baseline imbalances and provide the MSAC with confidence in the clinical claim". It is not clear how this aggregation of the severity categories relates to the persistent imbalances in the CLASP (weighted) and COAPT population characteristics. The removal of statistical significance of the differences in MR severity by regrouping the outcomes assessed on an ordinal scale, does not adjust for baseline differences. It may, however, improve the confidence in the Applicant's intention of pursuing non-inferiority rather than superiority in the clinical claim, but does not adequately addresses the underlying causes of potential bias. If the baseline MR severity is an effect modifier or a prognostic variable, a sensitivity analysis that also adjusts for this difference is needed to justify this conclusion.

MR severity at 24 months in the DMR/FMR population

Table 22 shows the proportion of patients in each MR severity group in the reweighted CLASP and EVEREST-II populations at 24 months (base case). A higher proportion of PASCAL patients had a MR severity grade of 0+ than MitraClip patients and the difference was statistically significant in both base-case and sensitivity analyses. However, the odds of PASCAL patients achieving MR severity in the next severity category (1+) were not statistically different from MitraClip patients (OR=2.23; 95%CI 0.87-5.68).

Table 22 MAIC of MR severity at 24 months in mixed population (FMR/DMR) (base case)

MR severity	CLASP (weighted)	EVEREST-II
None/trace or mild (0-1+)	65.02%	36.22%
None/trace (0)	10.88%	1.57%
Mild (1+)	54.14%	34.65%
Mild-moderate (2+)	34.75%	48.82%
Moderate-severe or severe (3+ or 4+)	0.23%	14.96%
Moderate-severe (3+)	0.23%	11.81%
Severe (4+)	0%	3.15%

MAIC=matching adjusted indirect comparison; MR=mitral regurgitation
Source: Table 2-55 in 1662.1 ADAR, Attachment 2.2 – MAIC CLASP vs EVEREST-II 24 month Table 3
Cells shaded in blue represent results previously considered by MSAC

While for the FMR population the current ADAR pooled the 24-month MR severity (0-1+) into a single category and estimated odds ratios for the base-case analysis, this was not replicated for the mixed population. However, as discussed above, the value of this additional analysis is uncertain.

The commentary to the previous ADAR suggested that the 24-month MR severity results would replace the 12-month results. The current ADAR responded with the 24-month data analyses. Table 23 replicates Table 9 from MSAC 1662 PSD with updated 24-month results of MR severity for DMR/FMR subgroup.

Table 23 Percentage of patients with MR grade 2+ or lower at 24 month follow up

MAIC	Matching	Follow-up	*CLASP (PASCAL) unweighted, %*	CLASP (PASCAL) weighted, %	MitraClip, %
CLASP vs COAPT	Base-case	24 months	95 (n=19)*	91.1	99.13
	Sensitivity analysis			95.79	99.13
CLASP vs EVEREST-II	Base-case	24 months	97 (n=36)#	99.77	85.04
	Sensitivity analysis			99.19	85.04

*FMR population only
#Mixed population (FMR/DMR)
Source: PSD of the1662. ADAR; Table 3 and Table 14 Attachment 2.2 to the 1662.1 ADAR
Cells shaded in blue represent results previously considered by MSAC

Unchanged from the previous ADAR, a higher proportion of CLASP patients had MR severity 0+ at 24 months compared with COAPT MitraClip population (Table 20), but MR grade 2+ or lower was achieved in 91.1% of CLASP (PASCAL) patients and 99.13% of COAPT MitraClip patients in the base-case analysis and 95.79% vs 99.13% in the sensitivity analysis, respectively.

Likewise, in the mixed population a higher proportion of CLASP patients had MR severity 0+ at 24 months compared with EVEREST-II MitraClip population (Table 22). Unlike in the FMR population, more PASCAL patients from the mixed population achieved the MR grade 2+ or lower than MitraClip patients: 99.8% and 85.04% respectively, in the base-case analysis and 99.19% vs 85.04% respectively, in the sensitivity analysis. No MAIC analyses were conducted in relation to these aggregated MR severity categories, and statistical significance of the difference is not established in relation to MR grade 2+ or lower. Interpretation of the results is limited by the remaining residual imbalances in the population characteristics, the potential bias due to time-varying confounding, with a possibility of the first generations of MitraClip devices used in the COAPT and EVEREST-II trials being compared with more advanced techniques and more experienced clinicians participating in the CLASP study that started later.

NYHA functional class at 24 months in the FMR and DMR/FMR population

Table 24 reproduces Table 10 from the MSAC 1662 PSD with updated and corrected numbers, for the combined NYHA class I or II at 24 months, that were not available for the mixed population in the previous ADAR. Also included are the odds ratios for the base case in both subgroups from MAIC analyses conducted specifically for the current ADAR. Sensitivity analyses for NYHA class I or II were not provided.

Table 24 MAIC of NYHA class I or II in FMR and mixed populations at 24 months

MAIC	Matching	Follow-up	CLASP (PASCAL) unweighted, %	CLASP (PASCAL) weighted, %	MitraClip (COAPT/ EVEREST-II), %	Odds ratio (95% CI)
CLASP vs COAPT FMR population	Base-case	24 months	88 (n=24)	86.13	66.67	3.11 (0.86 - 11.16)
	Sensitivity analysis			91.34		NR
CLASP vs EVEREST-II Mixed population	Base-case	24 months	93 (n=46)	98.76	99.24	0.61 (0.02 – 22.05)
	Sensitivity analysis			92.19		NR

Cells shaded in blue represent results previously considered by MSAC

At the 24 month follow-up, in the FMR population a higher proportion of CLASP patients achieved NYHA class I or II. The odds of achieving the NYHA class of I were significantly better for PASCAL patients, but aggregating NYHA function classes I and II into a single category has resulted in a loss of statistical significance. In the mixed population, at 24 months follow-up, the proportion of patients achieving NYHA class I or II in the CLASP population was slightly lower than in the MitraClip arm. The difference was not statistically significant.

