



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1192.2 – The reduction of mitral regurgitation through tissue approximation using transvenous/transeptal techniques

Applicant: Abbott Australasia Pty Ltd

Date of MSAC consideration: MSAC 67th Meeting, 28-29 July 2016

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

1. Purpose of application and links to other application

A resubmission requesting a new Medicare Benefits Schedule (MBS) listing for the reduction of severe mitral regurgitation (MR) through tissue approximation using transvenous/transeptal techniques in patients with severe degenerative mitral regurgitation (grade 3+ or 4+) considered to be high risk for surgery and a new MBS item for the multidisciplinary case conference was received from Abbott Australasia by the Department of Health.

This public summary document (PSD) should be reviewed in conjunction with the PSDs for Applications 1192 and 1192.1.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of reduction of severe mitral regurgitation (MR) through tissue approximation using transvenous/transeptal techniques in patients with severe degenerative mitral regurgitation (grade 3+ or 4+) considered to be high risk for surgery, MSAC was unable to support the application due to continued uncertainty about clinical effectiveness and cost effectiveness. However, MSAC noted that there is a clinical need in a small group of patients with severe degenerative mitral regurgitation who are unsuitable for surgery.

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

MSAC noted that it did not support public funding of the proposed intervention on two previous occasions (November 2012 and April 2014) due to uncertainty around safety, clinical effectiveness and cost effectiveness. MSAC recalled that comparative data on the safety and efficacy of the technique compared with medical management was lacking.

This resubmission restricted eligibility for the intervention to a more narrowly defined patient group than in previous applications. In this resubmission, the eligible patient population is patients with moderate to severe (grade 3+ or 4+) degenerative mitral regurgitation (DMR) who are assessed by a multidisciplinary team as being unfit for surgery because of a high mortality risk. Given that these patients are unfit for surgery, MSAC agreed the appropriate comparator is medical management.

MSAC considered the intervention to have a reasonable safety profile in this selected patient group. There was no significant difference in 30-day mortality between the intervention group (n = 78) and a retrospective control group (n = 36) in the EVEREST II HRR study (7.7% vs 8.3%, respectively; $p > 0.999$). In another study, 30 day mortality was 4.2% among the 239 patients in the intervention arm and 7.2% among 239 patients from an optimally matched retrospective control group (Velazquez EJ et al 2015). Two pooled analyses of single arm studies - each including around 3,000 patients - reported that procedure-related vascular events requiring surgical intervention occurred in 0.8–3.6% of patients (Philip F et al 2014; Vakil K et al 2014). Bleeding requiring two or more units of blood within 30 days of the procedure was reported in 4–18% of patients (EVEREST II HRR; Philip F et al 2014). Partial clip detachment or clip embolism during the procedure were reported in less than 2% of patients (EVEREST II HRR; Philip F et al 2014; Vakil 2014). Unsuccessful clip placement was reported in approximately 3% of patients and the need for reintervention with another clip during follow-up was reported in 1.3–4.2% of patients (EVEREST II HRR; Philip F et al 2014; Vakil K et al 2014).

MSAC noted that the EVEREST II HRR study included patients with both DMR (n = 45) and functional mitral regurgitation (FMR; n = 69). The retrospectively identified control group were patients who were screened for inclusion in the intervention arm of the EVEREST II HRR study, but did not enrol or were not anatomically eligible for the intervention. Most of the control patients were managed medically, however 14% underwent mitral valve surgery. MSAC considered that further information on why these patients underwent surgery despite being assessed as being at high risk of mortality would have been helpful, but noted that the applicant had provided evidence that a proportion of such patients choose to take that risk when no other options are available (Jamieson WRE et al 1999; Ambler G et al 2005; Mirabel M et al 2007).

