



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1361 – Transcatheter Aortic Valve Implantation (TAVI) via transfemoral or transapical delivery***

**Applicant:** Edwards LifeSciences Pty Ltd

**Date of MSAC consideration:** MSAC 63<sup>rd</sup> Meeting, 1-2 April 2015

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at [www.msac.gov.au](http://www.msac.gov.au)

#### **1. Purpose of application and links to other applications**

An application requesting new MBS listing of TAVI for use in patients who are symptomatic with severe aortic stenosis and who are determined to be at high risk for surgical aortic valve replacement or non-operable was received from Edwards LifeSciences Pty Ltd by the Department of Health in May 2013.

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

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of transcatheter aortic valve implantation (TAVI) via transfemoral or transapical delivery for patients with symptomatic severe aortic stenosis who are determined to be at high risk for surgical aortic valve replacement (SAVR) or who are inoperable, MSAC deferred the application to allow the applicant to re-present its economic model. The updated economic model would need to address the concerns raised by the critique and ESC, and would also need particular emphasis on the following:

- incorporate the recently published 5-year PARTNER trial data;
- incorporate rehospitalisation appropriately in the estimate of costs in the economic model;
- decrease the initial hospitalisation cost difference (compared with SAVR) in the economic model to reflect the current length of stays for TAVI and SAVR;
- provide stronger justification for assumptions relating to utilities;
- perform multivariate sensitivity analyses as well as univariate sensitivity analyses;
- consider using the most recently updated data from the Medtronic CoreValve trial to also inform the economic evaluation, at least in a sensitivity analysis; and
- the economic model should examine transfemoral delivery only (not transapical) with a separate ICER comparing TAVI to only SAVR or only medical management.

MSAC considered that the updated economic model should be made via ESC, accompanied by a contracted critique of the resubmission.

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

MSAC discussed the proposed new item descriptor to define what it would consider appropriate as part of any subsequent advice for MBS funding. The Committee proposed to define more tightly symptomatic severe aortic stenosis as a mean gradient of  $> 40$  mmHg and an aortic valve area of  $< 0.8$  cm<sup>2</sup>, in order to be consistent with the TGA approval of current TAVI devices, the trial eligibility criteria and current clinical practice guidelines. MSAC also considered whether to restrict eligibility to TAVI via transfemoral delivery due to the weak evidentiary support for the safety and effectiveness of TAVI via transapical delivery or other minimally invasive surgical approaches. However, MSAC concluded that this would be too restrictive and proposed that any item descriptor should specify transfemoral delivery of TAVI unless transfemoral delivery is contraindicated or not available, and that a note should explain the reasons for preferring transfemoral delivery.

MSAC preferred not to specify any particular TAVI device, for example by brand name or by specifying any particular device characteristic, such as a balloon-expandable device (to signal a preference for the applicant's SAPIEN device) or a self-expandable device (to signal a preference for Medtronic's CoreValve device). As noted below, the existing evidence does not justify discriminating against any particular device on clinical grounds, and there was no reason to inhibit price competition across device alternatives. In addition, MSAC considered whether the delivery of TAVI would require a specialised environment and so should only be adopted in centres of excellence, with other settings required to be successful in applying for centre of excellence status before delivering the service. The Committee however, concluded that it would not be necessary for the item descriptor to specify the type of institution in which the TAVI procedure is undertaken due to complexity of the procedure only lending itself to being provided in certain hospitals being available at only those locations.

MSAC thus foreshadowed consideration of the following details being included in the MBS item descriptor:

Transcatheter aortic valve replacement, via transfemoral delivery unless transfemoral delivery is contraindicated or not available, for the treatment of symptomatic severe aortic stenosis in a suitable patient formally assessed by a heart multidisciplinary team to have an unacceptably high risk for surgical aortic valve replacement. (Anaes.) (Assist.)

#### Explanatory notes

Symptomatic severe aortic stenosis as defined as an aortic valve area of less than 0.8 cm<sup>2</sup> and a mean transaortic gradient of greater than 40 mmHg.

In most cases, this item is claimable once per lifetime. In a small subset of patients where a repeat procedure is indicated; formal documentation of reassessment and consensus approval by the heart multidisciplinary team is required.

