



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### *Application No. 1192.1 – The reduction of severe mitral regurgitation through tissue approximation using transvenous/transseptal techniques*

**Sponsor/Applicant/s:** Abbott Vascular

**Date of MSAC consideration:** MSAC 61st Meeting, 3-4 April 2014

#### **1. Purpose of application**

In October 2013, a resubmission was received by the Department of Health requesting Medicare Benefits Schedule (MBS) listing for the reduction of severe mitral regurgitation (MR) through tissue approximation using transvenous/transseptal techniques in patients considered to be high risk for surgery and currently treated by medical management.

Application 1192.1 is a resubmission and this public summary document should be reviewed in conjunction with the Public Summary Document for 1192.

#### **2. 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 for interventional cardiologists 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.

Further information regarding the previous MSAC Application 1192 - Percutaneous reconstruction of an insufficient mitral valve through tissue approximation using transvenous/transseptal techniques can be viewed at <http://msac.gov.au>.

#### **3. Prerequisites to implementation of any funding advice**

MSAC noted that at the time it considered this application it was aware of two Therapeutic Goods Administration (TGA) entries for MitraClip® listed on the Australian Register of Therapeutic Goods (ARTG) by the Abbott Vascular Division of Abbott Australasia Pty Ltd.

ARTG	Start date	Description	Intended purpose
177709	Nov 2010	Mitral valve tissue repair system	Percutaneous reconstruction of an insufficient mitral valve through tissue approximation using transvenous/transseptal techniques
189720	Sep 2011	Mitral Valve Clip Delivery System	Reconstruction of the insufficient mitral valve through tissue approximation

Source: [www.fga.gov.au](http://www.fga.gov.au) accessed 30 January 2014

#### 4. Proposal for public funding

The resubmission proposed MBS items and explanatory note are presented in the following tables. The proposed fee for ‘percutaneous reconstruction of a mitral valve’ is based on MBS item 38272 Transcatheter closure of an atrial septal defect.

##### Applicant proposed MBS item descriptor and fee

Category 3 – Therapeutic Procedures
<p>MBS 38xxx  Percutaneous reconstruction of an insufficient mitral valve using transvenous/transseptal techniques in patients considered to be at high risk from surgery. (Anaes.) (Assist.)  It is recommended that a ‘heart team’ 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.  This item may not be claimed if this device cannot be placed satisfactorily in the patient; and abandon surgery item may be claimed in this case.  Fee: \$912.30 Benefit: 75% = \$684.25</p>

##### Applicant proposed explanatory note

<p>Explanatory Note Tx.xx  The ‘heart team’ should comprise two cardiologists (a medical and an interventional cardiologist) and a cardiothoracic surgeon.</p> <p>High risk patients are those defined as being symptomatic with grade 3+ to 4+ MR and a predicted surgical mortality risk of <math>\geq 12\%</math>, based on either the STS risk calculator or surgeon co-investigator estimated mortality risk following prespecified protocol criteria. Potentially criteria included high-risk patients with porcelain aorta, mobile ascending aorta atheroma, post-mediastinal radiation, functional MR with left ventricular ejection fraction (LVEF) <math>&lt; 40\%</math>, age older than 75 years with LVEF <math>&lt; 40\%</math>, previous median sternotomy with patent bypass graft(s), <math>&gt; 2</math> previous chest surgeries, hepatic cirrhosis, or <math>\geq 3</math> of the following STS high-risk criteria: creatinine level <math>&gt; 2.5</math> mg/dl, previous chest surgery, age older than 75 years, or LVEF <math>&lt; 35\%</math>.</p>
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The resubmission stated that MBS item 30001 would apply where surgery needs to be abandoned due to the device not being able to be satisfactorily implanted. However, Departmental advice is that item 30001 is for an “Operative procedure, being a service to which an item in this Group would have applied had the procedure not been discontinued on medical grounds”. The appropriateness of claiming item 30001 for the failed placement of a device would be based on meeting this legislative requirement.

