



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1192.3 – Reduction of mitral regurgitation through tissue approximation, using transvenous/transeptal techniques (Resubmission)

Applicant: Abbott Australasia Pty Ltd

Date of MSAC consideration: MSAC 78th Meeting, 3 April 2020

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

1. Purpose of application

A resubmission seeking Medicare Benefits Schedule (MBS) listing for reduction of mitral regurgitation through tissue approximation, using transvenous/transeptal techniques was received from Abbott Australasia Pty Ltd by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the public funding of reduction of mitral regurgitation through tissue approximation, using transvenous/transeptal techniques (TMVr). Funding was supported on a cost-minimisation basis against optimised medical management in patients with degenerative mitral regurgitation (DMR). For patients with functional mitral regurgitation (FMR), funding was supported on a cost-effectiveness basis against optimised medical management, but with the time-horizon adjusted to 7 years in the economic model. The combined price of service and the associated device was reduced so the incremental cost effectiveness ratio (ICER) is in the same range as previously (\$45,000–\$48,000 per quality-adjusted life year (QALY)).

MSAC agreed that the evidence presented in the COAPT trial supports the claim for non-inferior safety and superior effectiveness for the FMR population (Population 2) (FMR). MSAC noted the cost-effectiveness, safety and clinical effectiveness for the DMR population (Population 1) was less certain, but considered that on balance a conclusion of non-inferiority in safety and effectiveness was reasonable.

MSAC recommended that the Department further negotiate with the applicant regarding pricing as a condition of listing. MSAC also recommended establishing a transcatheter mitral valve replacement (TMVr) registry as a condition of listing.

Consumer summary

Abbott Australasia applied for Medicare Benefits Schedule (MBS) funding for a medical procedure called transcatheter mitral valve replacement to manage a condition in which the heart's mitral valve doesn't close tightly, which allows blood to flow backward in the heart (mitral regurgitation).

The medical procedure uses a device called MitraClip®. The interventional cardiologist or surgeon uses a customised catheter to thread the clip through a vein in the leg to the heart, where the clip is positioned near the faulty valve and then released to 'clip' the valve shut.

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

There are high quality studies that show that transcatheter mitral valve replacement with MitraClip is a safe and more effective than current procedures in patients with FMR who can't have open heart surgery. However, the Medical Services Advisory Committee (MSAC) recommended a lower price for the combination of the procedure with MitraClip, as the MSAC did not consider the applicant's requested price to be value for money.

For people with DMR who can't have open heart surgery, the evidence comparing transcatheter mitral valve replacement with MitraClip to current procedures is not as clear. The MSAC acknowledged that, although the evidence for DMR patients is of lower quality, these patients are very sick and have few other options. MSAC considered that the procedure was likely to be safe for these patients based on current evidence. MSAC also considered that, on balance, the proposed procedure with MitraClip was at least no worse in terms than current medical management. MSAC considered the cost of the combination of the procedure with MitraClip for people with DMR should not be more expensive than the cost of current treatment.

MSAC's advice to the Commonwealth Minister of Health

MSAC supported public funding of transcatheter mitral valve replacement with MitraClip for patients with mitral regurgitation due to FMR and DMR who can't have open heart surgery. MSAC felt that the procedure was effective and safe and – at a reduced price – cost-effective. MSAC recommended that a compulsory registry be established to ensure quality control, as a condition of listing.

MSAC proposed MBS item descriptors

Category 3 – Therapeutic procedures

MBS item

Transvenous/transseptal techniques for permanent coaptation of mitral valve leaflets using 1 or more tissue approximation devices (Mitraclip) in patients with moderate-severe or severe symptomatic degenerative mitral regurgitation (Grade 3+, 4+), who have left ventricular ejection fraction (LVEF) $\geq 20\%$, who are symptomatic (New York Heart Association [NYHA] functional class II or greater), who are determined by a MDHT to be ineligible for surgical intervention but suitable for the MitraClip procedure. Performed via transfemoral delivery, unless transfemoral delivery is contraindicated.

In a transmitral valve repair (TMVr) Hospital on a TMVr patient by a TMVr practitioner – includes all intraoperative diagnostic imaging that the TMVr practitioner performs upon the TMVr patient.

Category 3 – Therapeutic procedures
(Not payable more than once per patient in a five-year period) (See paragraph XX, XX of explanatory notes to this Category) Fee: \$1,455.10 Benefit 75% = \$1,091.35
MBS item ##### Transvenous/transseptal techniques for permanent coaptation of mitral valve leaflets using 1 or more tissue approximation devices (Mitraclip) in patients with moderate-severe or severe symptomatic functional mitral regurgitation (Grade 3+, 4+), with LVEF 20–50% and LVESD ≤70mm considered by the MDHT to be ineligible for surgical intervention, and whose symptoms (NYHA functional class II or greater) persist despite maximally tolerated guideline directed medical therapy (GDMT) as determined by the MDHT. Performed via transfemoral delivery, unless transfemoral delivery is contraindicated. In a transmitral valve repair (TMVr) Hospital on a TMVr Patient by a TMVr Practitioner – includes all intraoperative diagnostic imaging that the TMVr Practitioner performs upon the TMVr Patient. (Not payable more than once per patient in a five-year period) (See paragraph XX, XX of explanatory notes to this Category) Fee: \$1,455.10 Benefit 75% = \$1,091.35
MBS item ##### Coordination of a TMVr Case Conference by a TMVr practitioner where the TMVr Case Conference has a duration of 10 minutes or more (Not payable more than once per patient in a five-year period) Fee: \$51.70 Benefit 75% = \$38.80 85% = \$43.95
MBS item ##### Attendance at a TMVr Case Conference by a specialist or consultant physician who does not also perform the service described in the item ##### above for the same case conference where the TMVr Case Conference has a duration of 10 minutes or more. (Not payable more than once per patient in a five-year period) Fee: \$38.55 Benefit 75% = \$28.95 85% = \$32.80

MSAC proposed explanatory notes

TMVr Hospital

For item ##### a TMVr Hospital means a hospital, as defined by subsection 121-5(5) of the Private Health Insurance Act 2007, that is clinically accepted as being a suitable hospital in which the service described in Item ##### may be performed.

The Transmitral valve repair - Rules for the Accreditation of TMVr Practitioners developed by the assigned accreditation authority provides guidance on what are considered by the sector as minimum requirements that must be met in order to be a clinically acceptable facility that is suitable for TMVr procedures to be performed at.

TMVr Practitioner

For item ##### a TMVr Practitioner is either a cardiothoracic surgeon or interventional cardiologist who is accredited by the assigned accreditation authority.

Accreditation by the assigned accreditation authority must be valid prior to the service being undertaken in order for benefits to be payable under item #####.

TMVr Patient

A TMVr Patient means a patient who, as a result of a TMVr Case Conference, has been assessed as having an unacceptably high risk for surgical mitral valve replacement and is recommended as being suitable to receive the service described in item #####.

A TMVr Case Conference is a process by which:

- (a) there is a team of 3 or more participants, where:
 - (i) the first participant is a cardiothoracic surgeon; and
 - (ii) the second participant is an interventional cardiologist; and
 - (iii) the third participant is a specialist or consultant physician who does not perform a service described in Item ##### for the patient being assessed; and
 - (iv) either the first or the second participant is also a TMVr Practitioner; and
- (b) the team assesses a patient's risk and technical suitability to receive the service described in Item #####, taking into account matters such as:

- (i) the patient's risk and technical suitability for a surgical mitral valve replacement; and
- (ii) the patient's cognitive function and frailty; and
- (c) the result of the assessment is that the team makes a recommendation about whether or not the patient is suitable to receive the service described in Item #####, and
- (d) the particulars of the assessment and recommendation are recorded in writing.

While benefits are payable for an eligible TMVr Case Conference under Items ##### and #####, a claim for these services does not have to be made in order for a benefit to be paid under Item #####. Item ##### is only payable once per patient in a five year period.

TMVr CASE CONFERENCE - (ITEMS ##### AND #####)

Items ##### and ##### apply to a TMVr Case Conference organised to discuss a patient's suitability to receive the service described in Item ##### for Transmitral valve repair (TMVr).

For items ##### and ##### a TMVr Case Conference is a process by which:

- (a) there is a team of 3 or more participants, where:
 - (i) the first participant is a cardiothoracic surgeon; and
 - (ii) the second participant is an interventional cardiologist; and
 - (iii) the third participant is a specialist or consultant physician who does not perform a service described in Item ##### for the patient being assessed; and
 - (iv) either the first or the second participant is also a TMVr Practitioner; and
- (b) the team assesses a patient's risk and technical suitability to receive the service described in Item #####, taking into account matters such as:
 - (i) the patient's risk and technical suitability for a surgical mitral valve replacement; and
 - (ii) the patient's cognitive function and frailty; and
- (c) the result of the assessment is that the team makes a recommendation about whether or not the patient is suitable to receive the service described in Item #####, and
- (d) the particulars of the assessment and recommendation are recorded in writing.

TMVr Practitioner

For items ##### and ##### a TAVI Practitioner is either a cardiothoracic surgeon or interventional cardiologist who is accredited by Cardiac Accreditation Services Limited.

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

MSAC noted this is a resubmission requesting a new Medicare Benefits Schedule (MBS) listing for the reduction of mitral regurgitation through tissue approximation (TMVr), using a MitraClip device for the treatment of DMR and FMR in patients with mitral regurgitation who are not suitable for open heart surgery.

MitraClip is listed on the Australian Register of Therapeutic Goods, and the procedure is currently being performed by a number of centres in Australia, generally as part of a structural heart disease program.

MSAC noted that it had rejected a similar application three times previously due to uncertain clinical effectiveness, comparative safety and cost-effectiveness. MSAC noted that the three previous submissions sought listing in the DMR population only.

MSAC proposed including a limit on claiming of once every 5 years in the descriptor. MSAC also agreed that the Department consider defining the required specialties making up the multidisciplinary heart team (MDHT) conference in the item descriptor or explanatory note, as the MDHT was a crucial part of ensuring this technique is used for the correct patient population.

MSAC agreed that a specific anaesthesia management item for TMVr should be created.

The MSAC noted the comparator for the DMR population (Population 1), optimised medical treatment (OMT), is unchanged from the previous applications, and the same comparator is nominated for the FMR population (Population 2). The MSAC considered this appropriate.

MSAC considered that the new evidence presented for DMR patients (Population 1) to be insufficient to resolve MSAC's previous uncertainties regarding the comparative safety and effectiveness of TMVr with MitraClip compared to OMT. The additional evidence for the DMR population included in the current submission comprises transcatheter valve therapy registry data (Sorajja et al., 2017). This new evidence shows similar rates of safety and effectiveness outcomes as were reported in the comparative trials presented in the earlier applications, but does not resolve the previously identified uncertainties. However, MSAC accepted that on-balance, it was reasonable to conclude that TMVr with MitraClip was at least non-inferior to OMT for the DMR population, particularly in the context of a serious condition with limited treatment options.

MSAC agreed that the evidence presented in the COAPT trial supports the claim for non-inferior safety and superior effectiveness compared to OMT for Population 2 (FMR). MSAC noted the evidence presented in the MITRA-FR trial does not support the claim for superior effectiveness, however accepted the finding of no significant differences between TMVr and OMT in the overall MITRA-FR trial population was consistent with the recruitment of patients in whom mitral regurgitation is proportionately severe to the degree of left ventricular dilatation, and in whom a beneficial effect is not expected. MSAC agreed that the MITRA-FR trial is less applicable than the COAPT trial to the population for whom subsidy is sought, i.e. those with a disproportionately severe mitral regurgitation in relation to the degree of left ventricular dilatation.

MSAC considered that the difference in the requested fees for TMVr compared with transcatheter aortic valve implantation (TAVI) (\$1,748.45) was not well justified, and recommended the fee for TMVr be consistent with the fee for TAVI (\$1455.10).