MSAC noted that the evidence of clinical effectiveness remained uncertain and relied upon three non-randomised studies with retrospective control groups (EVEREST II HRR study; Velazquez EJ et al 2015; Swaans MJ et al 2014). MSAC noted that such studies carry an inherent risk of bias, although it was acknowledged that measures to minimise bias (eg, propensity matching, use of a central events committee) may have reduced some of these risks to a certain extent. MSAC noted that there are ongoing or completed randomised controlled trials (RCTs) of the intervention, but these are in a different patient population - patients with FMR instead of DMR. MSAC stated that higher quality evidence demonstrating clinical effectiveness of the intervention in DMR, such as an RCT, was preferred, but acknowledged that such evidence may not be forthcoming.

MSAC noted that comparative effectiveness data were restricted to 12-month mortality in these non-randomised studies. While survival at 12 months was better in the intervention arm compared with control in the EVEREST II HRR study, this was of borderline statistical significance (76% vs 56%, $p = 0.048$). In addition, the confidence interval around the mean difference was wide and included zero suggesting there is a chance that there is no difference in survival between the two arms (mean difference 20%; 95% CI -0.8%–40.9%). In the Swaans MJ et al 2014 study - used to inform overall survival in economic modelling - survival at 12 months was better in 81 intervention patients compared with historical controls, but once again, the confidence intervals were wide (hazard ratio 0.47; 95% CI 0.24–0.93). One-year survival was better in Velazquez EJ et al 2015 when compared with optimally matched historical controls, but again, the confidence intervals were wide (hazard ratio 0.66; 95% CI 0.45–0.99).

MSAC remained concerned about the uncertainty inherent in the cost effectiveness model and suggested that a cost minimisation analysis would have been informative. In considering cost effectiveness MSAC noted that in the base case, use of the intervention would incur a cost over 10 years of \$68,002 and lead to a gain of 2.58 QALYs compared with \$22,783 and 1.28 QALYs for medical management, resulting in an ICER of \$34,802 per QALY. However, MSAC was concerned that uncertain survival data at 12 months had been extrapolated to 10 years. Reducing the time horizon from 10 years to two years increased the ICER to \$104,782 per QALY. Similarly, while the hazard ratio of 0.47 from Swaans MJ et al 2014 was used to model overall survival in the base case, sensitivity analyses varying this from 0.24 to 0.93 resulted in the ICER ranging from \$24,219 to \$118,734 per QALY. MSAC was also concerned that the utility values used in the model were not based upon comparative data. Overall, MSAC considered that the modelled estimate of cost-effectiveness presented was unacceptable because the base case overestimated improvements in health outcomes and underestimated increased costs. The increased cost of this service is therefore not justified by the extent of improvement in outcomes.

MSAC noted that the costs of the intervention were highly uncertain given that estimates of the prevalence of heart failure in Australia, and hence mitral regurgitation, vary widely. To address this, the number of patients potentially eligible for the intervention was estimated using a market-based approach and an epidemiological approach. MSAC noted that the two different approaches gave widely different results. Using the epidemiological approach, up to 2,000 patients were potentially eligible for the intervention depending upon which Australian heart failure prevalence estimates were used. In the market-based approach, the number of patients receiving the intervention was 168 in the first year rising to 875 in year five. MSAC noted the applicant's argument that capacity issues were likely to restrict the number of people receiving the intervention, but remained concerned that uptake and costs would be greater than estimated. In addition, MSAC noted that MBS costs were likely to be underestimated if eligibility for the intervention was determined by a multidisciplinary team as the costings did not include consultations where the patient was deemed to be unsuitable for the intervention.

MSAC noted that consumer concerns around the intervention's success rate, access, equity and costs had been raised at ESC.

MSAC noted that there is a clinical need in a small patient population identified as being eligible for the intervention. However MSAC was unable to support the application due to continued uncertainty about clinical effectiveness and cost effectiveness.

4. Background

MSAC considered Application 1192 for patients with moderate to severe mitral regurgitation (MR) in November 2012 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. The PSD for this application can be viewed on the MSAC website.

MSAC considered Application 1192.1 at its April 2014 meeting. MSAC did not support public funding for the reduction of mitral regurgitation through tissue approximation using transvenous/transseptal 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. The PSD for this application can be viewed on the MSAC website.