The proposed MBS item for the removal of the prosthesis is presented in the following table.

**Applicant proposed MBS item for the removal of the prosthesis**

<b>Category3 – Therapeutic Procedures</b>
MBS 38xxx Subsequent removal of one or more tissue approximation devices as a result of post percutaneous reconstruction recurrent mitral regurgitation requiring further surgical or medical management. (Anaes.) (Assist.) Fee: to be determined

A number of differences were noted between the item descriptors outlined in the protocol for MSAC 1192 and the resubmission, 1192.1, including:

- The proposed MBS item for ‘percutaneous reconstruction of a mitral valve’ is not explicit whether insertion of any tissue approximation devices are involved with the procedure, and if so, the number of tissue approximation devices that can be used; and
- The proposed MBS item for device removal does not specify the circumstances of use, the number of devices that may be removed or a proposed fee.

The, 1192.1, resubmission included a definition of ‘high risk patients’ in the proposed explanatory note. However, it was unclear to MSAC how the grades, scores, clinical symptoms and conditions are to be applied in identifying the targeted patient population or how this relates to current practice within Australia. The resubmission noted in the definition of ‘high risk patients’ that previous chest surgery may exclude patients from receiving the intervention.

As per the protocol for MSAC application 1192, the MitraClip procedure is performed by an interventional cardiologist or cardiac surgeon with training and experience in the intervention, with the support of a multidisciplinary team during the procedure.

## **5. Summary of Consumer/Consultant Feedback**

Information regarding consumer feedback on MSAC Application 1192 - Percutaneous reconstruction of an insufficient mitral valve through tissue approximation using transvenous/transeptal techniques can be viewed in the Public Summary Document at [MSAC website](#).

## **6. Proposed intervention’s place in clinical management**

The resubmission proposed that percutaneous mitral valve reconstruction is an option for treating severe MR for high-risk surgical patients with either primary (organic) or secondary (functional) MR and have been assessed by a ‘heart team’ to be both at high risk for surgery and suitable for the intervention.

The final protocol for MSAC Application 1192 presented a clinical pathway adapted from the American College of Cardiology/American Heart Association Guidelines for the management of patients with valvular heart disease (2006) for “the management strategy for patients with chronic severe MR”.

However, the resubmission presented the clinical pathway from Neuss et al (2013) for “patient selection before MitraClip implantation vs. conventional mitral valve surgery or optimal medical therapy in the case of severe symptomatic chronic MR depending on

surgical risk and co-morbidities”. Based on this algorithm, the resubmission considered surgical risk models and co-morbidities in deciding patient appropriateness to receive MitraClip.

Additionally, based on the 2012 European Society of Cardiology Guidelines, decision-making should ideally be made by a ‘heart team’ with particular expertise in valvular heart disease, including cardiologists, cardiac surgeons, cardiac imaging specialists, anaesthetists and, if needed, general practitioners, geriatricians, or intensive care specialists. This ‘heart team’ approach is particularly advisable in the management of patients considered to be at high risk for surgery.

## **7. Comparator**

For MSAC Application 1192, MSAC determined that medical management was the appropriate comparator to the proposed intervention for patients unsuitable for surgery.

The proposed patient population in the resubmission was patients with severe MR considered to be high risk for surgery with the comparator of standard medical therapy.

MSAC agreed that the comparator was appropriate in the resubmission while noting that patients with heart failure may also be treated with cardiac resynchronisation therapy.

## **8. Comparative safety**

MSAC noted that at the time it considered these applications no randomised controlled trials (RCTs) or comparative studies were made available for the identified patient population for MitraClip therapy. Limited evidence from case studies was available to MSAC. All identified literature was single-arm evidence i.e. there were no data available from concurrent patients managed by medical therapy.

The resubmission re-presented the study by Whitlow et al (2012) - The EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study as pivotal evidence. This study was included in the original submission. The resubmission also included 19 non-comparative studies as supporting evidence, which were not presented in the original submission.

Issues with the identified evidence included:

- patient overlap in a number of the included studies; and
- some of the studies did not report high risk as a criterion for inclusion.