MSAC recalled it previously requested that the applicant submit a cost-minimisation analysis (CMA) for the DMR population (Population 1), but the applicant asserted that a cost utility/cost-effectiveness analysis was more appropriate in its re-submission and its pre-MSAC response. MSAC noted the results of the CMA analysis conducted by the Department at its request (see section 11) and agreed that TMVr with MitraClip would be acceptably cost-effective for use in patients with DMR who cannot have surgery at an MBS procedure fee of \$1455.10 and a device cost of **\$redacted**.

MSAC agreed the applicant's cost-effectiveness approach was appropriate for the FMR population (Population 2). However MSAC noted the outcome of the FMR model is very sensitive to the time horizon and agreed with its ESC that a 10 year time horizon is an issue for this model. MSAC noted the applicant's pre-MSAC comments that it considers a 10-year time horizon is justifiable in the context of MR patients, who are 72 years at baseline, to adequately capture the long-term benefits and costs in that population. MSAC agreed that a 5-year model time horizon (as used for TAVI) was too conservative for the TMVr population which is overall younger than the TAVI population, but considered a 7-year time horizon would provide a more appropriate basis for assessing the cost-effectiveness of the proposed intervention.

MSAC noted that if the time horizon in the applicant's FMR model is set to 7 years rather than 10 years, and the MBS fee is reduced from \$1748.45 to \$1455.10, the cost of the MitraClip device would need to be adjusted to approximately **\$redacted** to maintain the same ICER per QALY (see also Table 9).

MSAC noted the financial estimates provided by the applicant indicate around two-thirds of the patients who are expected to receive this intervention have DMR and one-third have FMR. On that basis MSAC recommended the price for the MitraClip device used in this procedure be no higher than \$redacted (See Table 11, assuming an MBS procedure fee of \$1455.10). MSAC recommended the same price be paid for the MitraClip device irrespective of the number of devices used in a single procedure.

MSAC noted that the application's financial estimates would need to be revised to take into account the outcomes of the MSAC's considerations.

MSAC agreed that providers should be accredited to be able to claim TMVr on the MBS, and agreed with the Department that the TAVI accreditation committee may also be appropriate for TMVr.

MSAC noted the consumer feedback strongly supporting a TMVr registry for quality assurance purposes. MSAC agreed that a registry should be a condition of listing, but noted the Department's advice that there is currently no legal basis to make such a registry compulsory. MSAC noted the Department's advice that it is working towards establishing a legal basis for this type of registry.

3. Background

This resubmission (Applicant Developed Assessment Report [ADAR]) is the fourth iteration of this application series (1192).

In November 2012, MSAC considered Application 1192 for patients with moderate to severe MR and did not support public funding. The then comparator was conventional surgery for repair or replacement of the mitral valve and, to a lesser extent, medical management for patients considered to be high risk. MSAC considered that MitraClip therapy may be beneficial to treat high risk patients. However, the MSAC noted that there would need to be a high-level study performed to address the lack of data.

In April 2014, MSAC considered Application 1192.1 and did not support public funding for the reduction of MR through tissue approximation using transvenous/transeptal techniques because of uncertain comparative safety, effectiveness and cost-effectiveness due to limited direct comparative data. MSAC considered it was difficult to define a clinical need in terms of the patient population likely to benefit.

In July 2016, MSAC considered Application 1192.2 and did not support the application due to continued uncertainty about clinical effectiveness and cost-effectiveness of reduction of severe MR through tissue approximation using transvenous/transeptal techniques in patients with severe DMR (grade 3+ or 4+) considered to be high risk for surgery. However, MSAC noted that there is a clinical need in a small group of patients with severe DMR who are unsuitable for surgery.

The Public Summary Documents (PSD) for Application 1192, 1192.1 and 1192.2 are available on the MSAC website.

4. Prerequisites to implementation of any funding advice

Items on the Australian Register of Therapeutic Goods (ARTG) that are relevant to this application are shown in Table 1.

Table 1 Mitral valve tissue repair systems listed on the ARTG

ARTG no.	Product no./ product category	Product description	Intended use	Sponsor
309700 Date: 26/09/2018	56280 / Medical Device Class III	<u>Mitral valve tissue repair system</u> The MitraClip NTR/XTR Systems consists of the Clip Delivery System (CDS) and the Steerable Guide Catheter (SGC). The CDS is introduced into the body through a SGC which includes a dilator. The CDS is used to advance and manipulate the MitraClip NTR/XTR device for proper positioning and placement on the mitral valve leaflets.	The MitraClip System is intended for reconstruction of the insufficient mitral valve through tissue approximation	Abbott Vascular
309701 Date: 26/09/2018	57790 / Medical Device Class III	<u>Mitral valve clip</u> The MitraClip NTR/ XTR Clip Delivery System (CDS0602) consists of three major components: The Delivery Catheter, the Steerable Sleeve and the MitraClip Device. The MitraClip NTR/XTR device is a percutaneously implantable mechanical Clip that grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle.	The MitraClip NTR/XTR CDS is used to advance and manipulate the MitraClip device which is intended for reconstruction of the insufficient mitral valve through tissue approximation	Abbott Vascular
292317* Date: 2/08/2017	37039 / Medical Device Class I	<u>MitraClip Accessories</u> Accessories used in conjunction with the MitraClip System: 1) a Stabilizer, 2) a Lift, 3) a Support (Plexiglas) Plate.	A device used to stabilize or support a variety of other devices, used in conjunction with surgical procedures.	Abbott Vascular
289168 Date: 19/05/2017	57790/ Medical Device Class III	<u>Mitral valve clip</u> The MitraClip NT Clip Delivery System (CDS0502) consists of three major components: the Delivery Catheter, the Steerable Sleeve and the MitraClip NT Device. The MitraClip NT device is a percutaneously implantable mechanical Clip that grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle.	The MitraClip NT CDS is used to advance and manipulate the MitraClip NT device which is intended for reconstruction of the insufficient mitral valve through tissue approximation	Abbott Vascular
289167 Date: 19/05/2017	56280 / Medical Device Class III	<u>Mitral valve tissue repair system</u> The MitraClip NT System consists of the Clip Delivery System (CDS) and the SGC. The CDS is introduced into the body through a SGC which includes a dilator. The CDS is used to advance and manipulate the MitraClip NT device for proper positioning and placement on the mitral valve leaflets	The MitraClip NT System is intended for reconstruction of the insufficient mitral valve through tissue approximation	Abbott Vascular

*Manufacturer change from Menlo Park to Abbott Vascular, Santa Clara

Source: Table 7, p43 of ADAR

5. Proposal for public funding

The ADAR proposed MBS item descriptors for TMVr in DMR and FMR modelled on the TAVI descriptor (MBS item 38495), shown below in Table 2. The explanatory notes, like those for the item 38495, will be included for the TMVr item.

Similar to TAVI, the applicant proposed two additional items listed related to the case conference for coordination of the TMVr service using a MDHT based on MBS items 6080 and 6081 (Table 2). The MDHT will have a key role in determining which patients are ineligible for surgical intervention that would benefit from the TMVr procedure. Based on feedback from PASC and local experts, it was suggested that the MDHT include a heart failure (HF) specialist. A minimum of three physicians will make up the MDHT.

Table 2 Proposed MBS item descriptors

Category 3 – Therapeutic procedures
<p>MBS item #####</p> <p>Transvenous/transseptal techniques for permanent coaptation of mitral valve leaflets using 1 or more tissue approximation devices in patients with moderate-severe or severe symptomatic degenerative mitral regurgitation (Grade 3+, 4+), who have left ventricular ejection fraction (LVEF) $\geq 20\%$, who are symptomatic (New York Heart Association [NYHA] functional class II or greater), who are determined by a MDHT to be ineligible for surgical intervention but suitable for the MitraClip procedure.</p> <p>The procedure to be performed in a transmitral valve repair (TMVr) Hospital on a TMVr Patient by a TMVr Practitioner – includes all intraoperative diagnostic imaging that the TMVr Practitioner performs upon the TMVr Patient.</p> <p>(Not payable more than once per patient in a five-year period)</p> <p>(See paragraph XX, XX of explanatory notes to this Category)</p> <p>Fee: \$1,748.45 Benefit 75% = \$1,311.35 85% = \$1,486.18</p>
<p>MBS item #####</p> <p>Transvenous/transseptal techniques for permanent coaptation of mitral valve leaflets using 1 or more tissue approximation devices in patients with moderate-severe or severe symptomatic functional mitral regurgitation (Grade 3+, 4+), with LVEF 20–50% and LVESD ≤ 70mm considered by the MDHT to be ineligible for surgical intervention, and whose symptoms (NYHA functional class II or greater) persist despite maximally tolerated guideline directed medical therapy (GDMT) as determined by the MDHT.</p> <p>The procedure to be performed in a transmitral valve repair (TMVr) Hospital on a TMVr Patient by a TMVr Practitioner – includes all intraoperative diagnostic imaging that the TMVr Practitioner performs upon the TMVr Patient.</p> <p>(Not payable more than once per patient in a five-year period)</p> <p>(See paragraph XX, XX of explanatory notes to this Category)</p> <p>Fee: \$1,748.45 Benefit 75% = \$1,311.35 85% = \$1,486.18</p>
<p>MBS item #####</p> <p>Coordination of a TMVr Case Conference by a TMVr practitioner where the TMVr Case Conference has a duration of 10 minutes or more</p> <p>(Not payable more than once per patient in a five-year period)</p> <p>Fee: \$51.70 Benefit 75% = \$38.80 85% = \$43.95</p>
<p>MBS item #####</p> <p>Attendance at a TMVr Case Conference by a specialist or consultant physician who does not also perform the service described in the item above for the same case conference where the TMVr Case Conference has a duration of 10 minutes or more.</p> <p>(Not payable more than once per patient in a five-year period)</p> <p>Fee: \$38.55 Benefit 75% = \$28.95 85% = \$32.80</p>

Source: Table 8, p45 of ADAR

The proposed MBS fee has increased from \$895.30 in Application 1192, to \$912.30 in Application 1192.1, to \$1720.90 in Application 1192.2, to \$1,748.45 in Application 1192.3. The ADAR claimed that the proposed MBS fee for TMVr was benchmarked to existing MBS item 38487 (open valvotomy of mitral valve) in the previous resubmission (1192.2). MBS

fees for this item, TAVI and associated case conference items increased in July 2019 (as part of the regular MBS fee increases). These increased MBS fees are reflected in the item descriptors.

The ADAR altered the descriptor for the proposed population for FMR. The ratified PICO specified that patients with FMR must have left ventricular ejection fraction (LVEF) $\geq 20\%$, this was altered to '20–50%' in the ADAR. The ADAR identified two trials relevant to the FMR population: the COAPT trial (Stone et al. 2018) and MITRA-FR trial (Obadia et al. 2018). The ADAR claimed there were clinically important differences in the baseline characteristics between the COAPT and MITRA-FR trials. Because of these differences, the ADAR proposed the FMR patient population eligible for TMVr be confined; based on patient eligibility criteria as per the COAPT trial. Therefore, the ADAR excluded the MITRA-FR trial from the clinical claim and presented the evidence from the MITRA-FR trial as evidence of patients who should not be eligible for TMVr on the MBS.

The commentary acknowledged that from the effective regurgitant orifice area (EROA) and LVEF measures in the two trial populations, the COAPT trial patients had more severe MR (higher EROA) than MITRA-FR, while having similar levels of LVEF. While this demonstrated the disproportionate MR in relation to LVEF in COAPT patients, this is not reflected in the PICO or MBS item descriptor, which includes only LVEF and not EROA. The commentary suggested there may be potential for patient leakage to the population in the MITRA-FR trial with the current MBS item descriptor.

In the pre-ESC response, the applicant reiterated that the MITRA-FR results are indicative of which patients should not be eligible for TMVr on the MBS and that these patients are not reflective of the specific subgroup of FMR patients ('COAPT-like patients') for whom MBS listing is sought. The applicant stated that after the completion of the COAPT trial, demonstrating superior mortality of TMVr versus optimal medical management (OMT), real world clinical practice is being shaped away from the MITRA-FR study in terms of patient selection and the application of the TMVr intervention.