Table 25 provides a summary of the base case MAIC results for key outcomes.

Table 25 Base-case MAIC results for key outcomes

Endpoint	Comparison	PASCAL	MitraClip	OR (95% CI) [a]
MAEs at 30 days	CLASP (reconstructed) vs COAPT (FMR only)	2.91%	2.98%	0.98 (0.20, 4.87)
MAEs at 30 days	CLASP vs EVEREST-II (mixed FMR/DMR)	4.38%	5%	0.87 (0.21, 3.58)
Overall survival at 24 months	CLASP vs COAPT (FMR only)	N/A	N/A	0.334(0.15, 0.76) [b]
Overall survival at 24 months	CLASP vs EVEREST-II (mixed FMR/DMR)	N/A	N/A	0.31 (0.11, 0.85) [b]
MR severity ≤1+ at 24 months	CLASP vs COAPT (FMR only)	77.96%	77.20%	1.045 (0.287, 3.800)
MR severity ≤1+ at 24 months	CLASP vs EVEREST-II (mixed FMR/DMR)	65.02%	36.22%	NR
NYHA functional class I-II at 24 months	CLASP vs COAPT (FMR only)	86.13%	66.67%	3.1 (0.86, 11.16)
NYHA functional class I-II at 24 months	CLASP vs EVEREST-II (mixed FMR/DMR)	98.76%	99.24%	0.61 (0.02, 22.05)

DMR=degenerative mitral regurgitation; FMR=functional mitral regurgitation; MAE=major adverse event; MR=mitral regurgitation; NYHA= New York Heart Association; OR=odds ratio
[a] OR from weighted logistic regression model
[b] Hazard ratio (95% CI) for overall survival from weighted Cox model
Cells shaded in blue represent results previously considered by MSAC

There were no statistically significant differences in the MAIC analyses of the safety and effectiveness outcomes presented in Table 16. However, the limitations of MAIC identified in the previous ADAR remains valid here:

- Reweighing is only able to be performed on the reported patient characteristics. This is particularly an issue with the EVEREST-II comparison where separate data for FMR and DMR populations is not available.
- Reweighing cannot be performed on characteristics that are unobservable, e.g. FMR patients in the EVEREST-II were sufficiently fit to undergo surgery which was not the case for COAPT.
- Comparisons made are performed on the best available clinical trial data and may not represent the outcomes that would be achieved by the devices in practice.

It was also commented that in addition to significant inherent uncertainty with MAIC analysis, due to the comparison of single arm trials there is an uncertainty arising from inability to validate the results of the unanchored MAIC (i.e. the codes were not provided).

Single-arm studies (Naïve comparisons)

MR severity

MR severity outcomes at 30 days, and 12 and 24 months from the single-arm studies are presented in Table 26 (FMR) and Table 27 (mixed population).

Table 26 Naïve comparison of MR severity reported in the included single-arm studies (FMR population)

MR severity grade (%)	CLASP (PASCAL)	COAPT (MitraClip)	CLASP (PASCAL)	COAPT (MitraClip)	CLASP (PASCAL)	COAPT (MitraClip)
	(N=85)	(N=302)	(N=53)	(N=210)	(N=19)	(N=114)
	30 days		12 months		24 months	
None/trace or mild (0-1+)	73%	72.9%	75%	69.1%	84%	77.2%
None/trace (0)	15%	0.7%	13%	0.5%	37%	0.9%
Mild (1+)	58%	72.2%	62%	68.6%	47%	76.3%
Mild-moderate (2+)	23%	19.8%	25%	25.7%	11%	21.9%
Moderate-severe or severe (3+ or 4+)	4%	7.3%	0%	5.3%	5%	0.9%
Moderate-severe (3+)	1%	5.8%	0%	4.3%	5%	0%
Severe (4+)	3%	1.5%	0%	1.0%	0%	0.9%

FMR=functional mitral regurgitation; MR=mitral regurgitation; NR=not reported
Cells shaded in blue represent results previously considered by MSAC

Once aggregated across 0 and 1+ categories, the difference in the proportion of patients from CLASP and COAPT studies became negligible. The proportion of MitraClip patients who at 30 days remained in the MR moderate-severity category was 7.3% vs 4% of PASCAL patients. More MitraClip patients remained in this category at 12 months (5.3%) while all PASCAL patients achieved at least mild-moderate (2+) degree of MR severity. By 24 months there remained too few PASCAL patients to make a meaningful comparison, although a higher proportion of CLASP patients reversed to the moderate-severe (3+) degree of MR severity. It is not clear how the imbalance at baseline (42.4% of PASCAL patients were in the severe (4+) MR category vs 51% of MitraClip patients) affected the MR severity clinical effectiveness outcomes.

Table 27 Naïve comparison of MR severity reported in the included single-arm studies (mixed FMR/DMR)

MR severity grade (%)	CLASP (PASCAL) N=124	Mauri 2020 (PASCAL) N=309	EVEREST-II (MitraClip) N=184	Mack 2022 (MitraClip) N=10,460	CLASP (PASCAL) N=85	EVEREST-II (MitraClip) N=153	CLASP (PASCAL) N=36	EVEREST-II (MitraClip) N=127
	30 days				12 months		24 months	
None/trace or mild (0-1+)	77%	65%	52.6%	92.5%ᵃ	78%	42%	78%	36.2%
None/trace (0)	15%	9%	1.2%		15%	6%	25%	1.6%
Mild (1+)	62%	56%	51.4%		62%	37%	53%	34.6%
Mild-moderate (2+)	20%	28%	31.2%		22%	39%	19%	48.8%
Moderate-severe or severe (3+ /4+)	4%	7%	16.2%	7.5%	0%	19%	3%	14.9%
Moderate-severe (3+)	2%	5%	11.0%	NR	0%	14%	3%	11.8%
Severe (4+)	2%	2%	5.2%	NR	0%	5%	0%	3.1%

FMR=functional mitral regurgitation; DMR= degenerative mitral regurgitation; MR=mitral regurgitation; NR=not reported
ᵃ Mack 2022 reports patients with "None/Trace/Mild/Moderate Mitral insufficiency" interpreted as MR severity ≤2+
Cells shaded in blue represent results previously considered by MSAC

As discussed in the context of MAEs, a meaningful comparison of MR severity outcomes in the mixed population is complicated by the differences in the split of FMR to DMR subgroups across the studies.