The study reported by Whitlow et al (2012) consisted of two patient cohorts:

- 78 prospectively enrolled patients from the High Risk Study (HRS), an arm of the EVEREST II trial, who underwent the MitraClip procedure. Patients with severe symptomatic MR and an estimated surgical mortality rate of  $\geq 12\%$  were enrolled. It should be noted that 30 of these patients had an STS score  $\leq 12\%$  but were considered high risk by the physician based on the presence of prespecified baseline comorbidities.
- A control arm comprised of 36 retrospectively selected patients who were screened for enrolment in the HRS but did not enrol or were not anatomically eligible for MitraClip device placement. Patients in the control arm consisted of patients treated by medical management (86%) or surgery (14%).

MSAC noted that patients in the high-risk group were elderly and had multiple comorbidities. However, the LVEF at baseline in this patient cohort was the highest across all the studies and was “preserved” ( $54.4\% \pm 13.7\%$ ; normal  $\geq 50\%$ ).

The study reported by Whitlow et al (2012) was considered to be case series evidence as the comparator group contained patients managed medically or surgically. Additionally, the comparator group included patients who did not have appropriate anatomic criteria for MitraClip placement. Therefore, patients in the two cohorts did not necessarily have comparable anatomic characteristics and may have received surgery (not an appropriate comparator).

The resubmission included a study on the long-term prognosis of medically treated patients (Agricola et al 2009), which prospectively enrolled 404 consecutive patients with left ventricular ejection fraction (LVEF)  $34.4 \pm 10.8\%$  and at least mild MR.

The resubmission also identified six registries worldwide supporting the use of MitraClip therapy for patients at high risk from surgery who suffer from severe MR.

The resubmission reported hospital deaths and 30 day mortality as measurements of the safety of the MitraClip procedure in the high risk patient group.

Surder et al (2013) reported a 4% rate of in-hospital deaths. The 30-day mortality (including in hospital deaths) was reported in most studies (range 0-8%). The majority of studies did not provide long term mortality data. No outcomes beyond two years were reported in any of the studies, and whether the death was related to the intervention was generally unclear.

The time point and cause of death were often unclear or not reported. Additionally, all-cause mortality varied across the included studies (range 8-29%), resulting in losses to follow-up that may have contributed to an over-interpretation of the reduction in MR in patients treated with MitraClip.

Three studies used the Kaplan-Meier method to estimate survival at one year:

- Neuss et al (2013) reported a 70% two year all cause survival.
- Whitlow et al (2012) reported a 75.4% freedom from mortality at 12 months.
- Treede et al (2012) reported a 1-year survival of 89.6%.

Whitlow et al (2012) reported a 12-month survival rate of 76% for patients receiving the Mitraclip device and 55% for the comparator group ( $p = 0.047$ ). The annual rate of hospitalisation for congestive heart failure in surviving patients with matched data decreased from 35 events to 18 events ( $p = 0.034$ ).

Clip detachment and clip migration potentially causing embolisation were reported in nine studies with a rate of between 0-5%. One study identified that myxomatous morphology was associated with a higher rate of partial clip detachment (Neuss et al 2013).

Where reported, the probability of major bleeding events ranged from 1-5%, with an exception in the Whitlow et al (2012) study which reported 31 events requiring a transfusion of  $\geq 2L$  of blood units at the 12-month follow-up.

Reported events of wound infections were negligible (0–1%). However, four studies reported events of septicaemia (1-4%) and pneumonia (4-5%) during the first 12 months. Chordal or papillary muscle rupture was experienced by 1-2% of the patients. However, it was not stated by the authors whether these tears were due to MitraClip placement or removal.

Other reported adverse events included:

- Heart failure (3-20%);
- Myocardial infarction (0-5%);
- Stroke (0–3%);
- Cardiac tamponade (0–2%); and
- Renal failure (0–6%).

It was not clear in any of the studies whether the patients required ventilation for over 48 hours.