The applicant stated that careful patient selection is critical to ensure that access to TMVr on the MBS is limited to FMR patients that will benefit from the intervention at a magnitude of effect similar to that observed in the COAPT study. As such, the applicant proposed the following strategies to ensure the eligible FMR population for treatment of TMVr on the MBS targets 'COAPT-like patients' and precludes 'MITRA-FR-like patients' from accessing treatment:

- Eligibility will be assessed and determined by a MDHT, by combining eligibility considerations such as: surgical risk assessment, frailty, major organ system dysfunction and procedure-specific impediments, anatomical suitability for MitraClip and for FMR, ensuring only patients in whom the MR is disproportionate to their left ventricular end diastolic volume (LVEDV) (MR grading 3+ or 4+; LVESD ≤ 70 mm). The MDHT will act as a gate keeper ensuring appropriate patient selection.
- A consensus/position statement will be prepared by a Working Group, including a multidisciplinary team of Key Opinion Leaders (with representatives from the Cardiac Society of Australia and New Zealand [CSANZ]), and the Australian and New Zealand Society of Cardiac and Thoracic Surgeons [ANZSCTS]), that further defines TMVr hospitals, practitioners and patients. This position paper will underpin the MBS listing for TMVr.

In the pre-MSAC response, the applicant noted that ESC considered the higher fee for TMVr than for TAVI is not justified (\$1,720.90 vs \$1,432.20). The applicant reiterated their justification for the proposed fee and maintained that the proposed fee for the TMVr

procedure is appropriate. Nevertheless, the applicant expressed willingness to work with MSAC and local experts in finalising the fee if necessary.

6. Summary of public consultation feedback/consumer Issues

See [Public Summary Document \(PSD\) Application No. 1192](#), Nov 2012.

7. Proposed intervention's place in clinical management

Description of Proposed Intervention

The proposed medical service is percutaneous reconstruction of an insufficient mitral valve through tissue approximation using transvenous/transseptal techniques. The procedure is performed under general anaesthesia by an interventional cardiologist and/or cardiothoracic surgeon, using a catheter-based device that enables physicians to perform percutaneous, transvenous/transseptal mitral valve repair in patients with MR while the heart is beating. The TMVr procedure is based on the principle of edge-to-edge repair but a mechanical clip (MitraClip) is used in place of a suture to allow permanent coaptation ('approximation') of the two malfunctioning mitral valve leaflets.

Description of Medical Condition(s)

MR occurs when the leaflets (or flaps) of the heart's mitral valve do not close properly and leak. The mitral valve is a one-way valve that separates the left atrium (a chamber in the heart which collects blood from the lungs) from the left ventricle (a chamber in the heart which pumps blood to the rest of the body). During left ventricular systole, the leak in the mitral valve causes blood to flow backwards into the left atrium (also known as regurgitant volume), thereby decreasing blood flow to the body (resulting in lower cardiac output and stroke volume).

To maintain blood flow to the body and compensate for MR, the left ventricle must increase its contraction. Backflow due to MR places an extra burden on the left ventricle and lungs. Eventually, this burden can cause other problems, such as: stroke, sudden death, irregular heartbeat, increasing damage to the heart muscle (progressive myocardial injury); and/or inability to maintain adequate circulation of blood (congestive heart failure).

The proposed medical service is specified for treating MR in two subset patient populations:

- Population 1: Degenerative mitral regurgitation (DMR)
Patients with moderate-severe or severe DMR (MR grading of 3+ or 4+) who are determined by a multidisciplinary heart team (MDHT) to be ineligible for surgical intervention.
- Population 2: Functional mitral regurgitation (FMR)
Patients with moderate-severe or severe FMR (MR grading of 3+ or 4+), who are considered by the MDHT to be ineligible for surgical intervention, and whose symptoms persist despite maximally tolerated Guideline-Directed Medical Therapy (GDMT) as determined by the MDHT.

The proposed clinical management algorithms for TMVr in the DMR and FMR population are presented in Figure 1 and Figure 2, respectively.

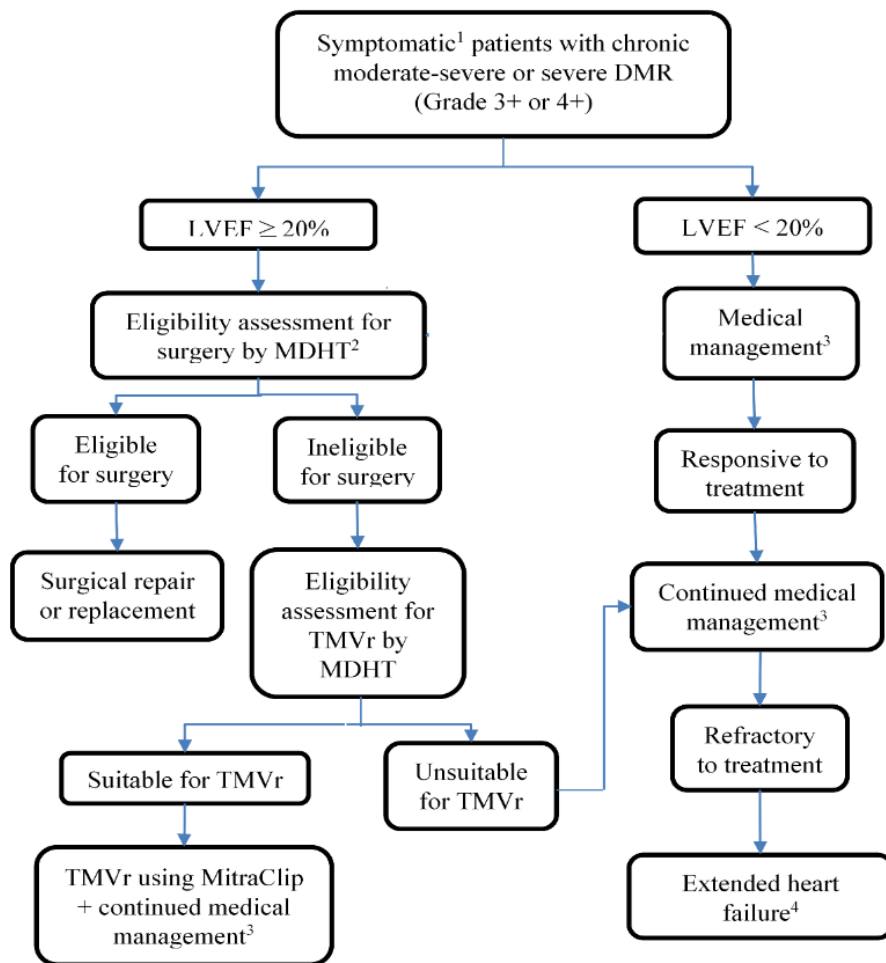


Figure 1 Proposed clinical management algorithm with introduction of TMVr – Population 1: DMR

DMR, degenerative mitral regurgitation; MR, mitral regurgitation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

¹ Symptomatic = NYHA functional class II or greater

² Patients considered ineligible for surgery as determined by a multidisciplinary heart team, combining surgical risk assessment, frailty, major organ system dysfunction, and procedure-specific impediments.

³ Medical management refers to maximally tolerated guideline directed medical therapy (GDMT)

⁴ Extended heart failure management includes cardiac resynchronisation therapy, ventricular assist devices, cardiac restraint devices and heart transplant

Source: Figure 7, p59 of ADAR

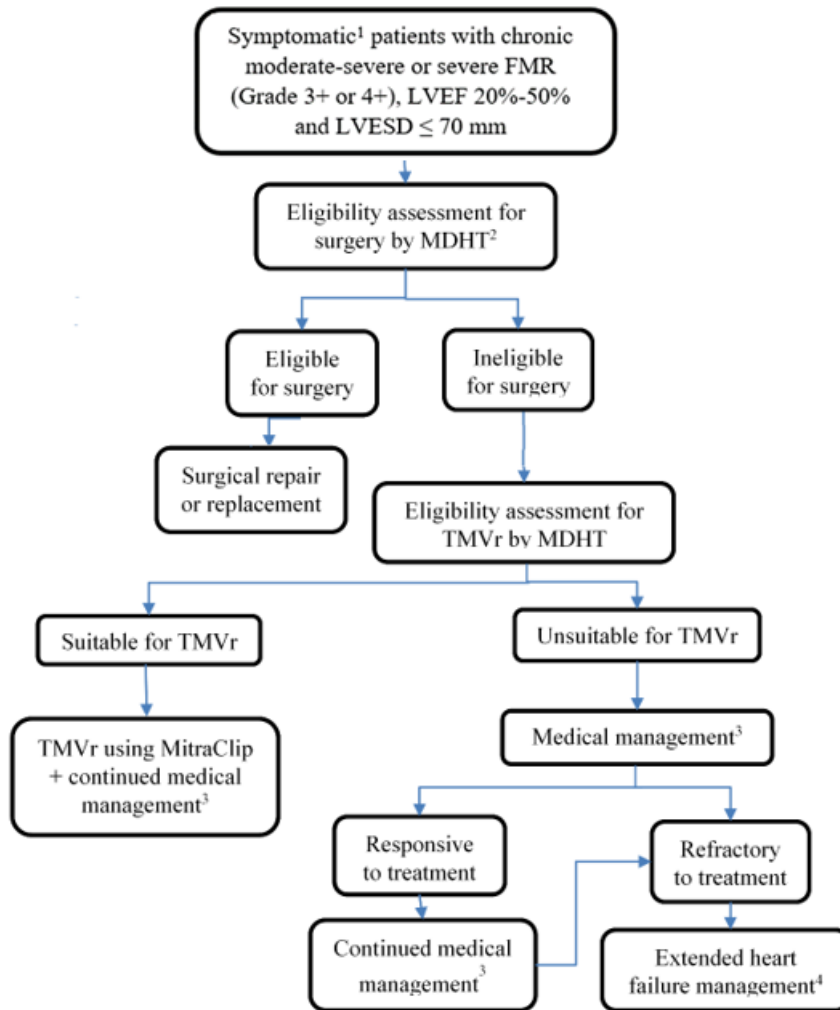


Figure 2 Proposed clinical management algorithm with introduction of TMVr – Population 1: DMR

FMR, functional mitral regurgitation; MR, mitral regurgitation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MDHT, multidisciplinary heart team; LVESD, Left Ventricular End Systolic Volume.

¹ Symptomatic = NYHA functional class II or greater

² Patients considered ineligible for surgery as determined by a multidisciplinary heart team, combining surgical risk assessment, frailty, major organ system dysfunction, and procedure-specific impediments.

³ Medical management refers to maximally tolerated guideline directed medical therapy (GDMT)

⁴ Extended heart failure management includes cardiac resynchronisation therapy, ventricular assist devices, cardiac restraint devices and heart transplant

Source: Figure 9, p62 of ADAR

8. Comparator

The comparator proposed in this resubmission (Application 1192.3) is medical management.

Medical management was previously considered by MSAC to be an appropriate comparator (see PSD Application No. 1192.2, p8).

9. Comparative safety

Population 1: DMR

No new comparative safety data was presented in this resubmission (Application 1192.3).

The three non-randomised comparative studies (EVEREST II HRR: Whitlow et al. 2012, Velazquez et al. 2015 and Swaans et al. 2014) were provided in the previous submission (Application 1192.2). The only additional evidence provided in this resubmission

(Application 1192.3) was one large, prospective, single arm, Society of Thoracic Surgery/American College of Cardiology Transcatheter Valve Therapy registry (TVT registry) of 2,952 patients (85.9% DMR) undergoing TMVr (Sorajja et al. 2017).

The ADAR stated that the incident rate of 30-day mortality with TMVr was lower than in the OMT cohort (TMVr: range 4.2-7.7% vs OMT: range 7.2-8.3%). The TVT registry (N=1867) reported similar 30-day mortality with TMVr.