The real-world PASCAL study Mauri (2020) recorded the second highest proportion of patients with mild-moderate (2+) MR severity (28%), similar to the proportion in EVEREST-II (31.2%). However, only 52.6% of EVEREST-II patients achieved the lowest MR grade (0-1+) at after 30 days post-procedure, while 16.2% remained in the moderate-severe or severe (3+ or 4+) category. The only study that had a similar proportion of DMR patients to EVEREST-II was (Mack 2022), but it did not report 12- and 24-month outcomes. The MitraClip registry records put 7.5% in the moderate-severe or severe (3+ or 4+) category, however there was inconsistency in result reporting, with some sites providing MR severity at discharge and others reporting within 30-days. The difference in the DMR/FMR split between CLASP and EVEREST-II studies effectively renders MR severity results not suitable for comparison, because aetiology of MR is essential for this particular outcome.

NYHA functional class

NYHA functional class outcomes at 30 days and 24 months from single-arm studies are presented in Table 28 (FMR) and Table 29 (mixed population).

At baseline, difference in NYHA class was the only characteristic that favoured COAPT patients over CLASP patients. The proportion with class III or IV at baseline was 57% and 64.8% respectively. At 30 days more PASCAL patients were in NYHA class I or II than MitraClip patients (87% and 76.3% respectively). The ADAR stated that this naïve comparison shows that at 24 months FMR patients from CLASP appear much more likely to have NYHA class I than patients from COAPT (38% vs 12.1% respectively), despite the fact that patients in CLASP had a worse NYHA class at baseline. By the 24-month observation point the proportion of patients in NYHA class III or IV was 12% and 21.7% in the CLASP and COAPT studies, respectively.

Table 28 Naïve comparison of NYHA functional class in single-arm studies (FMR population)

NYHA functional class, n (%)	CLASP (PASCAL) (N=84)	COAPT (MitraClip) (N=283)	CLASP (PASCAL) (N=24)	COAPT (MitraClip) (N=157)
	30 days		24 months	
Class I or II	87%	76.3%	88%	54.8%
I	29%	15.5%	38%	12.1%
II	58%	60.8%	50%	42.7%
Class III or IV	13%	22.9%	12%	27.7%
III	NR	19.4%	12%	21.7%
IV	NR	3.5%	0%	5.7%

DMR=degenerative mitral regurgitation; FMR=functional mitral regurgitation; NYHA=New York Heart Association
a   Percentages for COAPT do not include patients with heart failure or death

At baseline in the mixed population, just as in the FMR population, the difference in NYHA class favoured EVEREST-II patients over CLASP patients. The proportion with class III or IV at baseline was 52% and 60%, respectively. At 30 days more MitraClip patients from the EVEREST-II study were in NYHA class I or II than PASCAL patients from CLASP (89.9% and 88% respectively). In the Mauri (2020) PASCAL study, only 72% of patients were in in NYHA class I or II. The proportion of such patients from the MitraClip registry was 81% (Mack 2022). After 2 years only 37% of the original CLASP cohort was available for assessment. At that time the remaining patients treated with both types of TMVr seemed to continue improving: 93% of PASCAL and 99.2% of EVEREST-II patients were in NYHA class I or II.

Table 29 Naïve comparison of NYHA functional class in single-arm studies (mixed FMR/DMR population)

NYHA functional class, n (%)	CLASP (PASCAL) N=122 69% FMR 31% DMR	Mauri 2020 (PASCAL) N=264 51.5% FMR 32.7% DMR 15.9% both	EVEREST-II (MitraClip) N=168 27% FMR 73% DMR	Mack 2022 (MitraClip) N=10,460 15.07% FMR 68.3% DMR 11.2% both 4.% none	CLASP (PASCAL) N=46	EVEREST-II (MitraClip) N=168
	30 days				12 months	
Class I or II	88%	72%	89.9%	81%	93%	99.2%
I	38%	24%	50.0%	36.9%	54%	67.4%
II	50%	48%	39.9%	44.1%	39%	31.8%
Class III or IV	12%	28%	10.1%	19.1%	7%	0.8%
III	NR	26%	10.1%	16.4%	7%	0.8%
IV	NR	2%	0%	2.7%	0%	0%

DMR=degenerative mitral regurgitation; FMR=functional mitral regurgitation; NYHA=New York Heart Association
a   Percentages for COAPT do not include patients with heart failure or death

The current ADAR stated that these results are difficult to interpret because results from COAPT but not from CLASP include patients with HF or death, effectively increasing the total number of patients and reducing the proportion eligible for inclusion in NYHA class I.

Quality of life with Kansas City Cardiomyopathy Questionnaire (FMR population)

The current ADAR included quality of life results reported in the single-arm studies in heterogenous populations from different settings. Various instruments were used across the studies, which prevented any meaningful comparison. Since only CLASP and COAPT used the same Kansas City Cardiomyopathy Questionnaire (KCCQ), only FMR subgroup results were reported. Table 30 presents the results of changes in KCCQ scores from baseline to the 12-month observation point reported in the CLASP study. The COAPT trial results reported in the current ADAR were updated from the recent publication by Arnold (2019)[7].