For severe MR, Agricola et al (2009) reported survival free results of:

- 49% all-cause mortality (95% CI 27–65);
- 55% cardiac death (95% CI 30–77); and
- 18% heart failure (95% CI 15–32).

Agricola et al (2009) concluded that:

- The mortality and morbidity of patients with left ventricular dysfunction and functional MR remain high despite current standard pharmacological therapy; and
- Moderate-to-severe MR is an independent predictor of cardiac death and heart failure.

Due to the co-morbidities associated with the patient population and the underlying pathologies, it would be anticipated that patients receiving medical management would also suffer from similar adverse events. However, direct comparative data on this population is unavailable.

Regarding all-cause mortality, the proposed patient population is generally comprised of older patients with severe symptomatic MR and co-morbidities. MSAC noted ESC advice that given the lack of comparative data, it is unclear whether MitraClip therapy will provide a survival benefit over medical management alone.

MSAC considered that, as there are no direct comparative studies for the assessment of safety with the evidence limited to registries and case studies, there was a lack of clinical data for delayed adverse events and no analysis was provided of the adverse events associated with the intervention.

## **9. Comparative effectiveness**

The basis for MSAC Application 1192, with relevance to the comparison of MitraClip with mitral valve repair or replacement surgery, was derived from the endovascular valve edge-to-edge repair study (EVEREST) II RCT reported by Feldman et al (2011). As previously mentioned, the resubmission included the HRS reported by Whitlow et al (2012) as pivotal evidence for the current assessment.

The resubmission quoted the importance of MR  $\leq$  1+ at discharge from hospital as a key indicator of long-term efficacy. The papers that reported MR  $\leq$  1+ at discharge quoted

percentages between 38% and 95%. Neuss et al (2013) reported that, of 142 patients at discharge from hospital, 24% of patients had a MR grade of 1+ and 76% of patients had a MR grade of 2+.

In all studies, the majority of patients had MR reduction to  $\leq 2+$  at all reported time points. When reported, the proportion of patients with MR  $\leq 2+$  at six months and one year showed a downward trend. Whitlow et al (2012) reported that, in surviving patients with matched baseline and 12-month data, 78% of the MitraClip therapy patients had an MR grade of  $\leq 2+$ . However, the critique identified that losses to follow-up over the time from discharge may lead to an over-interpretation of the reduction in MR as patients who died or were lost to follow up are not included in the denominator.

The resubmission stated that procedural success between 90% and 100% is reported in 16 out of 19 studies (84%). The papers by Pleger et al (2013), Rudolph et al (2013) and Surder et al (2013) reported procedure success of 86%, 88% and 85% respectively. However, the number of clips placed, procedure time, time for recovery and post-procedure hospitalisation were not reported.

In the identified studies, the necessity for two clips was commonly reported. The need for three or more clips occurred in at least one patient in the majority of the studies when reported.

Surder et al (2013) examined predictors of long-term efficacy using a combined efficacy endpoint (freedom from death at six months, freedom from MR grade  $\geq 2+$  at six months, freedom from post-implant congestive heart failure and freedom from reoperation at six months). This was done using a regression analysis and patients had a median follow-up time of 15.7 months. The proportion of patients with the efficacy endpoint was higher in patients with an MR grade of 1+ at discharge as compared to patients with an MR grade of 2+ or more ( $p < 0.001$ ). Patient body mass index (BMI) was also a predictor of long-term efficacy. This study enrolled 100 patients, 15 (15%) of whom did not achieve procedural success.

Rates of reintervention were reported in the following studies:

- Rudolph et al (2013) reported 10 patients had repeat MitraClip procedures, of which two had subsequent valve repair, and seven patients had valve replacement.
- Treede et al (2012) reported 5.4% (11 of 202 patients) required surgical reintervention because of failed repair ( $n = 3$ ), recurrent severe MR ( $n = 7$ ) or despite good valve function ( $n = 1$ ) at a median of 38 days (range 0-468 days). Injury of the mitral leaflets caused by prior MitraClip device treatment was present in six patients, influencing the surgical strategy toward more complex repair techniques in three patients, and valve replacement in one patient. Whether the MitraClip device performed as a bridge to surgery in any instance was not reported.
- Neuss et al (2013) reported 6.0% (10 of 154 patients with initial, successful implantation procedures) had conventional surgery within six months.