Transfemoral delivery is preferred for TAVI

A heart multidisciplinary team is required to formally document approval regarding the patient's suitability for treatment. The core personnel of the heart team should include an interventional cardiologist, a cardiothoracic surgeon and a TAVI nurse / case manager. The multidisciplinary extended team could additionally include: a general cardiologist, a cardiac anaesthetist, an imaging cardiologist / radiologist, an intensive care physician, a geriatrician or general physician and a vascular surgeon.

MSAC noted the need for a corresponding separate MBS item for the proposed heart multidisciplinary team assessment, possibly modelled on current MBS items for case conferencing such as MBS item 871 used for oncology case conferencing.

MSAC agreed that patient eligibility for TAVI via transfemoral delivery should be determined by evaluating symptoms such as chest pain, dyspnoea, syncope; using an echocardiogram to demonstrate severe aortic stenosis; assessing whether the patient is deemed high operative risk or inoperable; assessing whether the patient has suitable anatomy (aortic size and route); and assessing whether the patient would die within 12 months of the procedure and, if this is the case, the patient would not be suitable for the procedure.

MSAC accepted that there was an unmet clinical need for TAVI, particularly by patients deemed to be at sufficiently high risk for surgical aortic valve replacement (SAVR) that they are inoperable. However, MSAC noted that the definition of patients who are deemed to be inoperable would need to be made clear. MSAC requested that the inoperable group be more clearly defined by the applicant.

MSAC agreed that there were two main comparators for TAVI:

- as an alternative to SAVR in high operative-risk patients
- as an alternative to medical management with or without balloon valvuloplasty in inoperable patients.

MSAC noted that data on safety and effectiveness of TAVI came mainly from two randomised controlled trials (PARTNER, Medtronic CoreValve). Results from observational registries were also supplied, but these had limitations, including that patients were not necessarily at high risk. MSAC expressed concerns about a bias towards TAVI in the randomised trials arising from potential conflict of interest due to sponsor involvement in the site selection, data management and analysis of the study; greater withdrawal rates in the SAVR group (because consent was withdrawn after being randomised to SAVR); and longer delays to receive SAVR than TAVI. MSAC also noted that, although participants were recruited into the PARTNER Cohort B trial because they were deemed to be inoperable, 150 (84%) of the 179 participants randomised to medical management received balloon valvuloplasty as a surgical intervention. MSAC was also concerned that the trials presented were not sufficiently powered to assess the comparative effectiveness or safety of TAVI via transapical delivery.

MSAC accepted that, compared to medical management, TAVI via transfemoral delivery was less safe after one year with increased stroke, vascular complications, and major bleeding. However, compared to SAVR, MSAC accepted that TAVI via transfemoral delivery had a different safety profile after one year with decreased major bleeding, but increased vascular complications, permanent pacemaker implantations (depending on device type), and paravalvular aortic regurgitation, and a trend to increased stroke. MSAC noted that the recently published 5-year results for the PARTNER trial (Kapadia et al. Lancet, 2015 and Mack et al. Lancet 2015) did not identify any new safety concerns, and suggested that some early safety concerns, such as stroke, did not increase over time. MSAC also accepted that, TAVI via transfemoral delivery had a lower use of associated procedural healthcare resources than SAVR.

MSAC accepted that the data of all-cause mortality after one year from the randomised trials showed TAVI via transfemoral delivery was more effective than medical management (PARTNER Cohort B, N=358) and non-inferior to SAVR (PARTNER Cohort A, N=699 and Medtronic CoreValve, N=795). MSAC also noted that the STACCATO trial (N=70)

comparing TAVI via transapical delivery with SAVR was stopped early due to poor TAVI outcomes.

MSAC noted that the recently published 5-year results for the PARTNER Cohort B trial (Kapadia et al. Lancet, 2015) demonstrated a continuing superior all-cause mortality for TAVI via transfemoral delivery over medical management (at 2 years: 57% alive on TAVI vs 32% alive on medical management; at 5 years: 28% alive on TAVI vs 6% alive on medical management). Similarly, MSAC noted that the recently published 5-year results for the PARTNER Cohort A trial (Mack et al. Lancet, 2015) demonstrated continuing non-inferior all-cause mortality between TAVI via transfemoral delivery and SAVR (at 5 years: 37% alive on TAVI vs 36% alive on SAVR).

MSAC considered that the 5-year results from the PARTNER trial strengthened the clinical case for public funding of TAVI, but noted that there was no update available for the Medtronic CoreValve trial beyond 2 years to confirm whether the suggested superior all-cause mortality for TAVI over SAVR is sustained.