Table 30 Kansas City Cardiomyopathy Questionnaire score at baseline and 12 months in CLASP and COAPT

KCCQ score	N	CLASP FMR (PASCAL)			N	COAPT (MitraClip)		
		Mean ± SD	Change from baseline ± SD	*p*-value		Mean ± SD	Change from baseline (95%CI)	*p*-value
Baseline	85	53 (NR)			302	*53.2 ± 22.8***		
12 months	57	70 (NR)	16 (NR)	<0.001	219	*71.8 ± 22.2***	*17.0 (13.6- 20.3)***	<0.001
24 months	NR	NR	NR	NR	128	70.9 ± 23.8**	18.4 (13.7 - 23.2)**	<0.001

FMR=functional mitral regurgitation; KCCQ=Kansas City Cardiomyopathy Questionnaire; SD=standard deviation
*   ITT sample; ** updated results from Arnold (2019)

In the CLASP study, the average KCCQ score improved by 16 points at 30 days (p <0.001) and was sustained at 1 year (16 points; p < 0.001). The COAPT trial did not report KCCQ score at 30 days. In relation to MitraClip patients, the current ADAR stated that the statistically significant improvement by 12.2 points over 12 months was more than twice the clinically meaningful improvement difference (MCID) of 5 points. The recently published updated results indicated that the COAPT patients achieved more than 3 times the MCID with average improvement by 17 points (Arnold, 2019). No statistical analysis of significance of the difference between the CLASP and COAP results was possible since standard deviations around the mean values of the KCCQ scores in CLASP trial was not presented.

HF hospitalisation (FMR population)

No MAIC comparison was undertaken in relation to this outcome. The HF rehospitalisation outcomes were reported in different formats across CLASP and COAPT trials making even naïve comparisons problematic. In the COAPT RCT, HF related hospitalisation within 24 months was a primary endpoint. The trial reported the proportion of patients with HF related hospitalisations within 24 months from index procedure (35.7%), hazard ratios for the number of HF hospitalisations over 24 months (HR=0.53; 95% CI 0.40-0.70; P<0.001) and an annualised rate (35.8% per patient-year). CLASP reported the reverse outcome – freedom from HF rehospitalisation in terms of rates over 24 months (77.5%), but no hazard ratios, and a 2-year reduction in annualised HF hospitalisation rate from the baseline rate of 1.16 (81%).

Naïve comparison interpretation

The naïve comparison consisted of results extracted from the single-arm studies that differ in design, settings and enrolled heterogenous populations. There is also a possibility of potential bias due to time-varying confounding, since CLASP began at the time when COAPT and EVEREST-II were

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[7] Arnold S. 2019. Health Status After Transcatheter Mitral-Valve Repair in Heart Failure and Secondary Mitral Regurgitation: COAPT Trial, Journal of the American College of Cardiology; 73 (17): 2123-2132.

nearing completion. Inability to separate outcomes for FMR and DMR populations precluded a meaningful comparison of results in the mixed population since the FMR/DMR split varied across the studies.

Numerous sources of bias are associated with observational studies which were not sufficiently addressed. For example, the baseline characteristics of the populations enrolled in the CLASP, COAPT and EVEREST-II studies were demonstrably different (Attachment 2.1). If that was not the case, there would be no justification for attempting a MAIC.

Clinical claim

On the basis of the benefits and harms reported in the evidence base, the ADAR proposes that, relative to MitraClip system, PASCAL system has non-inferior safety and non-inferior effectiveness.

The clinical claim is the same as that made in the previous ADAR and requires consideration given:

- The key clinical concerns outlined previously by MSAC in the 2021 consideration have not been fully addressed. MSAC previously 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. The current ADAR still relies on the same small-size, single-arm observational study for PASCAL (Szerlip, 2021) that was considered of low quality and did not adequately support the claim of clinical non-inferiority.
- Presentation of additional results from single-arm studies could not improve the degree of support for the non-inferiority claim by virtue of the non-comparative design of these studies. The informative value of naïve comparisons for decision making is uncertain because of the degree of potential bias associated with outcomes assembled across heterogenous populations, settings and study designs.
- The results from the unanchored MAIC largely unchanged from MSAC's previous 2021 consideration and was previously not sufficient to support TMVr using PASCAL.
- Although there is some recently published comparative evidence, the evidence is limited to trials with relatively small sample sizes that did not report safety and efficacy for the FMR and DMR subgroups separately.

The main argument in the current ADAR appears to be that the MAIC and especially the naïve comparison present evidence *of a similar standard to that included in MSAC Application No. 1192.3, which presented a series of observational studies to support the listing of TMVr using MitraClip for the DMR population. After consideration of these observational studies, the MSAC considered that on balance TMVr for the treatment of DMR should be considered non-inferior and recommended that the MitraClip procedure be listed on the MBS" (MSAC 1192.3 PSD).

This argument is poorly justified since the MSAC support for public funding of TMVr (MitraClip™) was based on the higher quality evidence [COAPT RCT], which supported the claim for non-inferior safety and superior effectiveness for the FMR population. In relation to DMR population, "MSAC acknowledged that, although the evidence for DMR patients is of lower quality, these patients are very sick and have few other options" (MSAC 1192.3 PSD). The current ADAR did not identify a population with an unmet clinical need who are unable to undergo TMVr using MitraClip but is able to undergo TMVr using PASCAL. However, unmet clinical need for the DMR population is addressed by the MBS listing for TMVr using MitraClip.

13. Economic evaluation

The previous ADAR (MSAC 1662) presented a cost-minimisation model with the time horizon of 30 days, that included the cost of the index procedure, revision surgery, and downstream cost. A cost-minimisation analysis was presented assuming that PASCAL is non-inferior in safety and efficacy compared with MitraClip. The type of the model and the overall approach was considered appropriate.

The MSAC previously noted that the uncertainty associated with MAIC affected the economic analysis both directly through the adjusted rates of adverse events, and indirectly through the clinical claim of non-inferiority (MSAC 1662 PSD, page 5). Attempts to address these concerns in the current ADAR were not completely successful and new uncertainties were generated in the process.

The economic evaluation is summarised in Table 31.