Quality of life was reported in the following studies:

- Neuss (2013) assessed quality of life using the Minnesota Living with Heart Failure questionnaire and patients were assessed at six and 12 months. Fifty one patients improved from 37(26–49) to 23(11–41) at six months ( $p$  value  $< 0.001$ ) and to 23(10–37) in 35 patients available at 12 months ( $p$  values  $< 0.25$ ).

- Van Den Branden (2012) assessed quality of life using the ‘Minnesota questionnaire’ at baseline and at six months. The authors report a reduction in quality of life index scores from  $56.5 \pm 21.9$  to  $39.4 \pm 20.5$  ( $p < 0.001$ ).
- Whitlow (2012) measured quality of life using the SF-36 Health Survey and found an improvement in the physical component score from  $31.6 \pm 9.1$  to  $36.5 \pm 10.6$  ( $p=0.02$ ) and in the mental component score from  $44.2 \pm 12.6$  to  $49.2 \pm 12.0$  ( $p=0.06$ ) from baseline to 12 months.

Due to the lack of comparative data, MSAC noted there is a high degree of uncertainty regarding the clinical benefit of MitraClip as compared to medical management alone, particularly with reference to survival and freedom from surgery.

It is expected that MitraClip would result in a reduction in MR as compared to medical management alone as current evidence does not suggest efficacy of pharmacological treatment for severity of MR. The reduction in MR that would confer a meaningful clinical benefit in patients at too high risk for surgery is unclear. The durability of this benefit is also uncertain due to a paucity of long term follow-up data.

Two clinical trials have a randomised study design comparing MitraClip treatment to medical management (NCT01626079 and NCT01772108) and a third is a comparative study comparing MitraClip to optimal standard of care therapy (NCT01920698). No results of these trials are available at this time.

The COAPT trial (NCT01626079) will be conducted in the United States. It will use the MitraClip device, an open label trial, and use of the STS or surgeon assessment to assess surgical risk. A central eligibility committee will be used to ensure:

1. surgical risk is adequately documented by the surgeon investigator when the STS score is less than 8%; and
2. confirmation that the patient has been adequately treated for heart failure.

The trial will randomise 420 patients (210 MitraClip and 210 medical therapy) with a primary effectiveness endpoint of recurrent heart failure hospitalisations. The trial was conditionally approved in February 2012 and as of February 2013, two patients have been enrolled.

The RESHAPE-HF trial (NCT01772108) will be conducted in Europe and will study patients with advanced heart failure and functional MR. This 800 patient trial will randomise patients 1:1 between MitraClip and medical therapy. The primary endpoint is a hierarchical composite of all-cause mortality and recurrent heart failure hospitalisations. The trial has begun recruitment.

MSAC considered that, as a result of no direct comparative studies for the assessment of clinical effectiveness, that there is uncertainty as to whether the proposed intervention is more effective in improving clinical outcomes.

## **10. Economic evaluation**

The resubmission presented a cost-utility analysis. A probabilistic sensitivity analysis was also performed to characterise uncertainty in the model parameters, such as mortality estimates.

The structure of the economic model presented in the resubmission was the same as presented in the previous submission, although some of the model inputs have been changed. The key



model drivers were the increased survival with the MitraClip device, the distribution of NYHA classes, including the utility values and probability of heart failure hospitalisation assigned to each class, and the cost of the MitraClip device. Overall, the incremental cost/LYG and cost/QALY gained were likely to be underestimated because the gain in survival was overestimated, the costs associated with identifying patients suitable for the MitraClip device were not considered, and the cost for the hospital admission for implantation of the MitraClip device was underestimated.