MSAC noted that the two TAVI devices were compared in a meta-analysis of mostly observational studies (Khatri et al. Ann Intern Med, 2013) and a randomised trial (Abdel-Wahab et al. JAMA, 2014), which had an intermediate endpoint as its primary outcome, and which was underpowered (N=238) to assess directly patient-relevant endpoints. The Committee concluded that neither source of evidence provided a confident basis to prefer one TAVI device over the other in terms of effectiveness or safety.

MSAC noted that the economic modelling was a cost utility analysis with a 10-year time horizon extrapolated from data from the PARTNER trial observed between the first 30 days and up to one year. The results suggested that TAVI would be dominant, that is both cheaper and more effective, when compared to SAVR; and would have an ICER/QALY of \$42,000 - \$61,000 when compared to medical management. According to the univariate sensitivity analyses, the key drivers for the model were the extent of survival gains in inoperable and high risk populations, and the avoidance of hospital-associated costs including extended stay, cannulation, perfusion and cardioplegia when compared with SAVR. It was unclear whether decreased hospitalisations compared to medical management were incorporated into the economic evaluation.

However MSAC noted that, overall, most of the assumptions in the economic model as presented were biased in favour of TAVI, for the following reasons:

- without directly supporting evidence at the time of submission, incremental benefit was assumed to continue at the same rate beyond one year (based on the reported 5-year outcomes, this was biased in favour of TAVI when compared with SAVR, but was biased against TAVI when compared to medical management)
- hospital unit costs were different across model arms resulting in overestimated hospital cost offsets, especially in the comparison with SAVR
- utility gains for TAVI across arms appeared overestimated, for example the health state defined as “no complications” attracted no decrement from the population normal utility despite the diagnosis of symptomatic severe aortic stenosis; and “other complications” attracted a hypertension disutility only, despite also including such complications as myocardial infarction and endocarditis
- other cost off-sets for TAVI across arms appeared overestimated, for example “other complications” only attracted a cost of “standard surveillance” and major bleeds transit to “heart failure” only
- transitions from one health state to another were inconsistent across model arms, for

example “vascular complications” transits to “other complications” for TAVI or SAVR, or to “HF follow-up” (which is associated with greater costs and disutilities) for medical management; and “no complications” transits to “no complication” for TAVI or SAVR, or to “standard therapy follow-up” (which includes daily clopidogrel, annual specialist visit, annual echocardiogram transthoracic echocardiography) for medical management

- assumptions built in to the economic model were not supported, for example all subsequent aortic valve replacements were assumed to occur in the first 30 days
- all major bleeds in the medical management group were treated with SAVR
- aortic regurgitation consequences were not incorporated in the model, however mortality was already included in the model (and the 5-year data were reassuring)
- pacemakers were not included in the model
- the inclusion of costs for the heart multidisciplinary team across all arms was inappropriate (ie. this would not currently be standard care for a patient being treated medically or with SAVR)
- the rationale for the proportions receiving subsequent TAVI/SAVR was unclear.

Although univariate sensitivity analyses suggested that, taken one by one, these concerns might not have large consequences for the ICER, no multivariate sensitivity analysis was provided to examine their cumulative effect despite the general consistency of the bias across these concerns.

Other concerns with the model included:

- the exclusion of the larger Medtronic CoreValve study
- the inclusion of results for transapical delivery, despite insufficient evidence for effectiveness.

MSAC was concerned with the cost of the TAVI device at \$33,348 compared to the cost of SAVR at \$5,925, and that the best value solution from competition in the market might not have been achieved yet.

MSAC was uncertain about the estimated cost effectiveness of TAVI. The Committee considered that inclusion of the recently published 5-year data would improve confidence in the results of the model. These trial results suggest that incremental overall survival might have been underestimated by the model for this 5-year period in the comparison with medical management, but overestimated in the comparison with SAVR. Overall, MSAC agreed that the overall consequences of improving these overall survival estimates and correcting the other biases favouring TAVI in the model were not clear.

In relation to recalculating the economic modelling in response to the deferral, MSAC requested that the estimate of costs and outcomes be limited to five years, and reflect the recently published 5-year PARTNER trial data as closely as possible, particularly for health outcomes, whilst appropriately reflecting Australian unit costs and systems of providing health care resources. A sensitivity analysis extrapolating the economic model out to 10 years would also be informative.