The ADAR also stated that the 30-day major adverse event (MAE) rate with TMVr in EVEREST II HRR was 26.9%, with the most common MAE being transfusion of ≥ 2 U of blood, which occurred in 14 patients (17.9%) at 30 days and in 19 patients (24.4%) at 12 months. Few device-related adverse events (AEs) were reported with TMVr and did not appear to differ between the EVEREST II HRR trial and the TVT registry. Single leaflet device attachment (EVEREST II HRR: 1.3% and TVT registry: 1.5%) and device embolisation (EVEREST II HRR: 0% and TVT registry: 0.1%) was comparable between the EVEREST II HRR and TVT registry patients. In EVEREST II HRR, beyond one year, all AEs were low and stable through five years, with no unexpected safety signal through long-term follow-up.

The commentary noted that the comparative data comes from a mixed population of DMR and FMR patients and that the data did not consist of primarily DMR patients. For the previous submission (Application 1192.2), MSAC considered that TMVr had a reasonable safety profile, however still noted that there was continued uncertainty in the safety evidence for the DMR population (see PSD Application No. 1192.2, p1). The commentary noted that the only new evidence presented is the single arm retrospective TVT registry study that reports similar rates of 30-day mortality and clinical adverse events. The commentary considered that TMVr continues to have uncertain safety for the DMR population.

In the pre-MSAC response, the applicant reiterated their claim that the TMVr procedure is safe, and that a claim of non-inferiority to OMT for the DMR population is reasonable. To support this the applicant reiterated their claims that:

- There is no indication of any safety risks specific to the DMR population.
- It is reasonable to extrapolate the safety of the TMVr procedure relative to OMT from the COAPT study (FMR population) to the DMR population as the procedure itself is the same irrespective of the MR aetiology.
- Typically, the main safety considerations for an implantable device relative to OMT are those that are procedure and device related. For these events, comparative evidence versus OMT is not necessary, and as such, the TVT registry, including a large sample size (N=1867 for safety assessment) is considered informative.
- The extended assessment of harms section of the ADAR reported safety data from a range of international registries additional to the TVT, including both FMR and DMR patients. Considering only those registries that included both aetiologies, safety data for a total of 2629 patients were reported of which 66% and 34% had FMR and DMR aetiology respectively. This is further supported by the MitraClip Asia-Pacific Registry (MARS) registry including 49 (30%) Australian patients (N=169) confirming that procedural mortality is similar between DMR and FMR patients (Tay et al., 2016).
- Local experts concur that there are no differential safety issues associated with TMVr in DMR and FMR patients (pre-MSAC response attachment – Letter from **redacted**).

Population 2: FMR

Two open-label randomised controlled trials (RCTs), COAPT (Stone et al. 2018) and MITRA-FR (Obadia et al. 2018), of 3- and 2-years follow-up respectively were presented. The GRADE assessment tool suggested the COAPT is of high quality whereas MITRA-FR is of moderate quality given the significant amount of missing data for key secondary outcomes.

The ADAR stated the COAPT trial reported a decreased risk of death and of heart failure-related rehospitalisation in the TMVr group, compared to the control group receiving continued OMT (Stone et al. 2018). The majority of events for which a statistically significant difference in favour of TMVr were reported, were consistent with the effectiveness of TMVr in reducing all-cause death, death due to cardiovascular causes and hospitalisations due to HF. However, a statistically significantly lower proportion of TMVr patients than OMT patients required a left ventricular assist device (LVAD) implantation (7.3% vs 11.4%; $p=0.03$) over 36 months suggesting a safety advantage with TMVr.

The ADAR stated the co-primary safety outcome in the COAPT trial was freedom from device related complications at 12 months. The Kaplan-Meier estimate of event-free rate was 96.6% with the 95% lower confidence limit (94.8%) exceeding the objective performance goal of 88.0% for the primary safety end point ($p<0.001$). A total of nine device related complications were reported of which three were LVAD implants, two were heart transplant, two were single leaflet device attachment and one device embolisation. One patient developed pericardial effusion and tamponade. No late device related complications were reported over 36 months. Device migration was not reported. The rates of 30-day mortality and stroke was low, at 2% and 0.7% respectively.

The ADAR reported the proportion of patients experiencing a myocardial infarction (MI) over 24 months was lower in TMVr than OMT patients (4.7% versus 6.5%) over 24 months. There were no adverse events reported in a statistically significantly higher proportion of TMVr than OMT patients, with the rates reported numerically lower in the TMVr subjects than OMT subjects consistently across all events.

The ADAR did not use the MITRA-FR trial results as part of its clinical claim. The ADAR claimed that there were clinically important differences in the baseline characteristics between the COAPT and MITRA-FR trials (discussed in section B.4 of the ADAR, p88-92). Therefore, the ADAR excluded the MITRA-FR trial from the clinical claim and claimed the MITRA-FR trial presented evidence of the population in which TMVr is less effective and not eligible for listing. In the MITRA-FR study, the mortality rate at 30 days was 3.3% (5 patients) in the TMVr group and 2.6% (4 patients) in the OMT group. The rates of ischaemic or haemorrhagic stroke (4.6% vs 0.7%), renal-replacement therapy (3.3% vs 0.7%), and severe haemorrhage (7.2% vs 3.9%) were higher in the TMVr group than in the OMT group.

The commentary noted the evidence presented in the COAPT trial supports the claim for non-inferior safety and superior effectiveness. However, the commentary raised two issues that add to uncertainty in the FMR population:

- i. the evidence presented in the MITRA-FR trial does not support the claim for superior effectiveness;
- ii. the ADAR excluded MITRA-FR results from the clinical claim.

The commentary acknowledged that the explanation provided in the ADAR for exclusion of MITRA-FR could be justified. The commentary also noted that the ADAR cited the MITRA-FR results (no significant differences in effectiveness outcomes) as indicative of which patients should not be eligible for TMVr on the MBS (i.e. those with MR proportionally severe to the degree of left ventricular dysfunction). However, the

commentary suggested the MITRA-FR setting may be more reflective of the real-world setting, which would argue for the inclusion of MITRA-FR results as part of the clinical claim.

Based on the COAPT and MITRA-FR trial, the commentary considered the safety profile of TMVr in the FMR population is uncertain.

10. Comparative effectiveness

Population 1: DMR

The ADAR claimed that the results from the comparative studies demonstrated that TMVr patients have a statistically significant higher survival rate at one year (range 76% to 86%) compared with patients who are receiving OMT (55% to 68%). This difference remained significantly different through three years (Swaans et al. 2014), with survival rates at two years (75.5% vs. 52.5%) and three years (62.3% vs. 45.8%) being statistically significantly higher in the TMVr arm than the OMT arm (at 3 years: HR=0.41, 95%CI: 0.22-0.78; p=0.006). The survival rate in the TVT registry at 12 months, 74.2%, was comparable to the comparative trials.

In EVEREST II HRR, 42% (33/78) of patients in the 12 months prior to TMVr had been hospitalised due to HF, compared with 16% (12/75) in the 12 months after the TMVr procedure (p=0.018). The ADAR suggested this demonstrated a significant treatment benefit with TMVr in terms of reducing rehospitalisations. The TVT Registry reported similar 12-month rate of rehospitalisation due to HF, at 20.2%.

The ADAR claimed that statistically significant and clinically meaningful improvements in MR grade and echocardiographic measurements from baseline through to follow-up were demonstrated with TMVr in the EVEREST II HRR. Similarly, patient-relevant outcomes such New York Heart Association (NYHA) functional class and quality of life measures reported to show significant improvements from baseline through to follow-up in the EVEREST II HRR.

On the basis of the benefits and harms reported in the evidence base (summarised below in Table 3), the ADAR claimed that, relative to OMT, TMVr has non-inferior safety and superior effectiveness in the DMR population.

Table 3 Balance of clinical benefits and harms of TMVr, relative to OMT, and as measured by the critical patient-relevant outcomes in the key studies: Population 1: DMR

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE) ^a	Relative effect (95%CI)	Risk with TMVr and OMT n/N (%)	RD / MD (95% CI); NNT	Comments
Pop 1: DMR						
Survival at 12 months	K=3 comparative; N=1621 K=1 TVT registry, N=1867	⊕⊖⊖⊖	HR: 0.47 (0.24, 0.93) ^a	TMVr: range: 76–86% vs OMT: range 55–68% TVT: 74.2%	EVEREST II HRR: 20.1%(-0.8, 40.9)	Statistically and clinically significant in favour of TMVr, registry survival supports real world effectiveness.
30-day mortality	K=2 comparative; N=1418 K=1 TVT registry N=1867	⊕⊖⊖⊖	–	TMVr: range 4.2-7.7% OMT: range 7.2-8.3% TVT: 5.2%	EVEREST II HRR: -0.6% (-13.5%, 12.2%)	No significant difference, registry supports real world safety
MR severity ≤2+ at 12 months	K=1 [pre-post comparison] N=78	⊕⊖⊖⊖	–	Baseline: 1/78 (1.3%) 12 months: 42/54 (77.8)	Difference vs baseline: 76.5%	The majority of TMVr patients had clinical improvements in MR severity at 12 mts
Rehospitalisation for HF at 12 months relative to 12 months prior TMVr	K=1 [pre-post comparison] N=78	⊕⊖⊖⊖	–	12 mts prior TMVr: 33/78 (42%) vs 12 mts post TMVr: 12/75 (16%)	Difference vs 12 mts prior TMVr: 26%	The rate of rehospitalisation in EVEREST II HRR at 12 mts, 16%, similar to registry, 20.2%

NYHA=New York Heart Association; KCCQ=Kansas City Cardiomyopathy Questionnaire; TMVr=transcatheter mitral valve repair; OMT=optimal medical management; NNT=number needed to treat; CI=confidence interval; RD=risk difference; RRR=relative risk reduction; OR=odds ratio; MD=mean difference; K=number of studies; N=number of participants; MR=mitral regurgitation; HF=heart failure; NR=not reported. ^a GRADE Working Group grades of evidence (Guyatt et al. 2013); ⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. ^bNot down graded despite open label nature of design and subjective outcome, because outcomes assessors were blinded to treatment assignment. ^c58 OMT patients received TMVr after 24 months and were included in the OMT arm of the ITT analysis, thus potentially biasing against TMVr.

Source: Table 2, p28 of ADAR.

The commentary noted that:

- The comparative data (Whitlow et al. 2012, Velazquez et al. 2015 and Swaans et al. 2014) is limited and was presented in the previous resubmission (Application 1192.2).
- The comparative evidence came from a mixed population of DMR and FMR, including primarily those with FMR.
- Survival at 12 months was marginally significant in favour of TMVr in the EVEREST II HRR trial, however this trial included primarily FMR patients.
- New data was presented in this resubmission. However, this data was from a single arm retrospective study.

The commentary considered based on the comparative effectiveness evidence presented TMVr has uncertain effectiveness in the DMR population, relative to OMT.

Overall, the commentary disagreed with the ADAR and considered, on the basis of the benefits and harms reported in the evidence base, TMVr has uncertain safety and uncertain effectiveness in the DMR population, relative to OMT.

In the pre-ESC response, the applicant stated that the new evidence presented in the ADAR for the DMR population (TVT registry) represents the largest reported experience in transcatheter treatment of DMR. Including almost 1500 patients with DMR of similar characteristics to those for whom listing is sought, the evidence provided a robust representation of the magnitude of absolute effect that can be expected with TMVr in these patients in the Australian clinical setting. The applicant claimed that the similarity in the rates of safety and effectiveness outcomes observed in the TMVr arm of the pivotal evidence (EVEREST II HRR) and the TVT registry (Sorajja et al 2017) support the reliability of this evidence base. Overall, the applicant maintained that the ADAR provided sufficient evidence to support a conclusion of non-inferior safety and superior effectiveness of TMVr versus OMT in the DMR population.