The model fitted parametric survival functions to clinical data to extrapolate short term data beyond the observation period in order to generate lifetime estimates. The 12 month survival data from the HRS (Whitlow et al 2012) was a primary source of data. The key model drivers were the increased survival with the MitraClip device, the distribution of NYHA classes, including the utility values and probability of heart failure hospitalisation assigned to each class, and the cost of the MitraClip device.

The incremental cost of MitraClip therapy compared to medical management was \$32,847 per QALY.

Overall, the incremental cost/LYG and cost/QALY gained were likely to be underestimated because the gain in survival was overestimated, the costs associated with identifying patients suitable for the MitraClip device were not considered, and the cost for the hospital admission for implantation of the MitraClip device was underestimated.

#### Population and circumstances of use

The model used in the resubmission aimed to reflect the patient population in the HRS reported by Whitlow et al (2012) i.e. patients with severe symptomatic MR and an estimated surgical mortality rate of  $\geq 12\%$ . The mean age of patients in the HRS was 77 years and 63% were male. The predicted perioperative mortality rate for patients receiving MitraClip was 18.2%.

The proposed MBS item in the resubmission recommended that a 'heart team' provide approval regarding the patient suitability for treatment. The explanatory note for the proposed MBS item defines high risk patients using the same criteria as the HRS.

The applicability of the results from the HRS to Australian clinical practice was not addressed in the resubmission. The proposed patient population was broad and thus the population in the model may not be representative of the population for whom MBS listing is sought.

#### Time horizon

The time horizon used in the economic evaluation was 40 years. The mean age of patients entering the model was 77 years, and therefore the model runs to a patient age of 117 years. The mean follow-up for patients in the HRS (Whitlow et al 2012) was not reported and the Kaplan-Meier estimates were provided to 12 months only.

The model for the previous assessment (MSAC 1192) also used a time horizon of 40 years and the ESC questioned why the model had a time horizon of 40 years when presumably the majority of patients receiving MitraClip would be aged 60 years and over (PSD 1192, page 13).

In the pre-MSAC response, the applicant addressed the time horizon and the impact of reducing it to 5 years produced an incremental cost-effectiveness ratio (ICER) of approximately \$38,000.

The sensitivity analyses presented in the resubmission demonstrate that one of the parameters the model results are sensitive to is the time horizon used.

### MBS costs

The resource use and associated costs for identifying the relevant patient population for treatment with the MitraClip device have not been included in the economic evaluation.

### **MBS items associated with identifying patients suitable for MitraClip therapy**

<b>Resource</b>	<b>Provider of resource</b>	<b>MBS item numbers</b>	<b>MBS fee (1 November 2013)</b>
Transthoracic echocardiography	Cardiologist	55113/55114/55115	\$230.65/\$230.65/\$230.65
Transesophageal echocardiography	Cardiologist	55118	\$275.50
Anaesthesiology for transesophageal echocardiography	Anaesthesiologist	21936	\$118.80
Electrocardiography	Cardiologist	11700/11701/11702	\$31.25/\$15.55/\$15.55
Chest x-ray	Cardiologist	58503	\$47.15
Cardiac catheterisation	Cardiologist	38203/38206	\$531.55/\$642.65
Consultation	Cardiologist	TBD	
Anaesthetic consultation	Anaesthesiologist	TBD	

The relevance of the cost for angioplasty was not discussed and a reference for the cost was not provided. It was stated in the PSD for the previous application (PSD 1192, page 10) that ‘theatre costs should be disaggregated to individual unit costs’.

MSAC considered that the main economic issues or areas of uncertainty were that the survival benefit was probably over-estimated and costs, such as the workup, hospitalisation and downstream costs, were not included in the resubmission.

## **11. Financial/budgetary impacts**

The resubmission estimated the volume of use of the proposed intervention per year based on an estimate of the annual incidence of severe MR minus patients treated with surgery (repair or replacement) in either the public or private sector. The applicant provided the following assumptions:

- 300,000 patients will have heart failure at any given time;
- 30,000 (10%) of heart failure patients will be new (incident) cases;
- 8,700 (29%) of incident cases will have severe MR;
- 6,573 (75%) of patients with severe MR will receive surgery and 2,127 patients will be managed medically; and
- 1,276 (60%) of patients receiving medical management will be treated in the private setting.