5. Prerequisites to implementation of any funding advice

The MitraClip System (ARTG 177709) and the Clip delivery system (ARTG 189720) are registered with the Therapeutic Goods Administration (TGA) on the Australian Register of Therapeutic Goods (ARTG).

6. Proposal for public funding

The proposed listing in the resubmission is patients with severe *degenerative* MR (grade 3+ or 4+) who are assessed by a multidisciplinary heart team to be ineligible for surgery due to the risk of high surgical mortality (attributed to the presence of multiple comorbidities, advanced age, or significantly impaired LVEF). The proposed item descriptor and explanatory notes are shown in Table 1.

Table 1: Proposed MBS item descriptor for using the MitraClip® system in patients with severe degenerative mitral regurgitation

Category 3 – Therapeutic Procedures
PERCUTANEOUS RECONSTRUCTION OF AN INSUFFICIENT MITRAL VALVE using transvenous/transseptal techniques for permanent coaptation of mitral valve leaflets using one or more tissue approximation devices in patients with severe degenerative mitral regurgitation (grade 3+ or 4+) who have been determined to be at ‘high risk’ for mitral valve surgery by a multidisciplinary heart team.
Multiple Services Rule (Anaes.) (Assist.)
Explanatory note A ‘multidisciplinary heart team’ is required to provide approval regarding the patient’s suitability for treatment. (See para Tx.xx of explanatory notes for definition of ‘high risk’ and recommended composition of the heart team)
Fee: \$1720.90 Benefit: 75%= \$1,290.70, 85%=1462.80

Explanatory note Tx.xx

The core personnel of the ‘multidisciplinary heart team’ should, at a minimum, comprise a cardiothoracic surgeon, an interventional cardiologist, and an echocardiologist. An extended team could additionally include: a general cardiologist, a geriatrician, a cardiac anaesthetist, or an intensive care physician. Severe degenerative mitral regurgitation (grade 3+ or 4+) to be defined by echocardiography.

High risk is determined by the clinical judgement of the multidisciplinary heart team. In most cases, this may include, but is not limited to, the presence of one or more of the following:

- a 30-day predicted surgical mortality risk of $\geq 10\%$ (determined using the Society of Thoracic Surgeons mortality risk calculator),
- porcelain aorta or extensively calcified mobile ascending aorta,
- age older than 75 years with LVEF < 40%,
- post-mediastinal radiation,
- previous median sternotomy with patent bypass graft(s),
- ≥ 2 previous chest surgeries,
- hepatic cirrhosis,
- patients with ≥ 3 of the following risk factors: creatinine level > 2.5 mg/dL, previous chest surgery, age older than 75 years, or LVEF < 35%.

The applicant’s preMSAC response provided revised separate MBS items for assessment by the multidisciplinary heart team as shown in Table 2 with further clarification on who can claim the item, and the purpose and duration of the case conference.

Table 2 Revised MBS item descriptors for assessment of suitability for mitral valve intervention in patients with severe degenerative mitral regurgitation

Category 1 – Professional attendances
<p>MBS xxx</p> <p>MULTIDISCIPLINARY MITRAL VALVE CASE CONFERENCE</p> <p>Attendance by a medical practitioner (including a specialist or consultant physician in the practice of his or her specialty or a general practitioner), as a member of a case conference team, to LEAD AND COORDINATE A MULTIDISCIPLINARY CASE CONFERENCE ON A PATIENT WITH SEVERE DEGENERATIVE MITRAL REGURGITATION TO DEVELOP A MULTIDISCIPLINARY TREATMENT PLAN, to determine suitability for mitral valve repair or replacement, or for permanent coaptation of mitral valve leaflets using one or more tissue approximation devices.</p> <p>The core personnel of the ‘multidisciplinary heart team’ should, at a minimum, comprise a cardiothoracic surgeon, an interventional cardiologist, and an echocardiologist. An extended team could include a general cardiologist, a geriatrician, a cardiac anaesthetist, or an intensive care physician.</p> <p>The case conference is of at least 10 minutes.</p> <p>(See para xxx of explanatory notes to this Category)</p> <p>Fee: \$80.30 Benefit: 75%= \$60.25 85%=68.30</p>