In the pre-MSAC response, the applicant reiterated its claim and stated there is no evidence to suggest that TMVr is non-inferior to OMT in these patients. The applicant proposed that the results of superiority of TMVr versus OMT be considered in context of the wider body of evidence, the biological plausible mechanism of the TMVr procedure in the DMR population and the high clinical need for an intervention directed at fixing the valve itself in patients ineligible for surgery. The applicant acknowledged that there is an RCT planned in the DMR population (REPAIR-MR) however, the applicant claimed that the RCT is in the wrong population (DMR patients eligible for surgery) and versus the wrong comparator (mitral valve surgery). Therefore, the study is not directly informative to the research question framed by the PICO in this assessment.

Population 2: FMR

The ADAR reported the COAPT trial demonstrated that TMVr was statistically significantly superior to OMT with respect to all primary and secondary effectiveness outcomes. The COAPT trial reported that 30.5% of TMVr group subjects experienced at least 1 HF hospitalisation through 24-month follow-up, compared with 48.4% in the OMT group and a significant 47.5% reduction in the risk of recurrent HF hospitalisation in favour of TMVr ($p < 0.0001$). This difference was maintained over 36 months (HR [95%CI]: 0.49 [0.37, 0.63]; $p < 0.0001$). All-cause mortality within 24 months was significantly lower with TMVr than with OMT alone (29.1% vs. 46.1%; HR [95% CI] 0.62 [0.46 to 0.82]; $p < 0.001$). The number needed to treat to save one life within 24 months was 5.9. The survival benefit was maintained over 36 months, based on the intention to treat (ITT) population, despite including cross overs (58 OMT patients received TMVr (HR [95% CI]: 0.67 [0.52, 0.85])).

The ADAR stated quality of life (Kansas City Cardiomyopathy Questionnaire [KCCQ] and NYHA functional class) was significantly better, functional capacity (6-min walk test [6MWT]) was more preserved and mitral regurgitation and left ventricular remodelling (MR grade and LVEDV) were less severe with TMVr than with OMT alone. The differences in KCCQ and 6MWT exceeded minimally clinically important differences (MCIDs) of five points and 24 metres respectively at 24 months.

The ADAR noted that the MITRA-FR trial showed no significant differences in effectiveness outcomes of TMVr relative to OMT. At 12 months and 24 months, MITRA-FR reported no significant differences for death, hospitalisation due to HF and major adverse cardiovascular events (Obadia et al. 2018). The ADAR claimed this is consistent with recruitment of patients in whom the MR is proportionately severe to the degree of left ventricular dilation and in

whom an effect is not expected based on the framework by Grayburn et al. (2019). The ADAR did not include the MITRA-FR trial in the clinical claim. Instead, the ADAR claimed that the results from MITRA-FR indicate which patients should not be eligible for TMVr on the MBS (i.e. those with MR proportionally severe to the degree of left ventricular dysfunction).

On the basis of the benefits and harms reported in the COAPT (summarised below in Table 4), the ADAR claimed that, relative to OMT, TMVr has non-inferior safety and superior effectiveness in the FMR population.

Table 4 Balance of clinical benefits and harms of TMVr, relative to OMT, and as measured by the critical patient-relevant outcomes in the key studies: Population 2: FMR

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE) ^a	Relative effect (95%CI)	Risk with TMVr and OMT n/N (%)	RD / MD (95% CI); NNT	Comments
Pop 2: FMR						
Recurrent hospitalisation for HF at 24 mts	K=1; N=614	⊕⊕⊕⊕	HR: 0.525 (0.40, 0.70)	48.4%	RD: 17.9% NNT=5.9	RRR of TMVr vs OMT is 48.5%, statistically and clinically significant; treatment effect maintained at 36 mts
All-cause mortality at 24 months	K=1 N=614	⊕⊕⊕⊕	HR: 0.62 (0.46, 0.82)	46.1%	RD: 17% NNT=5.9	RRR of TMVr vs OMT is 38%, statistically and clinically significant
All-cause mortality at 36 months	K=1 N=614	⊕⊕⊕⊕	HR: 0.67 (0.52, 0.85)	42.8%	RD: 12.7% NNT [95% CI]=7.9 [4.6, 26.1]	The survival benefit with TMVr was maintained at 36 mts based on the ITT population ^c
MR severity ≤2+ at 12 months	K=1 N=614	⊕⊕⊕⊕	OR: 20.52 (10.44, 40.33)	46.9%	RD: 48% (40, 56) NNT: 2	Statistically and clinically significant in favour of TMVr; 5.2% of TMVr pts remained MR 3+ / 4+
KCCQ change at 12 months	K=1 N=465	⊕⊕⊕⊕ ^b	–	–	MD: 16.1 (11.0 to 21.2)	Statistically and clinically significant; treatment effect maintained at 24 mts MD > 5 points (MCID)
NYHA class I or II at 12 months	K=1, N=469	⊕⊕⊕⊕ ^b	OR: 2.64 (1.80, 3.87)	49.6%	RD: 23% [14, 31]	Statistically and clinically significant. NB groups not balanced at baseline
LVAD or heart transplantation at 36 months	K=1 N=NR	⊕⊕⊕⊕	0.49 (0.25, 0.94)	11.4%	RD: 4.1%	Statistically and significantly relevant outcome in the context of the proposed population

NYHA=New York Heart Association; KCCQ=Kansas City Cardiomyopathy Questionnaire; TMVr=transcatheter mitral valve repair; OMT=optimal medical management; NNT=number needed to treat; CI=confidence interval; RD=risk difference; RRR=relative risk reduction; OR=odds ratio; MD=mean difference; K=number of studies; N=number of participants; MR=mitral regurgitation; HF=heart failure; NR=not reported. ^a GRADE Working Group grades of evidence (Guyatt et al. 2013); ⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊕ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕⊕⊕ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⊕⊕⊕⊕ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. ^bNot down graded despite open label nature of design and subjective outcome, because outcomes assessors were blinded to treatment assignment. ^c58 OMT patients received TMVr after 24 months and were included in the OMT arm of the ITT analysis, thus potentially biasing against TMVr.

Source: Table 2, p28 of ADAR

The commentary noted that the COAPT and MITRA-FR trials reported different results. At 12 months and 24 months, MITRA-FR reported no significant differences for death, hospitalisation due to HF and major adverse cardiovascular events; while COAPT reported

differences in favour of TMVr, for all-cause mortality and hospitalisation due to HF at 24 and 36 months (Obadia et al. 2018, Stone et al. 2018). The commentary considered based on the evidence presented TMVr has uncertain effectiveness in the FMR population, relative to OMT.

Overall, the commentary disagreed with the ADAR and considered, on the basis of the benefits and harms reported in the COAPT and MITRA-FR trials, TMVr has at least non-inferior safety and uncertain effectiveness in the FMR population, relative to OMT.

In the pre-ESC response, the applicant reiterated that:

- The COAPT trial supports the claim of non-inferior safety and superior effectiveness of TMVr versus OMT in the FMR population.
- The results from the MITRA-FR study do not corroborate those of the COAPT study, the results from the MITRA-FR study are explained by patient selection and therefore, these patients should not be eligible for TMVr on the MBS.

In the pre-MSAC response, the applicant acknowledged there are further clinical trials planned, EVOLVE-MR and RESHAPE-HF2. However, the applicant claimed that the EVOLVE-MR is not likely to be informative given that the trial includes moderate severe MR patients (2+ and 2-3+) and explicitly excludes severe MR patients. In regards to the RESHAPE-HF-2 study, the applicant stated that whilst this study stipulates the inclusion of patients with moderate-to-severe or severe MR, eligibility is not limited to those with disproportionate MR applicable to the ADAR. As such, the applicant claimed these trials are likely to be largely uninformative. Further, the applicant claimed that the compelling results from the COAPT study, where patients were carefully selected, it would be counterintuitive to delay access to TMVr in these patients on the MBS.

Clinical claim

The applicant claims that TMVr is non-inferior in safety and superior in clinical effectiveness compared to OMT in patients with DMR and at least non-inferior in safety and superior in clinical effectiveness compared to OMT in FMR.

As described in Section 3 of this PSD, the MSAC considered this claim to be uncertain for the DMR indication but reasonable for the FMR indication.

11. Economic evaluation

The ADAR requested an MBS fee of \$1748.45 for the MitraClip insertion procedure and **\$redacted** for the MitraClip device. The total cost of the MitraClip procedure (Pre-procedural heart team assessment, MBS insertion fee, hospitalisation fees, Post-procedural/Pre-discharge TTE) was estimated by the ADAR as \$13,663.22 (without device) or **\$redacted** (with device).

The ADAR presented a cost-utility analysis, using a Markov partitioned survival model, to estimate the cost-effectiveness of TMVr compared to OMT. The ADAR presented separate models for the DMR population (Population 1) and FMR population (Population 2).

The applicant did not present a cost-minimisation analysis for the DMR Population 1 as requested by the MSAC at its last consideration (PSD 1192.2, page 3).

The commentary noted that the structure of the DMR model has not changed since the previous submission (1192.2), and the FMR model (not presented previously), used the same

structure and methods as the DMR model. The key difference between the previous model and the current model is the use of FMR data from the COAPT trial.

A summary of the characteristics of the economic evaluation is presented in Table 5.

Table 5 Summary of the economic evaluation

	ADAR 1192.3	Previous submission 1192.2 (2016)
Perspective	Health care sector	Health care sector
Comparator	Optimal medical therapy (OMT)	Optimal medical therapy (OMT)
Type of economic evaluation	Cost-utility analysis (CUA), partitioned survival analysis	Cost-utility analysis (CUA), partitioned survival analysis
Sources of evidence	COAPT, EVEREST II HRR	EVEREST II HRR
Time horizon	10 years	10 years
Outcomes	LYs and QALYs	LYs and QALYs
Methods used to generate results	Markov partitioned survival / area under the curve	Markov partitioned survival / area under the curve
Health states	Alive (stratified by NYHA class); dead	Alive (stratified by NYHA class); dead
Cycle length	One month	One month
Discount rate	5% p.a.	5% p.a.
Software packages used	Microsoft Excel	Microsoft Excel

CUA= cost-utility analysis, NYHA= New York Heart Association, OMT= Optimal medical therapy, QALY=Quality adjusted life year
Source: Table 34, p57 of the commentary

The ADAR stated that the key assumptions included:

- The economic model is a partitioned survival or ‘area under the curve’ analysis, where the overall survival curves for TMVr and the comparator – OMT determine the comparative effectiveness of the analysis. Population specific probabilities of treatment efficacy, overall survival, and resource utilisation including adverse events are utilised.
- Trial reported Kaplan-Meier curves are used to model overall survival during the within trial period of the models for Population 1 (DMR: 12 months) and Population 2 (FMR: 24 months).
- The OMT overall survival curve is extrapolated beyond the trial to a 10-year horizon using fitted parametric curves, with the extrapolated TMVr overall survival curve estimated via a constant hazard ratio applied over time to the OMT curve.
- Estimated overall survival over the 10-year model horizon is ‘partitioned’ according to NYHA class distributions for each treatment arm at 1-month intervals (i.e. cycle length). Trial evidence is used to populate NYHA class distributions for the corresponding period of the economic model (i.e. 12-months for Population 1 and 24-months for Population 2). NYHA class distributions are assumed to be static beyond the trial duration(s). Utility values are defined on the basis of NYHA class, with the NYHA class distribution determining the average quality of life value (and hence Quality adjusted life year [QALY]) each cycle of the model in each treatment arm.