The resubmission assumed that the number of procedures would double over the first four years and then flatten out at 75% from year four onwards i.e. the percentage of the eligible patients treated with the MitraClip device in years one, two, three, four and five is 19%, 35%, 56%, 75% and 75%, respectively. The other 25% of patients either refuse the intervention or have other morbidities (not necessarily associated with MR) that are more likely to cause death within a short time period.

The resubmission calculated the number of patients with severe MR receiving surgery by combining the total for 2009-10 of:

- Australian Institute of Health and Welfare (AIHW) data for mitral valve repair, replacement or reconstruction; and
- MBS services for cardiac valve repair or replacement.

However, the AIHW data includes public and private hospitals in Australia. Additionally, the MBS items identified are for cardiac valve repair and replacement and include valves other than the mitral valve. Therefore, there may be double counting of the private patients treated with surgery and underestimating the number of patients eligible for MitraClip.

The incidence of heart failure increases with age, with very few heart failure patients aged less than 55 years. Of the 4,554 procedures in the AIHW dataset for mitral valve repair, replacement or reconstruction in 2008/2009 or 2009/2010, 24% were in patients aged less than 55 years and unlikely to be in heart failure patients. Therefore, the number of heart failure patients treated with surgery is likely to be overestimated and the number of patients eligible for MitraClip further underestimated.

In the pre-MSAC response, the applicant provided alternative AIHW 2009-10 data for mitral and aortic valve repair/replacement to address the above concerns with potential overestimation of patients treated with surgery and underestimation of the number of patients eligible for MitraClip. Based on this data, the alternative estimate for the potential patient population for tissue approximation using transvenous/transseptal techniques – MitraClip, was 1,144 compared with the original estimate of 1,276.

The majority of patients are expected to undergo one MitraClip procedure in their lifetime.

The resubmission estimated the number of patients eligible for the MitraClip procedures by calculating the number of new (incident) heart failure patients with severe MR that are not treated with mitral valve surgery.

The resubmission sourced estimates of the incidence and prevalence of heart failure in Australia from the 2003 AIHW publication ‘Heart failure...what of the future’ which stated:

- There are no Australian data on the incidence and prevalence of heart failure in Australia. Based on overseas findings, it is estimated that at least 300,000 Australians have chronic heart failure (or about 4% of the population aged 45 or more), with 30,000 new cases diagnosed each year.
- Two major barriers in determining the incidence and prevalence of heart failure in Australia are the lack of a universally agreed definition and difficulties in diagnosis, particularly when the condition is mild.

A more recent 2011 AIHW report noted that there are no national data on the incidence of heart failure in Australia and quotes the 30,000 estimate included in the 2003 AIHW report.

The Assessment critique indicated that, in the long-term, it is appropriate to use the incident patient population. However, initially a proportion of the prevalent pool is also likely to be treated with the MitraClip device.

The resubmission estimated the total MBS fee (surgeon, assistant surgeon and anaesthetist) per procedure to be \$1,391.76 (75% benefit = \$1,043.85).

The total cost to the MBS presented in the resubmission did not include the following services and additional costs in the financial forecasts:

- MBS items for cardiac catheterisation and imaging services, as outlined in the protocol for MSAC application 1192;
- MBS services likely to be provided to treat adverse events associated with the MitraClip procedure;
- Repeat procedures; and
- Patient co- contributions of the MBS fees.

The resubmission estimated that the total average cost per patient would be \$65,109 based on costs to the MBS, patient and private health insurer. The cost of the device accounts for a large proportion of the total cost for the service.

The current total average cost per patient for medical management for the same patient population was estimated at \$21,950 based on pharmaceutical costs and procedures resulting from worsening co-morbidities.