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<p>MBS xxx</p> <p>MULTIDISCIPLINARY MITRAL VALVE CASE CONFERENCE</p> <p>Attendance by a medical practitioner (including a specialist or consultant physician in the practice of his or her specialty or a general practitioner), as a member of a case conference team, to PARTICIPATE IN A MULTIDISCIPLINARY CASE CONFERENCE ON A PATIENT WITH SEVERE DEGENERATIVE MITRAL REGURGITATION TO DEVELOP A MULTIDISCIPLINARY TREATMENT PLAN, to determine suitability for mitral valve repair or replacement, or for permanent coaptation of mitral valve leaflets using one or more tissue approximation devices.</p> <p>The core personnel of the ‘multidisciplinary heart team’ should, at a minimum, comprise a cardiothoracic surgeon, an interventional cardiologist, and an echocardiologist. An extended team could include a general cardiologist, a geriatrician, a cardiac anaesthetist, or an intensive care physician.</p> <p>The case conference is of at least 10 minutes.</p> <p>(See para xxx of explanatory notes to this Category)</p> <p>Fee: \$37.40 Benefit: 75%= \$28.05 85%=31.80</p>

For the purposes of these items:

- patients in public or private hospitals or the community with clinically significant DMR (grade 3 or 4+), classified using echocardiography and either present with symptoms, or be asymptomatic with evidence of LV dysfunction or dilatation, or have new onset atrial fibrillation or pulmonary hypertension, or be refractory to medical management;
- the billing medical practitioner may be from any area of medical practice and must be a treating doctor of the patient discussed at the case conference. A treating doctor should generally have treated or provided a formal diagnosis of the patient's MR in the past 12 months or expect to do so within the next 12 months;
- only one practitioner is eligible to claim item XXX for each patient case conference. This should be the doctor who assumes responsibility for leading and coordinating the case conference, ensures that records are kept and that the patient is informed of the outcome of the case conference. In most cases this will be the lead treating doctor;
- each billing practitioner must ensure that his or her patient is informed that a charge will be incurred for the case conference for which a Medicare rebate will be payable;
- participants must be in communication with each other throughout the case conference, either face-to-face, or by telephone or video link;
- in general, it is expected that no more than one case conference per patient per year will be billed by a practitioner; and
- the multidisciplinary heart team case conference is expected to review the patient’s medical condition and valve abnormality, determine if the possible interventions that

are indicated are technically feasible and reasonable, and discuss potential risks and benefits.

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. The applicant justified this increase due to:

- the increase in average surgical time (compared with the repair of an atrial septal defect)
- the complexity of the procedure
- the complexity of TOE imaging