Table 31 Summary of the economic evaluation

Component	Description
Perspective	Australian Healthcare System
Comparator	MitraClip
Therapeutic claim: effectiveness	Based on the clinical evidence presented in Section 2, the effectiveness of PASCAL is assumed to be non-inferior to MitraClip
Therapeutic claim: safety	Based on the clinical evidence presented in Section 2, the safety of PASCAL is assumed to be non-inferior to MitraClip
Evidence base	Matching adjusted indirect comparison of PASCAL and MitraClip
Time horizon	30 days
Direct health technology costs	The direct healthcare cost (procedural cost) of PASCAL is equivalent to MitraClip
Downstream costs	Included costs of device-related revision surgery, stroke, myocardial infarction and renal replacement therapy

MI=mitral regurgitation; MAE=major adverse event; MAIC=matched adjusted indirect comparison
Cells shaded in blue represent results previously considered by MSAC

As in the previous ADAR, the current ADAR reported the costs of the procedure including prosthesis, revision surgery costs and adverse event costs. The most expensive inputs in the cost-minimisation analysis were the costs of TMVr devices (prostheses) followed by the procedural costs. These costs comprised the largest part (97%-99%) of the total cost and were assumed to be equivalent for PASCAL and MitraClip and equally applied to the FMR and DMR populations. As in the previous ADAR, the current ADAR used a weighted approach to determine the overall result of the cost-minimisation analysis. However, instead of using a 54% FMR to 46% DMR split, the new proportions of 42% and 58% for FMR and DMR, respectively, applied. The rationale for the change in the proportions of FMR/DMR were not provided.

The difference between the cost-minimisation model presented in the previous ADAR and the one in the current ADAR entirely related to the downstream cost, which included the costs of adverse events.

The cost-minimisation model in the current ADAR differs from the model in the previous ADAR with respect to the following:

- The detected double-counting in the total cost that comprised the composite MAE and its components – stroke and MIs was corrected. The cost of a composite MAE was removed from the base case analysis.

- Instead of the composite MAE, as in the previous ADAR, the base case analysis included the individual MAE components of revision surgery, stroke and MI. Renal replacement therapy, that was not previously included, was added. Nevertheless, the list of AEs was limited, but even for these selected AEs the available evidence was scarce.
- The scarcity of clinical evidence from the key trials for the estimates of the rates of selected AEs was addressed by including the evidence from the single-arm studies in the sensitivity analysis.
- The composite MAE was altered by removing the AE of "bleeding" from the definition. The altered MAE was referred to as the "reconstructed" MAE. The adjusted rates of the "reconstructed" MAEs were estimated with the updated MAIC and used in the sensitivity analyses;

As in the previous ADAR, no longer-term safety outcomes of mortality, hospitalisations due to heart failure, or device-related surgical revisions were available.

Table 32 presents the results of the cost-minimisation analyses.

Table 32 Total weighted cost-minimised cost across both FMR and DMR populations presented in the 1662.1 ADAR

	PASCAL	MitraClip
Total cost FMR	$█	*$36,194.69**
Total cost DMR	$█	$35,627.86
Total cost all MR – weighted[a]	$█	*$35,866.52**
Total incremental cost of PASCAL	████████████	

[a] Weighting FMR = 42%, DMR= 58%
*Corrected by the evaluators, the difference in costs due to the detected error is negligible

The total weighted cost for all MR (FMR and DMR) for PASCAL and MitraClip are $███ and $35,866.52 respectively (Table 32). The total incremental cost of PASCAL to MitraClip using the weighted populations of all MRs is ███.

As in the previous ADAR, sensitivity analyses were conducted with respect to two alternative concepts of the adverse events: the composite "reconstructed" MAE, with the advantage of the adjusted rates from MAIC that were available for both the FMR and DMR populations; and the individual components of the composite MAE limited to revision surgery, stroke, MI and renal replacement therapy. Adjusted rates from MAIC were available for stroke and MIs in the FMR population and for stroke in the DMR populations.

The spreadsheet with results of the sensitivity analyses was not made available for the evaluators. The 30-day sensitivity analyses were limited to the pre-selected number of AE parameters, for which 1-3 or no events were observed in the clinical evidence described in Section 2. The attempt to estimate the longer-term comparative safety was reduced to substituting 30-day AE rates with 12- and 24-month AEs, that did not include bleeding. The longer-term safety results were equally limited by scarcity of evidence and did not include mortality or hospitalisations due to heart failure. Only univariate sensitivity analyses were presented.

Table 33 Results of the Sensitivity Analysis as reported in the current ADAR

Variable or assumption	Base case setting	Scenario setting	Total cost (PASCAL)	Total cost (MitraClip)	Incremental cost of PASCAL
Base case			$■	*$35,866.52*	
Adverse* events	Individual MAEs, from MAIC where available	Aggregate mixed MAEs from MAIC	$■	$36,040.27	
	Base case MAIC outcomes	Sensitivity analysis MAIC	$■	$35,864.83	
	Base case MAIC	Naïve comparison from individual studies (CLASP, COAPT and EVEREST-II) at 30-days	$■	$35,797.36	
	30-day MI rate from MAIC	24-month MI rate from MAIC (FMR only)	$■	$35,977.22	
	Base case MAIC, 30-day results	24-month individual AE rates, naïve comparison from CLASP and COAPT, FMR and DMR assumed same	$■	$38,107.26	
	Base case MAIC, 30-day results	12-month mixed AEs, naïve comparison from CLASP and EVEREST-II, FMR and DMR assumed same	$■	$38,211.57	
	Base case MAIC	Naïve comparison using real-world results reported in Mauri 2020 for PASCAL and Mack 2022 for MitraClip, FMR and DMR assumed same	$■	$36,145.55	
Revision* surgery	*FMR:* CLASP 30-day MAE, MitraClip assumed same *DMR:* CLASP 30-day MAE, EVEREST-II 30-day MAE	20% increase in revision surgery for FMR with PASCAL	$■	$35,864.83	
		20% increase in revision surgery for FMR with MitraClip	$■	$35,908.29	
		Rate for FMR comes from COAPT study "30-day unplanned mitral valve intervention"	$■	$35,828.62	
		Rate for PASCAL and MitraClip comes from CLASP study 30-day outcomes, FMR and DMR assumed the same	$■	$36,335.61	
Population split*	42% FMR/ 58% DMR	65% FMR/35% DMR from (Coffey 2021)	$■	$35,993.68	
		37% FMR/ 63% DMR from predicted utilisation MSAC Application No. 1192.3, Table 10	$■	$35,834.17	

AE, adverse event; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; MAE, major adverse event; MAIC, matching adjusted indirect comparison; MI, myocardial infarction
* Not independently validated or corrected for the minor error as in the base case analysis

Given multiple and not sufficiently explained assumptions underlying most of the calculations presented in Table 33, these results could not be independently validated. Only selected sensitivity analyses from Table 33 where the content of "scenario setting" could be deciphered were replicated. Every single scenario analysis produced a small per-person saving. The current

ADAR has interpreted the results as evidence of cost-neutrality. A key driver of the model appears to be the FMR/DMR split.