Based on the maximum potential patient population (1,276) and the proposed fee for the MitraClip procedure (\$1,043.85), the estimated total cost of the service to Government was \$55 million per year.

Based on the maximum potential patient population (1,276) and incremental cost per patient (\$43,159), the estimated direct cost to the MBS (based on 75% of fees) was \$1.3 million per year.

## **12. Other significant factors**

Nil

## **13. Summary of consideration and rationale for MSAC's advice**

MSAC noted that Application 1192 was considered in November 2012 for the proposed intervention as an alternative treatment to mitral valve surgery or medical management (high-risk patients not suitable for surgery). MSAC noted it did not support public funding for the intervention at that time based on inferior clinical effectiveness compared to mitral valve surgery, and lack of comparative data compared to medical management. The resubmission is for the intervention in patients with severe mitral regurgitation considered to be at high risk for surgery and currently treated by medical management.

In evaluating the resubmission, MSAC considered that it was difficult to define the patient population who would clinically benefit from the intervention. The key issues for defining the patient population are:

- There are no clinical trials comparing the proposed intervention to medical management;
- The patient population who are medically unfit for surgery has not been clearly defined;
- The patient population has been based on level III/IV evidence only;
- There are a lack of clinical data for the patient group;
- There is likely to be leakage of the patient population;
- The number of patients treated with surgery is uncertain and therefore, the number of patients estimated for the proposed intervention is likely to be underestimated; and
- The prevalent population has been excluded from the estimated patient population.

MSAC noted there was limited comparative evidence, in particular long term data, to compare effectiveness between the proposed intervention and medical therapy, with the included observational studies subject to bias.

MSAC questioned the validity of the economic model, which modelled an ICER of \$32,847 per QALY, and considered it to be an underestimate of costs. In particular, MSAC noted that the model relied on data from the EVEREST II trial which did not provide strong comparative data or long term outcomes. Given the average age of patients in the model was 77 years, MSAC considered that the model 40 year time horizon was inappropriate. MSAC accepted advice from ESC that setting the time horizon to 10 years approximately doubled the cost per QALY gained.

MSAC noted that there were several translation issues with economic and financial impact, particularly as the submission did not include factors such as the potential removal of the device, diagnostic tests and aftercare.

MSAC agreed with the MBS item descriptor proposed by the Department. MSAC agreed that the proposed explanatory note should include an echocardiologist.

MSAC suggested that the estimated severe mitral regurgitation incident rate based on 29% of incident heart failure cases was reasonable. However, MSAC was concerned that the number of mitral valve surgery cases was over-estimated (double counting of AIHW/MBS data; many mitral valve surgery cases do not have heart failure). Therefore, the number of patients managed medically is likely to be underestimated. There may also be leakage with the complex definition of high risk/subjective symptoms. MSAC noted that the cost of the “heart” team, for the determination of the high risk surgical cohort, had not been included in the financial analysis.

MSAC was also concerned about the high cost to the MBS, estimated at \$1.3 million in the submission.

MSAC noted that several prospective trials were currently being conducted, particularly for patients with functional MR; therefore further trial data would be available in the future.

MSAC considered that any reapplication should be made via ESC and would require external evaluation.

#### **14. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to safety, effectiveness and cost-effectiveness, MSAC did not support public funding for the reduction of mitral regurgitation 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.

#### **15. Applicant's comments on MSAC's Public Summary Document**

Although there are limitations in the evaluation of individual studies referenced in the submission, the totality of evidence regarding MitraClip therapy has demonstrated its efficacy and consistent improvement across multiple outcomes in patients considered to be too high risk for surgery due to comorbid conditions and other risk factors. These outcomes benefits include reduction of MR, left ventricular reverse remodelling, improvements in NYHA functional class and quality of life, and reductions in heart failure hospitalizations. Patients identified as too high risk for surgery via a qualified heart team assessment represent a group with no other treatment options, and the MitraClip therapy addresses an unmet need.

#### **16. Linkages to other documents**

Further information is available on the MSAC Website at: [www.msac.gov.au](http://www.msac.gov.au).