7. Summary of Public Consultation Feedback/Consumer Issues

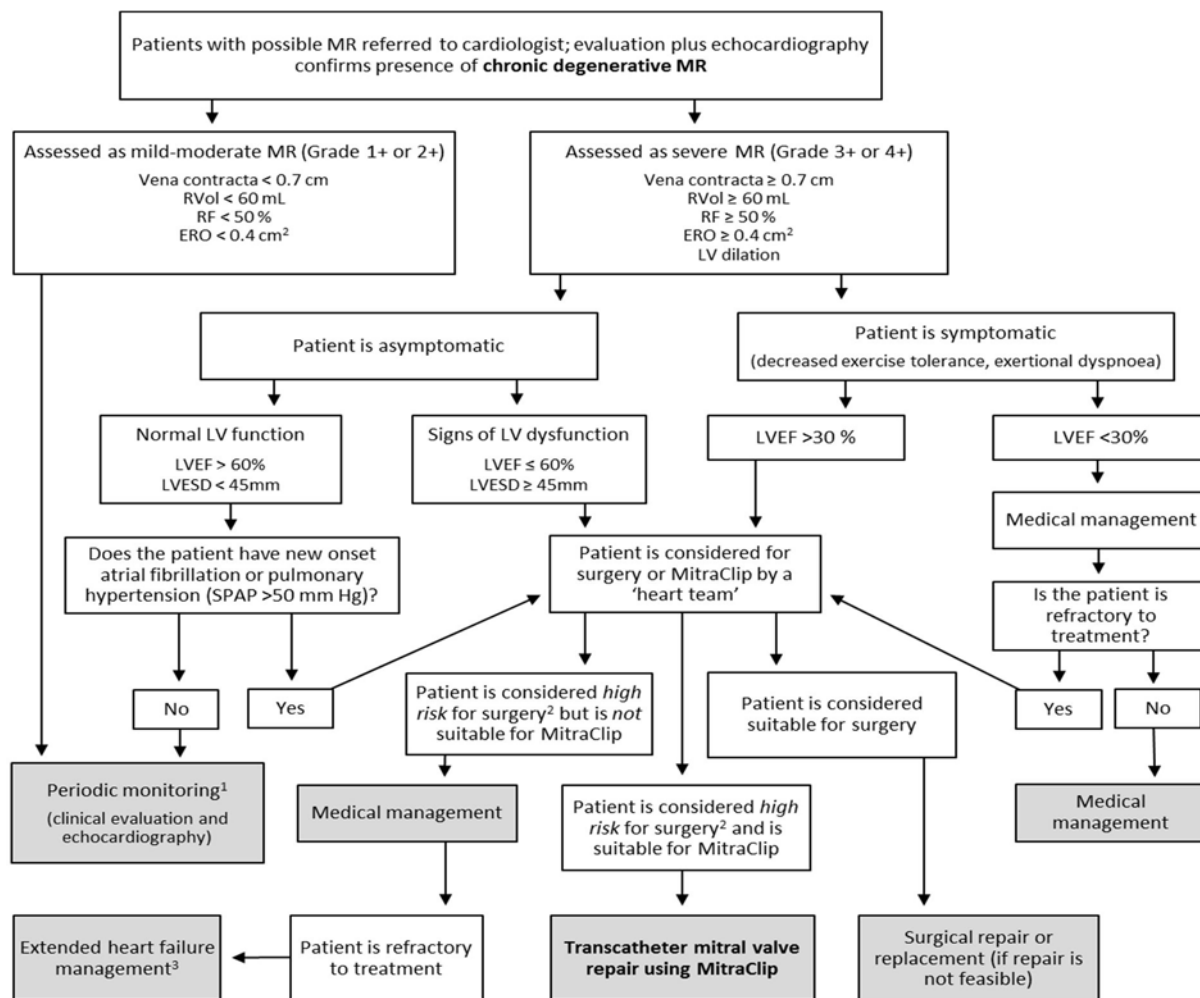
See MSAC Application 1192 Public Summary Document.

8. Proposed intervention's place in clinical management

The resubmission stated that the proposed clinical management algorithm is based on American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) guidelines. Changes to the clinical management algorithm from the previous applications for MitraClip® are based on expert opinion and the recommendations of current guidelines.

The proposed clinical management algorithm includes the possibility to use MitraClip® in patients who are at high risk of surgery while still suitable for the MitraClip® intervention. Patients who, in current clinical practice, would be high risk to surgery would be medically managed and flow onto extended heart failure management.

Figure 1 - Proposed clinical management algorithm for degenerative mitral regurgitation with MitraClip®



Abbreviations: LVEF, Left Ventricular Ejection Fraction; LVESD, Left Ventricular End Systolic Dimension; MR, Mitral Regurgitation; NYHA, New York Heart Association; SPAP, Systolic Pulmonary Arterial Pressure.

1. For patients with normal LV function, periodic monitoring is suggested every 3-5 years for progressive DMR (mild severity), every 1-2 years for progressive DMR (moderate severity), and every 6-12 months for severe DMR(11).

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

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

9. Comparator

MSAC agreed that medical management is the appropriate comparator as nominated in the resubmission.