The cost-minimisation model presented by the current ADAR was insufficient for a broad estimate of the total cost of the downstream events. Only a limited number of the AEs were included in the downstream costs. For those that were included, there was a paucity of short-term (30 days) and longer-term (12- and 24-months) evidence to obtain reliable estimates. It is likely that the short-term downstream costs, even after being enhanced with the comprehensive number of AEs, will remain a smaller part of the overall cost of a TMVr. However, it is these costs that relate to the incremental cost difference and, with respect to the longer time horizon could contain the factors that substantially differentiate the costs of PASCAL and MitraClip. On the basis of the available evidence that provided the inputs for the cost-minimisation model, it remains uncertain as to whether cost neutrality between TMVr using PASCAL and MitraClip was established.

14. Financial/budgetary impacts

The ADAR used ███ ███ ███ approach to estimate the financial implications to the MBS only. Unchanged from the previous ADAR, it was assumed PASCAL would account for ███ ███ ███ ███ ███ ███ ███ ███ ███ ███ ███.

The number of total TMVR procedures Year 1 was assumed to be ██ █ ██ █ ██ █ ██ █ ██ █ ██ ██ ██ ██ █ ██ █ ██ █ ██ █ ██ ██ ██ █ ██ █ ██ █ ██ █ ██ █ ██.

The financial implications to the MBS resulting from the proposed listing of PASCAL Transcatheter Mitral Valve Repair System for the treatment of patients with DMR or FMR are summarised in Table 34.

Unlike the previous ADAR, the current financial implications do not consider device or hospital costs. The PASCAL system consists of the Implant System, Guide Sheath as well as the optional Stabiliser and cardiac implantation catheter table. The applicant is asked to clarify in its pre-ESC response whether the proposed Prosthesis List benefit fully reimburses the price of the Implant System and Guide Sheath.

Table 34 Net financial implications of PASCAL to the MBS

	Year 1	Year 2	Year 3	Year 4	Year 5
TMVr procedures for **DMR** conducted with PASCAL					
Previous ADAR					
Change in TMVr procedures for DMR conducted with MitraClip					
Net change in MBS item 38461 utilisation					
Increased cost of PASCAL in the DMR population at 75% benefit					
Update to reflect new schedule fee					
Decreased cost of MitraClip in the DMR population at 75% benefit					
Update to reflect new schedule fee					
Net change in MBS cost					
Previous ADAR					
TMVr procedures for **FMR** conducted with PASCAL					
Change in TMVr procedures for FMR conducted with MitraClip					
Net change in MBS item 38463 utilisation					
Increased cost of PASCAL in the FMR population at 75% benefit					
Update to reflect new schedule fee					
Decreased cost of MitraClip in the FMR population at 75% benefit					
Update to reflect new schedule fee					
Net change in MBS cost					

TMVr=transcatheter mitral valve repair; DMR=degenerative mitral regurgitation; FMR=functional mitral regurgitation
Cells shaded in blue represent results previously considered by MSAC

The assumptions in the financial analysis presented in the ADAR are that:

- There is no difference in the adverse events between a TMVr procedure with MitraClip and PASCAL. The ADAR has not identified any adverse events or any difference in adverse events between the two systems, and the use of MBS items to treat patients. This type of surgery can result in serious adverse events, and to the extent that there is a difference between the two systems, the financial analysis has underestimated the implications for the MBS.

- The number of TMVr procedures was adjusted for retreatments, at 1.28% and 2.98% for DMR and FMR respectively, in Application 1192.3 (MitraClip). ███████████████████████████.

- The same MBS items that were costed in Application 1192.3 as being used either pre-surgery or post-surgery were also costed in this ADAR. However, these items do not include the cost of

imaging done prior to surgery (transthoracic and transesophageal echocardiography) used to provide detailed morphological analysis of the mitral valve and annulus (Gercek 2021 and Moonen 2022). Absence of the inclusion of these MBS items underestimates the cost to the MBS if the use of these services differ between PASCAL and MitraClip.

- The average fee of the proposed technology per patient per course is: $2,009.15 or $1,506.86 (75% benefit). This proposed fee includes other MBS items associated with the TMVr procedure (case coordination, anaesthetics, post-procedure echocardiogram, valvuloplasty) but as already discussed could be an underestimate.

- It is proposed that the frequency of use of the proposed technology is the same as for MitraClip, that is it can only be provided once every five years.

15. Other relevant information

Nil

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The current ADAR did not provide sufficient additional evidence to support a clinical claim of non-inferior safety and effectiveness for PASCAL compared to MitraClip:

  o The ADAR mostly re-presented the unanchored matched adjusted indirect comparison (MAIC) presented in the current ADAR. This did not substantially differ to that presented in the previous ADAR.

  o Although there is some additional comparative evidence, the evidence is limited to the small, non-randomised studies that did not report safety and efficacy for the FMR and DMR subgroups separately. This evidence presented in the ADAR was not of sufficient quality to support 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.

  o Additional comparative data from the CLASP IID study for the DMR population was provided in the pre-ESC response and not evaluated

- No comparative evidence (either direct or MAIC) specific for the DMR subgroup, as requested by MSAC, was presented in the ADAR. The ADAR relied on the studies that do not report results separately by DMR and FMR subgroups, reporting instead the outcomes for a "mixed" DMR/FMR population. The available sources of evidence did not identify the long-term safety outcomes (specifically device-related outcomes) for the PASCAL TMVr system.