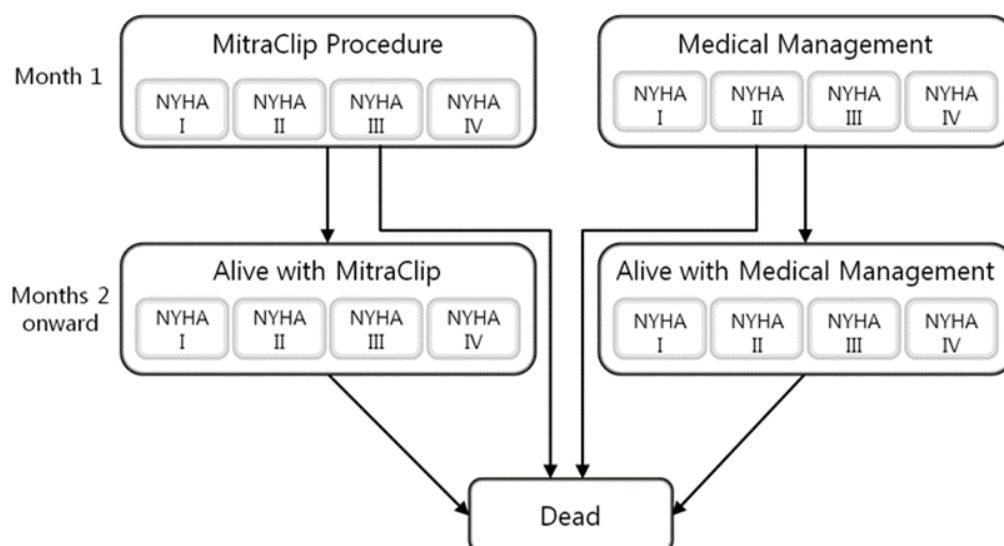


Figure 3 Model structure of the economic evaluation

Source: Figure39, p177 of ADAR

The commentary highlighted the following key limitations for the ADAR’s models:

- The DMR model still uses data from a heterogeneous population to inform clinical benefit, and therefore introduces uncertainty of the magnitude of clinical benefit.
- Due to the structural uncertainty of the model, as patients do not move between NYHA classes after 24 months, the impact of any analysis of parameter uncertainty (quantified in the sensitivity analyses) is significantly reduced.

The primary driver of difference in both models is the life years gained due to the continuing benefit accruing to MitraClip for lifetime, this favours the intervention. For the DMR model, there is also a 0.13 difference in utility carried forward past 24 months. This has a moderate effect on the estimates of cost-effectiveness.

The base-case cost-effectiveness results are presented in Table 6. The estimated ICERs for TMVr compared to OMT were \$redacted and \$redacted respectively for Population 1 (DMR) and Population 2 (FMR).

Table 6 Base-case: Incremental cost-effectiveness

Outcome	TMVr	OMT	Incremental
<i>Population 1 (DMR)</i>			
Costs	\$redacted	\$redacted	\$redacted
QALYs	\$redacted	\$redacted	\$redacted
ICER			\$redacted
<i>Population 2 (FMR)</i>			
Costs	\$redacted	\$redacted	\$redacted
QALYs	\$redacted	\$redacted	\$redacted
ICER			\$redacted

Source: Table 4, p32 of ADAR

The ADAR claimed, based on the results of the model; for both indications, i.e., DMR (Population 1) and FMR (Population 2), ICERs of \$redacted and \$redacted respectively for TMVr compared to OMT can be considered as cost-effective from the Australian healthcare system perspective.

Previously ESC raised four main concerns in regards to MSAC 1192.2 (PSD Application No. 1192.2, p12). These concerns were: utility measures used were not based on comparative analysis; survival benefit extrapolated on very short-term data for the comparator group; the ICER is potentially underestimated with a greater likelihood that it is significantly higher; and the ICER is highly sensitive to the hazard ratio. The ADAR presented sensitivity analyses testing utility values, and hazard ratios; however, survival benefit over very short-term data was not tested.

The ADAR modelled results were most sensitive to the TMVr hazard ratio for overall survival, and to the model horizon. Also identified as important drivers of the modelled cost-effectiveness of TMVr are the TMVr procedure hospitalisation cost, CHF hospitalisation rates, and selected utility values (Tables 7, 8 and 9).

Table 7 Key drivers of the economic model

Description	Method/Value	Impact
TMVr procedure hospitalisation cost – net of prosthesis cost (\$redacted)	\$redacted	Moderate
TMVr overall survival hazard ratio (DMR: 0.47; FMR: 0.62)	Population 1 (DMR) = 0.47 Population 2 (FMR) = 0.62	Moderate
Utility values	Gohler et al (2009); NYHA I = 0.90, NYHA II = 0.83, NYHA III = 0.74, NYHA IV = 0.60)	Moderate
Annual rate of CHF hospitalisation	Population 1 (DMR) TMVr = 0.36 OMT = 0.65 Population 2 (FMR) TMVr = 0.358 OMT = 0.679	Moderate, low uncertainty
Model horizon	10 years	High

Source: Table 5, p32 of ADAR

The commentary further tested the variables in the model. The variables which impacted the ICER the most are shown in Figure 6 and Table 8 for the DMR model and Figure 7 and Table 9 for the FMR model.

Redacted

Figure 4 Tornado diagram of key drivers of the DMR model

Source: Figure 29, p83 of the commentary

Redacted

Figure 5 Tornado diagram of key drivers for the FMR model

Source: Figure 30, p83 of the commentary

Table 8 Results of the sensitivity analyses (DMR model)

Analyses	Incremental cost	Incremental QALY	ICER	% change ICER
DMR population base case	\$redacted	redacted	\$redacted	-
TMVr overall survival hazard ratio (base case: 0.47)				
95% LCL 0.24	\$redacted	Redacted	\$redacted	-21%
95% UCL 0.93	\$redacted	Redacted	\$redacted	73%
Same as FMR (0.62)	\$redacted	Redacted	\$redacted	18%
TMVr procedure hospitalisation cost – net of prosthesis cost (base case: \$redacted)				
F19B (\$8,317)	\$redacted	Redacted	\$redacted	7%
F09B (\$22,122)	\$redacted	Redacted	\$redacted	23%
OMT adverse event costs per cycle (base case: \$0.00)				
Equal to TMVr post-procedural adverse event cost (\$164.41 per cycle)	\$redacted	Redacted	\$redacted	9%
Mitral valve surgery costs (base case: \$41,961.89)				
F08A (\$60,406.60)	\$redacted	Redacted	\$redacted	13%
F08B (\$32,075.20)	\$redacted	Redacted	\$redacted	7%
CHF hospitalisation cost (base case: \$8,794.18)				
F62A (\$12,212.63)	\$redacted	Redacted	\$redacted	0%
F62B (\$5,378.45)	\$redacted	Redacted	\$redacted	0%
Utility values (base case: Gohler et al, 2009; 0.90,0.83,0.74,0.60)				
Fox et al 2007 (0.93,0.78,0.61,0.44)	\$redacted	Redacted	\$redacted	8%
Lewis et al 2001 (0.97,0.80,0.65,0.30)	\$redacted	Redacted	\$redacted	13%
Adjustment of NYHA class distributions for baseline differences (base case: Set baseline OMT values to TMVr distribution, then extrapolation assumptions)				
No adjustment	\$redacted	Redacted	\$redacted	3%
Set baseline and post-baseline OMT values to TMVr distributions	\$redacted	Redacted	\$redacted	18%
NYHA class distribution extrapolations – annual probability of class progression (base case: 0% in both treatment arms)				
10% in both treatment arms	\$redacted	Redacted	\$redacted	1%
20% in both treatment arms	\$redacted	Redacted	\$redacted	2%
Annual rate of CHF hospitalisation – OMT (base case: 0.65)				
Equal to TMVr (0.36)	\$redacted	Redacted	\$redacted	11%
Annual rate of CHF hospitalisation – TMVr (base case: 0.36)				
95% LCL (0.24)	\$redacted	Redacted	\$redacted	9%
95% UCL (0.54)	\$redacted	Redacted	\$redacted	13%
Model horizon (base case: 10 years)				
5 years	\$redacted	Redacted	\$redacted	61%
15 years	\$redacted	Redacted	\$redacted	15%
20 years	\$redacted	Redacted	\$redacted	21%
Discount rate (base case: 5%)				
0%	\$redacted	Redacted	\$redacted	19%
3.5%	\$redacted	Redacted	\$redacted	6%

CHF=chronic heart failure, DMR= degenerative mitral regurgitation, NYHA, New York Heart Association, OMT= Optimised medical treatment, TMVr, Transcatheter Mitral Valve Repair

Source: Table 49, p83 of the commentary

Table 9 Results of the sensitivity analyses (FMR model)

Analyses	Incremental cost	Incremental QALY	ICER	% change ICER
FMR population base case	\$redacted	Redacted	\$redacted	-
TMVr overall survival hazard ratio (base case: 0.62)				
95% LCL 0.46	\$redacted	Redacted	\$redacted	-20%
95% UCL 0.82	\$redacted	Redacted	\$redacted	36%
TMVr procedure hospitalisation cost – net of prosthesis cost (base case: \$11,396)				
F19B (\$8,317)	\$redacted	Redacted	\$redacted	-7%
F09B (\$22,122)	\$redacted	Redacted	\$redacted	25%
OMT adverse event costs per cycle (base case: \$114)				
FMR +25% (\$142.49 per cycle)	\$redacted	Redacted	\$redacted	-2%
FMR -25% (\$85.50)	\$redacted	Redacted	\$redacted	2%
Mitral valve surgery costs (base case: \$41,961.89)				
F08A (\$60,406.60)	\$redacted	Redacted	\$redacted	-2%
F08B (\$32,075.20)	\$redacted	Redacted	\$redacted	1%
CHF hospitalisation cost (base case: \$8,794.18)				
F62A (\$12,212.63)	\$redacted	Redacted	\$redacted	-4%
F62B (\$5,378.45)	\$redacted	Redacted	\$redacted	4%
Utility values (base case: Gohler et al, 2009; 0.90,0.83,0.74,0.60)				
Fox et al 2007 (0.93,0.78,0.61,0.44)	\$redacted	Redacted	\$redacted	6%
Lewis et al 2001 (0.97,0.80,0.65,0.30)	\$redacted	Redacted	\$redacted	7%
Adjustment of NYHA class distributions for baseline differences (base case: Set baseline OMT values to TMVr distribution, then extrapolation assumptions)				
No adjustment	\$redacted	Redacted	\$redacted	-6%
Set baseline and post-baseline TMVr values to OMT distributions	\$redacted	Redacted	\$redacted	2%
NYHA class distribution extrapolations – annual probability of class progression (base case: 0% in both treatment arms)				
10% in both treatment arms	\$redacted	Redacted	\$redacted	3%
20% in both treatment arms	\$redacted	Redacted	\$redacted	7%
Annual rate of CHF hospitalisation – OMT (base case: 0.679)				
Equal to TMVr (DMR: 0.358)	REDACTED	Redacted	\$redacted	18%
Annual rate of CHF hospitalisation – TMVr (base case: 0.358)				
95% LCL (0.27)	\$redacted	Redacted	\$redacted	-7%
95% UCL (0.48)	\$redacted	Redacted	\$redacted	10%
Model horizon (base case: 10 years)				
5 years	\$redacted	Redacted	\$redacted	84%
7 years	\$redacted	Redacted	\$redacted	30%
15 years	\$redacted	Redacted	\$redacted	-16%

Analyses	Incremental cost	Incremental QALY	ICER	% change ICER
20 years	\$redacted	Redacted	\$redacted	-20%
Discount rate (base case: 5%)				
0%	\$redacted	Redacted	\$redacted	-22%
3.5%	\$redacted	Redacted	\$redacted	-7%

CHF=chronic heart failure, DMR= degenerative mitral regurgitation, NYHA, New York Heart Association, OMT= Optimised medical treatment, TMVr, Transcatheter Mitral Valve Repair

Source: Table 50, p85 of the commentary

The commentary noted that both the DMR and FMR model are driven by the survival gains in the TMVr arm. For the DMR model, switching the life years for quality of life increases the ICER for \$redacted/LYs gained to \$redacted/QALY gained. This 1.0% increase in ICER is because the incremental difference between the life years gain and the QALYs gain in the two treatment arms is similar at each time point. The small increase in benefits (either LYs or QALYs) is due to the proportion of patients in each health state not changing after 24 months, and only survival determining utility gains after month 24. For the FMR model, adjusting the life years for quality of life increases the ICER for \$redacted/QALY gained to \$redacted/QALY gained. This 24.5% increase in ICER is due to the ability of patients to change NYHA class health state up to month 24, however, after 24 months, the accumulation of benefit is highly uncertain.