10. Comparative safety

No relevant randomised controlled trials evaluating the safety or effectiveness of MitraClip compared with medical management in the proposed patient population were identified.

Three relevant non-randomised comparative studies (4 citations) that evaluated the effectiveness of MitraClip compared with medical management in patients with MR who were not suitable for surgery and two systematic reviews of single-arm studies were included in the assessment report.

The resubmission stated that the results for the primary safety endpoint in the EVEREST II HRR showed that high risk patients who undergo the MitraClip procedure do not have an increased risk of early mortality compared with patients managed by standard care ($p > 0.999$). There were six deaths among the 78 patients who received MitraClip, corresponding to a procedural (30-day) mortality rate of 7.7% (all cardiac-related). In comparison, there were three deaths (8.3%) out of 36 patients the standard care group (all cardiac related). Similar results were reported by Velazquez (2015), with fewer deaths observed at 30-days among 239 patients who received MitraClip, compared with the optimally matched standard care cohort.

An extended assessment of safety and adverse events data showed that the MitraClip procedure is associated with a low rate of adverse events, with the most common being bleeding complications that necessitate transfusion of ≥ 2 units of blood.

The critique noted that a comparative safety analysis of MitraClip® with medical management was not provided. The data presented was a change in adverse events at 30 days and 12 months in a patient population treated with MitraClip® based on the EVEREST II HRR trial, along with the meta-analyses of single arm studies (Philip 2014, Vakil 2014). The rates of adverse events were not compared with the control arm.

11. Comparative effectiveness

The resubmission stated that for the primary effectiveness endpoint of 12-month survival, all three comparative studies demonstrated that high risk patients who receive MitraClip® have a statistically significant survival benefit (range 76% to 86%) compared with patients who are medically managed (range 55% to 68%). Velazquez (2015) estimated that the number needed to treat (NNT) to prevent one death was 10 and Swaans (2013) demonstrated that the survival benefit was sustained through three years. The consistency across all three comparative studies suggested that any unmeasured confounding variables within the studies were unlikely to have contributed to the overall interpretation of results.

The EVEREST II HRR study also demonstrated that the MitraClip® device provides a sustainable reduction in MR in high surgical risk patients, with 77.8% of patients having an MR severity grade of $< 2+$ at 12 months. These data are consistent with that observed in the single-arm studies, with Vakil (2014) reporting data from nine studies that showed the mean MR grade was reduced from 3.5 ± 0.1 at baseline to 1.8 ± 0.1 at follow-up.

Other clinical measures of benefit also demonstrated to show sustained improvement at 12-months among patients who received MitraClip®, included NYHA functional class, quality of life, measures of LV function and re-hospitalisations for congestive HF.

The critique noted that comparative evidence was only available for 30 day and 12 month survival of patients treated with either MitraClip® or medical management. Survival at

12 months was marginally statistically significant, as reported in the EVEREST II HRR trial ($p=0.0482$). A mean difference of 20.1%, in favour of MitraClip® was reported, with a confidence interval of between -0.8% and 40.9%. As the confidence intervals cross the line of no effect (i.e. 0%), the critique found the clinical significance of this finding questionable. Additionally, the data is from a single small study of limited applicability and at high risk of bias, which further diminished confidence in the claims of superiority. There was no statistical difference between the two interventions for mortality at 30 days ($p>0.99$) when comparing MitraClip® surgery with the concurrent control group.

On the basis of the benefits and harms reported in the evidence base, the resubmission proposed that, relative to medical management, MitraClip® has non-inferior safety and superior effectiveness. The critique concluded that, based on limited data, it is not possible to support these claims.

12. Economic evaluation

The resubmission presented a stepped economic evaluation. The preESC response to the critique provided a revised base case cost-effectiveness result for MitraClip compared with medical management alone. The revised ICER, including three heart team professionals and updated costs, was estimated to be \$**redacted**/QALY. The preMSAC response noted this was consistent with other published economic models, Cameron (2014) and Mealing (2013), which both reported an ICER between A\$20,000 and A\$30,000 per QALY. One-way sensitivity analyses showed that the ICER was most sensitive to the time horizon and hazard ratio for mortality. However, the ICER remained below \$45,000 per QALY in the majority of scenarios tested.