- MSAC may want to consider if the emerging evidence from the RCT (presented at a conference and in press as an uncorrected proof at the time of the ESC review) in the pre-ESC response is sufficient or whether longer-term data beyond 6 months are needed.

Economic issues:

- The cost-minimisation model in the current ADAR is inconclusive due to uncertainty regarding comparative adverse events and long-term safety outcomes including mortality, hospitalisations and device-related surgical revisions.

Financial issues:

- The financial implications do not consider device or hospital costs and are based on an assumption of a nil net impact on the MBS.

ESC discussion

ESC noted that this application from Edwards Lifesciences requested Medicare Benefits Schedule (MBS) listing for transcatheter mitral valve repair (TMVr) using PASCAL for treatment of patients with degenerative mitral regurgitation (DMR) or functional mitral regurgitation (FMR).

ESC noted that MBS items 38461 and 38463 are for TMVr by transvenous or transeptal techniques for DMR and FMR with the MitraClip system. At its November 2021 meeting, MSAC considered Application 1662 and did not support amendment of these MBS items to make them device agnostic. ESC noted that MSAC considered the quality of evidence for TMVr using the PASCAL system to be low and did not adequately support the claim of clinical non-inferiority for safety and effectiveness. MSAC's previous 2021 consideration advised that higher quality evidence would be needed to support the claim of non-inferiority. The previous MSAC also considered that an unmet clinical need for an alternative device was not clearly demonstrated.

ESC noted product information in the ███████ ████ for ██ ████ indicates that the device is intended to be used in treatment of ██ █ █ █ ████ █████. ESC considered that there is a clinical unmet need for ███ ███ █ ████ but this indication will need a separate MSAC application with supporting data.

ESC considered that valve-in-valve intervention (following failed surgical or transcatheter implanted valve) rather than the existing native valve repair services may need separate health technology assessment as the evidence presented in this application related to intervention on a native mitral valve. In this case, MSAC may wish to consider any potential restrictions on the current MBS items being utilised for valve-in-valve intervention. ESC considered balloon valvuloplasty (MBS item 38270) was inherent to the procedure (complete service) and should be blocked from co-claiming with items 38461 and 38463.

ESC noted that the original applicant-developed assessment report (ADAR), like this ADAR, was based on the ratified PICO for application 1192.3 (for MitraClip) and bypassed PASC.

ESC noted that two letters of support were received from consumer groups, which noted that this procedure reduces hospital time and improved quality of life. ESC noted that the issues in the descriptor wording raised by MSAC in November 2021 have been addressed to reflect the clinical algorithm and remove 'symptomatic' from the descriptor.

ESC noted that the current ADAR reformatted the same evidence from the MAIC and complemented it with additional 24-month follow-up observational data for the mixed FMR/DMR population (CLASP and EVEREST-II). The primary sources of evidence presented in the current ADAR consisted of two single-arm studies for PASCAL (CLASP and Mauri 2020), the MitraClip arms from two RCTs (COAPT and EVEREST-II) and data from the STS/ACC TVT Registry for MitraClip (Mack 2022). Results of these five observational datasets were presented as naïve comparisons.

ESC noted that the matching-adjusted indirect comparison (MAIC) of the outcomes from a single-arm study of PASCAL TMVr (CLASP) and the MitraClip arms of two comparative trials (COAPT and

EVEREST-II) that formed the core evidence in the previous ADAR was largely replicated in the current ADAR. The same patient characteristics were used for matching and results were mostly unchanged from the previous ADAR except for an increase to 24 months follow-up data for the mixed FMR/DMR (CLASP and EVEREST-II) comparisons.

ESC noted that additional non-randomised, comparative clinical studies (Geis 2022, Haschemi, 2022) were presented in Appendix D of the ADAR but not the main body. The commentary conducted an independent quality assessment of these comparative clinical studies and assessed results from the two studies as having a low to medium level of bias (Geis 2022, Haschemi, 2022), however ESC considered the new studies did not address MSAC previous advice 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 or request for longer-term comparative data.

ESC noted that the ADAR quotes the study from Moonen et al. 2022, which included patients treated under compassionate use ($N = 17$; the reason for the compassionate use not explained) and some patients described as having anatomically complex mitral regurgitation ($n = 9$), which were considered technically difficult or anatomically challenging for successful treatment with available therapies, had the TMVr procedure. Only the PASCAL system was used in this study. ESC considered the ADAR did not identify a group of patients that represent an unmet need (i.e. cannot use MitraClip but can use PASCAL). ESC considered that in the pre-ESC response submitted by the applicant, the registry component of the CLASP IID and CLASP IIF study may provide data on unmet need through patients considered suitable for the PASCAL system but ineligible for MitraClip due to complex anatomical features.

The ADAR referenced a non-inferiority margin of 1.5 for the hazard ratio (HR) for overall survival (OS), which was poorly substantiated (i.e., taken from MitraClip randomised controlled trial), where it refers to hospitalisation rates (not OS), and relates to a comparison with best-supportive care (rather than the alternative TMVr). However, most outcomes also showed no statistically significant differences between the two devices.

ESC noted that the pre-ESC response presented the latest data for the primary safety and efficacy outcomes from the CLASP IID study (for the DMR population), which were presented at the Transcatheter Cardiovascular Therapeutics (TCT) conference in September 2022 and published as an uncorrected proof [8]. ESC noted the pre-specified interim analysis of 180 patients (117 PASCAL, 63 MitraClip) was brought forward due to meeting the required Bayesian predictive probability for trial success. The interim analysis found the rate of major adverse events (MAEs) at 30 days was 3.4% for PASCAL treated patients compared to 4.8% for patients treated with MitraClip (point estimate, –1.3%; one-sided 95% confidence interval [CI] upper bound 5.1%). The upper bound of the one-sided CI (5.1%) was within the pre-specified 15% non-inferiority margin. The safety profile of both devices persisted to 6 months; the MAE rate for PASCAL was 6.1% vs 11.1% for MitraClip.