The commentary also noted that these sensitivity analyses identify parameter uncertainty only. The impact of these parameters would likely be altered by changes to the structure of the model. Thus the structural uncertainty, the uncertainty regarding the movement between health states, needs to be rectified to fully comprehend the impact of parameter uncertainty.

In the pre-ESC response, the applicant claimed it was not possible with available data to model overall survival by NYHA class-specific data, or to model NYHA class progression (i.e. transition probabilities) which could have been used to drive a change in the NYHA distribution over time. Further, that applicant stated the sensitivity analyses presented in the ADAR that removed all differences in NYHA class distributions between treatment arms over time or modelled a hypothetical rate of progression had little impact to the modelled ICERs.

The applicant reiterated that for the modelling of both populations, it is the survival gains of TMVr over OMT driving the incremental QALY gains rather than constant utility values resulting from unchanged NYHA class distributions that proved instrumental to the modelled results. The application acknowledged a degree of uncertainty in the quality of life in the medium term (which impacts both treatment arms). However, the applicant claimed that this does not impact the magnitude of modelled QALY gains as demonstrated in the sensitivity analyses presented, and certainly does not preclude the findings of significant modelled QALY gains for TMVr in both models and does not represent a ‘structural uncertainty’ in the model.

In the pre-MSAC response, the applicant defended the 10-year horizon used in the economic model. The applicant claimed extrapolation of trial reported survival gains is necessary to capture the benefit of avoiding premature mortality with TMVr, noting that the functional benefits offered by TMVr (and thus their QoL/cost implications) would persist into the future and for many patients be permanent. Note that stopping the model at 10-years in the base-case analysis effectively truncates survival gains for 20-25% of TMVr patients across the FMR/DMR populations in the economic model. Therefore, the application claimed that in the

context of MR patients, who are 72 years at baseline, a 10-year horizon is justifiable to adequately capture the long-term benefits and costs in that population.

The applicant also provided clarification regarding inclusion of mitral valve surgery costs in the modelling given a multi-disciplinary heart team (MDHT) would ensure patients are not eligible for mitral valve surgery. The applicant stated that the cost of mitral valve surgery was included in both TMVr and OMT arms as part of resources utilised which was informed by the utilisation in the COAPT study for the FMR population (very low rates). For the DMR population, 14% patients in the comparator arm had mitral valve surgery and not OMT (EVEREST II HRS study). Thus, the OMT arm realised survival benefits from the mitral valve surgery, in turn justifying the inclusion of the cost of mitral valve surgery. However, the applicant acknowledge that if mitral valve surgery is deemed to be not applicable to the target populations, and to be identified by MDHT, the ICER increases to \$redacted (up from \$redacted) and \$redacted (up from \$redacted) in FMR and DMR populations respectively.

Table 10 provides the results of a cost-minimisation analysis in the DMR population conducted by the Department at the request of the MSAC, in which the cost of the MitraClip device is adjusted so the combined cost of the device and procedure is equivalent to the cost of OMT over 7 years. The analysis in Table 10 uses an MBS fee of \$1455.10 (in place of the requested MBS fee of \$1748.45) and incorporates an offset for the cost of adverse events associated with the use of the device. Consistent with the approach taken in the ADAR economic model, the analysis assumes both the OMT and intervention groups will incur the same costs for maintenance disease management in terms of pharmacotherapy and doctor visits, but that a higher proportion of the patients in the OMT group will go to develop congestive heart failure requiring hospitalisation or to require mitral valve surgery. The MSAC agreed it was reasonable to include mitral value surgery costs in the OMT group in the cost-minimisation analysis, because although patients in this group would be deemed unsuitable for surgery at initial assessment, they would likely eventually be offered surgery on a compassionate basis if their condition progressed despite OMT.

Table 10: DMR Cost-Minimisation Analysis

Optimised Medical Treatment				TMVr with MitraClip	
Sequelae	Proportion developing sequelae over 7 years	Cost	Contribution to weighted cost		
Congestive Heart Failure Hospitalisation	86% ¹	\$redacted	\$redacted	Number of procedure	Redacted
Surgery	64% ¹	\$redacted	\$redacted	Adverse event costs	\$redacted
				Ancillary costs	\$redacted
				MitraClip Price	\$redacted
		Total	\$redacted		

1. ADAR Economic model DMR, resource use tab: Monthly probability CHF hospitalisation intervention 2.96%, OBT 5.27% (Whitlow et al. 2012 (Table 3)); Monthly probability surgery in OBT group 1.24% (EVEREST II HRSS CSR (4.10.8, p120)) ; Probability Mitraclip replacement 1.28% (one off, Whitlow et al. 2012 (Table 134)).

2 ADAR Economic model DMR, Cost inputs tab

3 ADAR Economic model DMR, Adverse event tab, adjusted to 7 year timeframe

4 ADAR Economic model DMR, Mitraclip procedure worksheet tab with MBS fee adjusted to \$1455.10 (from \$1748.45)

If the time horizon in the FMR model is set to 7 year rather than 10 years, and the MBS fee reduced from MBS fee of \$1748.45 with a fee of \$1455.10, the cost of the MitraClip device

would need to be adjusted to approximately \$redacted to maintain the same ICER per QALY (see also Table 9).

Table 11 provides a weighted MitraClip device price, using the estimated proportions of FMR and DMR patients at year 5 in Table 12.

Table 11: Weighted MitraClip Price Calculation

Population	MitraClip Price	No patients at 5 years	Patient Proportion	Contribution to weighted price
DMR	\$redacted	333	Redacted	\$redacted
FMR	\$redacted	193	Redacted	\$redacted
			Weighted MitraClip Price	\$redacted

Source: created during evaluation.

12. Financial/budgetary impacts

The ADAR used an epidemiological approach for assessing estimated extent of use and financial implications, as previously suggested by MSAC (PSD Application No. 1192.2, p11). This approach was also considered appropriate for the proposed indication whereby TMVr is positioned for patients who are ineligible for the currently available surgical interventions, making a market share approach impractical and not feasible. The financial implications to the MBS resulting from the proposed listing of TMVr are summarised in Table 12.

Table 10 Total costs to the MBS associated with TMVr

Year	Year 1	Year 2	Year 3	Year 4	Year 5
For the DMR indication					
Total number of TMVr procedures^	174	235	275	303	333
Costs to the MBS:					
- MDHT coordination (proposed)	\$8,973	\$12,159	\$14,208	\$15,685	\$17,204
- MDHT attendance (proposed)	\$20,071	\$27,200	\$31,782	\$35,085	\$38,484
- TMVr procedure (proposed)	\$303,444	\$411,216	\$480,490	\$530,438	\$581,823
- Anaesthetics (MBS Item 21936)	\$20,930	\$28,364	\$33,142	\$36,587	\$40,131
- Post-procedure echocardiogram (MBS Item 55113)	\$40,029	\$54,246	\$63,385	\$69,974	\$76,752
Total, DMR only					
- Full benefit	\$393,447	\$533,185	\$623,006	\$687,768	\$754,395
- 75% benefit	\$295,085	\$399,889	\$467,255	\$515,826	\$565,796
For the FMR indication					
Total number of TMVr procedures^	100	136	159	176	193
Costs to the MBS:					
- MDHT coordination (proposed)	\$5,194	\$7,039	\$8,225	\$9,080	\$9,960
- MDHT attendance (proposed)	\$11,620	\$15,747	\$18,399	\$20,312	\$22,280
- TMVr procedure (proposed)	\$175,672	\$238,065	\$278,169	\$307,085	\$336,834
- Anaesthetics (MBS Item 21936)	\$12,117	\$16,421	\$19,187	\$21,181	\$23,233
- Post-procedure echocardiogram (MBS Item 55113)	\$23,174	\$31,405	\$36,695	\$40,510	\$44,434
Total, FMR only					
- Full benefit	\$227,778	\$308,676	\$360,676	\$398,169	\$436,740

Year	Year 1	Year 2	Year 3	Year 4	Year 5
- 75% benefit	\$170,833	\$231,507	\$270,507	\$298,626	\$327,555
Total combined					
- Full benefit	\$621,224	\$841,861	\$983,682	\$1,085,937	\$1,191,135
- 75% benefit	\$465,918	\$631,396	\$737,761	\$814,453	\$893,351
<i>Relevant to MBS assuming 54% of services provided at private centres*</i>	\$251,596	\$340,954	\$398,391	\$439,804	\$482,410

Abbreviations: DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; MDHT, multidisciplinary heart team; TMVr, transcatheter mitral valve repair.

Note: See the attached spreadsheet for full calculation details.

^ Adjusted for retreatments at 1.28% and 2.98% for DMR and FMR, respectively (Whitlow et al. 2012, Stone et al. 2018).

* 54% of Australians aged +60 years old were covered by private health insurance (as of Dec 2018; <https://www.apra.gov.au/private-health-insurance-annual-coverage-survey>).

Source: Table 6, p33 of ADAR.

The commentary noted a number of issues/uncertainties that impact on the financial estimates presented in the ADAR:

- The financial implication analysis was not validated against the clinical data. As such, the estimates are based on either significantly underestimated FMR rates, or overestimated DMR rates, and are uncertain.
- The ADAR inappropriately assumed the MBS would not pay for patients treated in a private hospital. MBS items still apply to private patients and should not be excluded. Therefore, there is potential for the net cost/year to the MBS to be significantly greater than estimated in the ADAR.
- Uptake assumptions were applied to reflect the applicant's argument that supply issues (i.e. not enough specialists or locations to conduct the surgery) will limit the uptake of TMVr. The commentary notes such uptake assumptions were applied in the previous resubmission (Application 1192.2) and were criticised for introducing high uncertainty (PSD Application No. 1192.2, p11).
- The model used uptake rates of 15% in year 1 increasing to 27% in year 5 which the ADAR claimed to be similar to the use of TAVI on the MBS. However, the commentary reports that for TAVI MBS item 38495, 1003 services were claimed in the first year (between December 2017 and November 2018), while 1452 services were claimed in the second year (December 2018 to November 2019), representing a 44.8% increase in utilisation. The difference between the uptake rates used in the model and the uptake rates observed for TAVI indicate that uptake rates have been significantly underestimated.

The commentary presented additional sensitivity analysis considering only MBS costs and considering all patients covered by the MBS. The financial impact is between \$465,918 (year 1) to \$893,351 (year 5) (Table 13). Identified uncertainty in the parameters included in the financial impact analysis included the proportion of eligible patients who were either FMR or DMR, annual uptake rates, the proportion of patients that were inoperable for current surgery, and the proportion of patients who were deemed suitable for TMVr by a MDHT. These variables were all tested by applying the maximum possible value (i.e. 100%) to assess the impact on the financial impact (Table 13).