The preESC response to the critique noted that the average number of Clips implanted is **redacted** clips per patient, however because the MitraClip system is priced per procedure the associated costs with MitraClip surgery are unchanged.

Utilities accrued by health state (NYHA state) were presented as undiscounted and discounted results.

The critique considered that the economic model was flawed. To increase the transparency of the results, it would have been beneficial if the applicant had also supplied the incremental cost effectiveness results using a shorter time horizon, using only the trial results along with the results if no discounting had been applied.

The critique also noted that while the methodology used in the survival analysis was appropriate, the data used in the economic evaluation of MitraClip® is insufficient to accurately represent the cost effectiveness of the intervention. The EVEREST II HRR trial may be the best available evidence, but the lack of comparative data, along with data that may not be comparable to the MBS descriptor, flaws in the inputs of the model (such as unadjusted costs derived from different years), inappropriate transition state probabilities, and using the extrapolated data from month 0 rather than the end of trial data, reduces the accuracy and certainty around the ICER.

The critique further raised concerns regarding the hazard ratio and the time horizon, which were the two main inputs which drove the model, particularly due to the uncertainty regarding the clinical data. Additionally, neither transitional probabilities (patient movement between NYHA states) nor the starting time cycle of extrapolation were tested in the sensitivity analyses. The only multivariate analysis tested was differing the data set of utilities used in the model.

The critique considered that as superiority of MitraClip® was not established based on the clinical evidence, a cost minimisation step would have been informative, where the cost of MitraClip® was decreased until the cost of the MitraClip® intervention was equal to the overall cost of medical management.

13. Financial/budgetary impacts

The resubmission presented an epidemiological and market approach to estimate the financial implications from the proposed listing of MitraClip®.

The financial implications based on the market approach, are summarised in Table 4.

Table 4 Total costs to the MBS associated with MitraClip®

	2015-16	2016-17	2017-18	2018-19	2019-20
Number of services	168	360	475	600	875
MitraClip®	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Heart Team Assessment	\$11,474	\$24,588	\$32,443	\$40,980	\$59,763
General Anaesthesia	\$16,986	\$36,360	\$47,975	\$60,600	\$88,375
Intra-operative transesophageal echocardiography (TOE)	\$50,501	\$108,216	\$142,785	\$180,360	\$263,025
Fluoroscopy	\$36,977	\$79,236	\$104,548	\$132,060	\$192,588
Post-operative transthoracic echocardiography (TTE)	\$32,945	\$70,596	\$93,148	\$117,660	\$171,588
Total cost	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Abbreviations: TOE, Transesophageal Echocardiography; TTE, Transthoracic Echocardiography

An updated financial analysis was provided in the preMSAC response of net costs to public and private hospitals over five years. The net cost to hospitals for treatment with MitraClip ranged from \$redacted in 2016 to \$ redacted in 2020.

The applicant’s preMSAC response noted that there are significant capacity constraints with performing the proposed procedure. The anticipated uptake is contingent upon the limited number of centres and qualified practitioners with the capacity to perform the procedure in accordance with the requirements specified in the proposed MBS descriptor.

The critique stated that a market-based approach, based on estimated supply side capacity constraints, was used as the base case in determining the number of procedures per site per year. An epidemiological approach was used as a sensitivity analysis. The critique considered that the assumption that each clinical site would only conduct one operation per month was questionable – particularly when the epidemiological estimates showed that the potential demand for the treatment is substantially higher. The difference between the two methods indicated that neither may be correct, and an alternative approach may be more appropriate.