The interim analysis found the proportion of patients with MR≤2+ at 6 months was 96.5% for PASCAL treated patients compared to 96.8% for patients treated with MitraClip (point estimate of difference, –0.3%; one-sided 95% confidence interval [CI] lower bound -6.2%). The lower bound of the one-sided CI (-6.2%) was within the pre-specified -18% non-inferiority margin. In the echocardiographic corelab subset of patients, ESC noted the reduction of MR severity ≤1+

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[8] Lim D, Smith R, Gillam L, et al. Randomized Comparison of Transcatheter Edge-to-Edge Repair for Degenerative Mitral Regurgitation in Prohibitive Surgical Risk Patients. *J Am Coll Cardiol Intv.* Sep 17, 2022

appeared to be sustained over 6 months for the PASCAL system. ESC noted that the study will continue to report 2-year and 5-year outcomes.

ESC considered that the emergent evidence suggested likelihood of non-inferiority for PASCAL device up to 6 months in the DMR population, however the additional data from the CLASP IID study was not able to be formally evaluated as it was not included in the ADAR.

ESC noted that the procedure time for PASCAL was ███ minutes compared to ███ minutes for MitraClip, but that this ███ would likely ███ over time due to ██ ██ ██ ██ ██ ██ ██ ██ ██ ██ ██.

Overall, ESC considered the evidence presented likely supported the claim of short-term non-inferior safety (up to 6 months). ESC considered the evidence presented did not sufficiently address the previous MSAC's request for long-term effectiveness and safety data for TMVr using the PASCAL device.

ESC noted that the previous ADAR (1662) presented a cost-minimisation model with a time horizon of 30 days. The cost-minimisation analysis was presented assuming that PASCAL is non-inferior in safety and efficacy compared with MitraClip. ESC considered that the type of the model and the overall approach used were both appropriate. However, ESC noted MSAC's previous assessment that the uncertainty associated with MAIC affected the economic analysis both directly through the adjusted rates of adverse events, and indirectly through the clinical claim of non-inferiority.

As in the previous ADAR, ESC noted that the current ADAR reported the costs of the procedure including prosthesis, revision surgery costs and adverse event costs. The most expensive inputs in the cost-minimisation analysis were the costs of TMVr devices (prostheses) followed by the procedural costs. These costs comprised the largest part (97–99%) of the total cost and were assumed to be equivalent for PASCAL and MitraClip, and equally applied to the FMR and DMR populations. As in the previous ADAR, the current ADAR used a weighted approach to determine the overall result of the cost-minimisation analysis. However, instead of using a 54% FMR to 46% DMR split, the new proportions of 42% and 58% for FMR and DMR, respectively, were applied. The rationale for the change in the proportions of FMR/DMR were not provided.

ESC noted that the ADAR claimed that all sensitivity analyses had minimal impact on the results of the cost-minimisation model, with PASCAL remaining slightly cost-saving in all scenarios assessed and that overall, the model result is robust and a conclusion of cost neutrality between PASCAL and MitraClip is appropriate. However, the commentary noted that only a limited number of the adverse events were included in the downstream costs. For those that were included, there was limited short-term (30 days) and longer-term (12 and 24 months) evidence to obtain reliable estimates. It is likely that the short-term downstream costs, even after being enhanced with the comprehensive number of adverse events, will remain a smaller part of the overall cost of a TMVr. However, it is these costs that relate to the incremental cost difference and, with respect to a longer time horizon, could contain the factors that substantially differentiate the costs of PASCAL and MitraClip. ESC noted that on the basis of the available evidence that provided the inputs for the cost-minimisation model, it was uncertain if long-term cost neutrality between PASCAL and MitraClip was established.

ESC considered the additional data did not represent a material improvement to the model however the results of the economic evaluation are reliant on and secondary to whether the clinical claim of non-inferiority was adequately supported by the clinical evidence.

In terms of financial impact, ESC noted it was reasonable to expect that the increase in utilisation of PASCAL would be offset by a reduction in the use of MitraClip but considered if design differences between the two devices could lead to additional unmet need being satisfied, there

would be incremental utilisation. ESC noted the impact to other health system budgets (such as hospitalisation costs) was not considered. However, ESC advised that TMVr using PASCAL is likely to have the same hospital costs as TMVr using Mitraclip.

ESC noted that, in the pre-ESC response, the applicant confirmed that the proposed Prosthesis List benefit will fully reimburse the price of the PASCAL device, implant system and guide sheath. ESC noted that the department was aware that hospitals are being charged costs higher than the Prosthesis List Benefit for cardiac devices. This cost would be incurred by the hospital or patient. ESC noted that the procedural costs (excluding AEs) included in the economic model were the same for PASCAL and MitraClip. These included the prosthesis cost (including the aforementioned devices for the PASCAL system), hospital costs (ICU and non-ICU), and MBS items (TMVr procedure, post-procedure echocardiogram, anaesthetics, multidisciplinary heart team attendance and coordination). ESC considered this was reasonable as the TMVr procedure is expected to be similar for PASCAL and MitraClip.

ESC noted that MBS item 38519 cannot be claimed by a cardiothoracic surgeon when explanting a TMVr implant during surgical mitral valve repair. ESC also noted that balloon valvuloplasty is inherent to the procedure (complete service) so it cannot be co-claimed with MBS items 38461 and 38463.

17.   Applicant comments on MSAC's Public Summary Document

Edwards Lifesciences are disappointed with the decision from MSAC not to support public funding of PASCAL. Edwards Lifesciences are looking forward to working with the Department on addressing any uncertainty thereby allowing Australian patients access to an alternative TEER device in the Australian healthcare system.

18.   Further information on MSAC

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