Table 11 Additional sensitivity analysis for the financial impact model (75% Benefit)

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Base case (presented in ADAR)	\$251,596	\$340,954	\$398,391	\$439,804	\$482,410
100% covered by MBS	\$465,918	\$631,396	\$737,761	\$814,453	\$893,351
Proportion of DMR patients – 100% ^a	\$559,109	\$757,684	\$885,324	\$977,355	\$1,072,035
Proportion of FMR patients – 100% ^a	\$361,764	\$490,250	\$572,838	\$632,385	\$693,647
Annual uptake rates – 100% ^a					
DMR	\$2,138,067	\$2,230,951	\$2,302,048	\$2,361,931	\$2,423,096
FMR	\$1,433,973	\$1,557,424	\$1,643,371	\$1,710,332	\$1,778,964
DMR+FMR	\$3,106,122	\$3,156,979	\$3,207,658	\$3,257,811	\$3,308,709
Eligibility					
% Inoperable -100% ^a (base case 40.64%)	\$715,425	\$969,518	\$1,132,844	\$1,250,604	\$1,371,755
% suitable by MDHT -100% ^a (base case 36%)	\$769,622	\$1,042,964	\$1,218,662	\$1,345,344	\$1,475,672
% inoperable and suitable by MDHT – 100% ^a	\$1,462,695	\$1,982,192	\$2,316,114	\$2,556,877	\$2,804,570

^a Sensitivity analysis includes 100% of patients covered by MBS (base case assumed 54% of patients covered by MBS)
ADAR=Applicant Developed Assessment Report, DMR=Degenerative mitral regurgitation, FMR=Functional mitral regurgitation, MBS= Medicare Benefits Schedule, MDHT=Multi-disciplinary heart team
Source: Table 58, p95 of the commentary

The commentary noted that the other financial costs associated with listing TMVr presented in the ADAR (shown below in Table 14) may underestimate the incident population and thus the financial impact may be underestimated. This is primarily due to the estimated number of FMR patients being significantly less than the number of estimated DMR patients, while in clinical practice it is expected that the number of DMR patients will be less than the number of FMR patients.

Table 14 Other financial costs associated with the listing TMVr to other government health budgets

Year	Year 1	Year 2	Year 3	Year 4	Year 5
For the DMR indication					
Total TMVr procedures	174	235	275	303	333
- In-hospital resource use	\$1,977,777	\$2,680,213	\$3,131,725	\$3,457,272	\$3,792,189
- Prosthesis	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total, DMR only	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
For the FMR indication					
Total TMVr procedures	100	136	159	176	193
- In-hospital resource use	\$1,144,991	\$1,551,651	\$1,813,044	\$2,001,512	\$2,195,406
- Prosthesis	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total, FMR only	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total combined					
- In-hospital resource use	\$3,122,769	\$4,231,865	\$4,944,769	\$5,458,784	\$5,987,595
- Prosthesis	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total combined	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

DMR=Degenerative mitral regurgitation, FMR=Functional mitral regurgitation, TMVr=Transcatheter mitral valve repair
Source: Table 57, p94 of the commentary

In the pre-ESC response, the applicant sought clarification on the following commentary statement; “as the MBS covers both private and public patients, all patients would be covered by the MBS” (pg 94). The applicant noted that in the circumstance whereby a patient is accessing MitraClip via the Prosthesis List, then it is true that this particular item number will

only cover privately insured (or otherwise privately funded) patients. As such, Section E correctly accounts for a likely proportion of patients receiving the procedure in a private setting (54%; based on the private health insurance statistics on coverage among Australians aged ≥ 65 years). The applicant acknowledges this estimate is a proxy as uninsured patients could privately pay for the procedure and the MitraClip device. However, this proportion is expected to be small (not 100% as assumed in the Critique).

In response to the commentary's statement that the assumed uptake was underestimated, the applicant acknowledged it is difficult to estimate year to year uptake accurately (ie, pattern of uptake). However, the applicant stated that the TAVI uptakes in practice in the first 2 years of listing would have little relevance in estimating the "steady state" uptake of TMVr. The applicant's local clinical expert stated "*the driver for TAVI uptake is due to the new evidence which became available through the MBS listing and the TAVI technology has essentially supplanted Aortic Valve Replacement for the majority of patients. This assumption is unlikely to be the same for TMVr*". The applicant considered TMVr to be a very specialised procedure, meaning the overall usage would be limited by the available caseload (ie, constrained by the supply). The applicant argued that their estimate of roughly "1 out of 3" is more realistic than the 100% uptake explored in the commentary.

13. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Population in the descriptor	ESC considered that for the FMR population, only those with severe MR and some cardiac reserve (dilatation <70 mm and EF >20%) should be considered for a TMVr item. This matches the population in the COAPT trial, for which there is stronger evidence.
Comparative safety	ESC noted continued uncertainty in the safety evidence for TMVr in the DMR population. Evidence presented in the COAPT trial supports the claim for non-inferior safety for the FMR population.
Comparative effectiveness	ESC was of the opinion that evidence continues to be lacking for the DMR population. However, a randomised clinical trial is planned. There is evidence from the COAPT randomised controlled trial in the FMR population. Inconsistencies in published study results from this study and the MITRA-FR study can be explained by risk of bias in the MITRA-FR trial, and a biologically plausible mechanism that better identifies those who would benefit from TMVr. Further clinical trials are planned.
Proposed fee	ESC considered the higher fee for TMVr than for TAVI is not justified (\$1,720.90 vs \$1,432.20).
Modelled economic evaluation for DMR population	ESC noted the continued uncertainty in the benefit of TMVr over the comparator in the DMR population may make a cost-minimisation approach more appropriate for this population (see also MSAC PSD for 1192.2).
Survival curve analysis favours the intervention	ESC advised that the analysis assumes ongoing benefit over 10 years which favours the intervention. A shorter time horizon results in a large increase in the ICER.
Wide confidence intervals around the benefit (survival hazard ratio).	ESC considered that the benefit may not be as high as modelled.
Accreditation for providers	ESC advised that an accreditation process for providers may be appropriate.

ESC discussion

ESC noted this was the third resubmission for reduction of mitral regurgitation through tissue approximation, using transvenous/transeptal techniques. ESC noted that MSAC did not support the previous submissions for TMVr on the basis that there was uncertain clinical effectiveness and cost-effectiveness due to the lack of high-quality clinical trial data.

ESC noted this resubmission included two patient populations: patients with degenerative mitral regurgitation (DMR; Population 1) and patients with functional mitral regurgitation (FMR; Population 2). ESC noted that Population 2, patients with FMR, was a new patient population that had not been included in the previous submissions.

ESC noted the proposed fee for TMVr (\$1,748.45) was higher than the current MBS fee for transcatheter aortic valve implantation TAVI (\$1,455.10). ESC considered the proposed higher fee for TMVr compared to TAVI was not justified. ESC noted the addition of case conference MBS items, which it considered to be crucial for proper patient selection for the procedure.

ESC accepted the proposed clinical management algorithms for the DMR and FMR populations. ESC noted that patients not eligible for TMVr would likely undergo medical management or may qualify for another device or a transplant.

ESC noted that, for the DMR population, the only new data since the 2016 submission was observational data from a TVT registry. ESC agreed with the commentary that the new registry data (Sorajja et al. 2017) supported the evidence presented in the previous submissions in terms of clinical effectiveness and safety, but it did not resolve the uncertainty in the evidence due to the ongoing lack of high-quality comparative clinical evidence. ESC also noted there is a potentially relevant RCT, the REPAIR-MR¹ (n = 500), planned to be completed February 2027.

For the FMR population, ESC considered that the COAPT² trial supports the applicant's claim of superior clinical effectiveness and non-inferior safety. This study had low risk of bias and was sufficiently powered to detect differences in interventions. ESC considered that the MITRA-FR³ trial did not support the conclusion of superior effectiveness, but noted that the trial had a high risk of bias and was underpowered. The MR of the patients included in the MITRA-FR trial was proportionate to the degree of left ventricle dilatation. The finding of no significant differences between TMVr and optimal medical therapy in the overall MITRA-FR trial population is biologically plausible and consistent with the recruitment of patients in whom MR is proportionately severe to the degree of LV dilation and in whom an effect is not expected. ESC agreed with the pre-ESC response that the MITRA-FR study may therefore not be relevant to the application and advised that MSAC may wish to consider its exclusion from the clinical claim. ESC considered that the appropriate FMR population is the one included in the COAPT trial. ESC also noted there are two potentially relevant ongoing RCTs: RESHAPE-HF2⁴ (n = 420) planned to be completed March 2021 and EVOLVE-MR⁵ (n = 174) planned to be completed January 2022.

In summary, ESC advised MSAC it considers the applicant's clinical claim may not be substantiated for the DMR population but may be reasonable for the FMR population.

ESC considered that the issue of whether Cardiac Accreditation Services Limited (CASL) should be the appropriate accreditation provider for this service is an issue which should be considered further by the Department.

ESC noted the applicant has used the same modelling approach to the DMR population as in the previous MSAC submission (1192.2). ESC noted that MSAC, in its consideration of the previous submission, been concerned about the uncertainty inherent in the cost effectiveness model (given the uncertainty in the clinical claim) and suggested that a cost minimisation analysis would have been informative. ESC advised MSAC that given the current application does not appear to address the clinical uncertainty, the same concerns with the approach taken to the economic analysis remain.

If MSAC considers the modelled evaluation appropriate for the DMR population, ESC advised the ICER of **\$redacted** per QALY to be highly uncertain. As with the previous

¹ Percutaneous MitraClip Device or Surgical Mitral Valve REpair in PATients With PrImaRy MItral Regurgitation Who Are Candidates for Surgery (REPAIR-MR)

² Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT)

³ Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation

⁴ A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF2)

⁵ Transcatheter Mitral Valve Repair for the Treatment of Mitral Valve Regurgitation In Heart Failure (EVOLVE-MR)

application, sensitivity analysis showed that changing the assumed survival benefit and time-horizon substantially increased the ICER for this population (see Table 8).

In particular, ESC considered the extrapolated survival curves for DMR to be inappropriate, as 9% of patients who received the intervention would be alive at age 100, compared with 1% for the control group. ESC noted that the curves cannot be altered in the model, unlike the model for the FMR population. ESC advised that alternatively it may be appropriate for the model to switch off benefits in the intervention group after 5 years post-intervention.

However, ESC considered that the ICER for the FMR population of \$redacted per QALY was more certain. The sensitivity analyses showed that the ICERs do not change substantially when model parameters are changed, especially in the first 2 years. However, the time horizon is also an issue for this mode.

The ESC also noted the cost of mitral valve surgery was included in the comparator group costs in the economic models but was not included in the intervention group. The commentary stated this to be inappropriate, given that the Australian indication is explicitly for people not considered eligible for mitral valve surgery. ESC considered that the multi-disciplinary heart team (MDHT) would ensure patients are not eligible for mitral valve surgery therefore, the costs of mitral valve surgery should not be included in the comparator group.

ESC disagreed with the commentary advice that MR grade should have been used to assign utilities, and not NYHA class. ESC noted that this would be ideal, but MR grade data are not available, and other studies use NYHA class as standard. ESC queried why the FMR model did not use the utility weights from the COAPT trial.

ESC also disagreed with commentary's argument that the inability to move health states beyond month 24 is problematic to assigning utility values. ESC instead agreed with the pre-ESC response, that it would be inappropriate to model changes in NYHA without data, and that this would create additional uncertainty. This uncertainty pertains to the DMR population.

ESC noted that for the financial impact modelling, the commentary presented additional sensitivity analyses considering only MBS costs and assuming that 100% of patients will be funded through the MBS. The ESC agreed with the applicant's pre-ESC response that a proportion of patients will continue to be treated in a public hospital and will not be eligible for MBS funding. However, ESC agreed with the commentary there would be potential for cost shifting from the public to private setting.

ESC noted the small financial impacts to the MBS if TMVr were to be publicly funded, as there are a small number of patients that would be eligible for the procedure. However, the cost of the device itself would have a large impact on the Prostheses List. ESC noted a procedure can use more than one device; however the sponsor proposes to charge the same device fee, irrespective the number of devices used.

14. Other significant factors

Nil

15. Applicant comments on MSAC's Public Summary Document

Abbott Australasia Pty Ltd. (Abbott) is pleased with the advice made by MSAC for public funding of TMVr for the patients with DMR and FMR, thereby addressing a high clinical need for an effective and safe treatment option in these patients. Abbott disagrees with the approach to economic evaluation proposed by MSAC but is looking forward to working with the Department of Health to list the MitraClip device on the Prostheses List and enable patient access to the TMVr procedure in the Australian healthcare system.

16. Further information on MSAC

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