The critique noted that the prevalence of heart failure and therefore mitral regurgitation are difficult to assess, and reports range from 100,000 to 400,000 heart failure patients in Australia. The estimate (used in the resubmission) of the incidence of heart failure is 10%. This translated to 1,653 patients with severe MR in the first year increasing to 1,754 per year

after five years. These statistics are based on 2004 data and have not been adjusted to increases in the Australian population. Therefore the epidemiological approach underestimated the potential number of patients treated with MitraClip®. This approach considerably differs from the market approach which estimates 168 patients to be treated with MitraClip® in the first year, increasing to 875 in the fifth year. The applicant has also assumed the number of patients who are high risk and treated with medical management and who would elect surgery even with the associated risks, are transferable between the EVEREST II trial and in an Australian health care setting. This may not be the case, and no justification has been provided.

The critique considered that the resubmission did not appropriately account for the number of multi-disciplinary care items; only counting those where a MitraClip procedure was deemed viable, but not for those where patient was deemed unsuitable for the procedure.

There is potential for the net cost/year to the MBS to be greater than estimated in the SBA.

14. Key issues from ESC for MSAC

Comparative safety

ESC raised concerns that the evidence presented in this resubmission to support safety and benefit claims was based on three small non-randomised trials, with the potential for bias in favour of MitraClip®. However, ESC questioned whether better evidence is likely to be forthcoming. ESC noted that the only reported safety outcomes from the EVEREST II HRR trial were adverse events at 30 days and 12 months, and there was no comparison to medical management. This evidence does not support claims of non-inferior safety.

Comparative Effectiveness

ESC noted that the resubmission has a potential bias in comparative effectiveness.

ESC noted the resubmission has potential study bias, with the pivotal trial consisting of both degenerative and functional mitral regurgitation patients. It was also noted that in this trial, 30 patients were excluded from the comparator group, which raised concerns of selection bias.

Economic evaluation

ESC raised concerns that:

- Utility measures used were not based on comparative analysis;
- Survival benefit extrapolated on very short-term data for the comparator group;
- ICER of \$redacted per QALY is potentially underestimated with a greater likelihood that it is significantly higher; and
- The ICER is highly sensitive to the hazard ratio.

MBS item descriptor issues

It is unclear whether the proposed MBS item for professional attendances would be claimed by each medical practitioner of the case conference team (which is indicated by the wording of the MBS descriptor) or one item would be claimed by the entire team (as indicated by the costing in Section D and E of the application). Further clarification on who can claim this item, as well as its purpose and duration of the case conference is needed.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

Abbott Vascular would like to thank MSAC for its consideration of the proposed listing of the reduction of mitral regurgitation through tissue approximation using transvenous/transseptal techniques in patients with severe DMR (grade 3+ or 4+) who are considered too high risk for surgery. The intent of the proposed listing is to address an area of high unmet need in patients with severe DMR who are not eligible for surgery. The applicant is pleased MSAC has acknowledged the intervention has a reasonable safety profile and noted that there is a clinical need in this small patient group who have no other treatment options; however, Abbott Vascular is disappointed with MSAC's decision and is keen to work with all relevant stakeholders to ensure MitraClip becomes available to all DMR patients who are eligible for this intervention. The areas of uncertainty outlined in this PSD were addressed in the applicant's responses to the evaluation and ESC reports, and, although some inherent limitations with the available comparative evidence exist, the applicant has some concerns that these areas of uncertainty have been overstated. Given the unmet need in this defined patient group, randomised controlled trials would be challenging and are believed not feasible. The applicant reiterates that there is a vast body of real world evidence that has demonstrated the efficacy and cost-effectiveness of this innovative intervention. Transcatheter mitral valve repair with MitraClip results in improvements in heart functioning, NYHA functional status, quality of life and reduces heart failure hospitalisations. In addition, Australian cardiothoracic surgeons and cardiac specialists have recognised that MitraClip offers a valuable alternative for these difficult-to-treat patients and its use in this setting is supported by US and European guidelines. Further, the applicant reaffirms that the market-based approach to estimating costs is the most appropriate. As validated in other countries, the uptake and costs of the intervention would be limited by the specialised expertise and multi-disciplinary approach needed for the assessment, treatment, and management of these complex valve disease patients.

17. Further information on MSAC

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