MSAC noted that the net annual financial implications to government health budgets and private health insurance of funding TAVI were estimated to be between \$33 million and \$38 million. However, MSAC was unsure about the associated volume of uptake with a range of 700-800 patients receiving TAVI per year. From a prevalence perspective, some 4,200 patients are currently being medically managed, so estimating that the uptake of TAVI would be limited to 593 could only be considered reasonable by noting the current limited capacity of the specialist cardiac centres to perform the procedure. The financial analyses may also

need to be updated in a resubmission to retain alignment with related changes to the economic model.

In deciding to defer the application, MSAC noted that, due to imprecision in distinguishing between the two requested groups of patients, it would not be appropriate to support funding one group and not the other. In addition, patients currently have access to TAVI, so deferral of the application would not have any significant consequences for patient management.

#### 4. Background

The proposed medical service was currently not funded under the MBS and had not been previously considered by MSAC. However, legal access to TAVI has been provided to patients under the following avenues:

- special access scheme and authorised prescribers; and
- participation in clinical trials and clinical registries.

#### 5. Prerequisites to implementation of any funding advice

Several devices are listed on the Australian Register of Therapeutic Goods for use in patients with symptomatic aortic stenosis (aortic valve area  $<0.8\text{cm}^2$ ) requiring aortic valve replacement who have high risk for operative mortality, or are "non-operable", as determined by an objectively predicted operative mortality of at least 10% according to STS or an equivalent validated scoring system. Decision for use should be reviewed by three independent medical specialists, including one cardiologist and one cardiothoracic surgeon.

The ARTG listing for some devices also states that implantation is intended to be performed via transfemoral access without cardiopulmonary bypass.

#### 6. Proposal for public funding

It was proposed that TAVI be used in patients with symptomatic aortic stenosis (aortic valve area  $< 1.0\text{ cm}^2$ ) and who have been assessed by specialist medical team to have high risk for operative mortality, or are 'non-operable'.

##### Proposed MBS item descriptors

Category 3 – Therapeutic Procedures
<p>MBS XX</p> <p>Transcatheter aortic valve replacement for the treatment of symptomatic severe aortic stenosis in a suitable patient formally assessed by a heart MDT to have an unacceptably high risk for surgical aortic valve replacement. (Anaes.) (Assist.) (i) Percutaneous approach</p> <p>Explanatory notes</p> <p>A multidisciplinary 'heart team' is required to formally document approval regarding the patient's suitability for treatment. The core personnel of the heart team should include an interventional cardiologist, a cardiothoracic surgeon and a TAVI nurse / case manager. The multi-disciplinary extended team could additionally include: a general cardiologist, a cardiac anaesthetist, an imaging cardiologist / radiologist, an intensive care physician, a geriatrician or general physician and a vascular surgeon.</p> <p>In most cases, this item is claimable once per lifetime. In a small subset of patients where a repeat procedure is indicated; formal documentation of reassessment and consensus approval by the heart team is required.</p>
Fee: \$1,909.60

## MBS XX

Transcatheter aortic valve replacement for the treatment of symptomatic severe aortic stenosis in a suitable patient formally assessed by a heart MDT to have an unacceptably high risk for surgical aortic valve replacement.  
(Anaes.) (Assist.)

(i) Minimally invasive surgical approach

## Explanatory notes

A multidisciplinary 'heart team' is required to formally document approval regarding the patient's suitability for treatment. The core personnel of the heart team should include an interventional cardiologist, a cardiothoracic surgeon and a TAVI nurse / case manager. The multi-disciplinary extended team could additionally include: a general cardiologist, a cardiac anaesthetist, an imaging cardiologist / radiologist, an intensive care physician, a geriatrician or general physician and a vascular surgeon.

In most cases, this item is claimable once per lifetime. In a small subset of patients where a repeat procedure is indicated; formal documentation of reassessment and consensus approval by the heart team is required.

Fee: \$1,909.60

Source: Table 7, p30 of the submission-based assessment, MDT=multidisciplinary team

It was noted that the cut-point for the aortic valve area in the proposed descriptor differs from the approved TGA use and the inclusion criterion for TAVI clinical trials, but that the nominated cut-point reflects that change in international guidelines for management of aortic stenosis.

TAVI should be undertaken with a multidisciplinary 'heart team', including an:

- interventional cardiologist;
- cardiothoracic surgeon; and
- TAVI nurse case manager/co-ordinator.

The multidisciplinary team may also include: a general cardiologist, a cardiac anaesthetist, an imaging cardiologist/radiologist, an intensive care physician, a geriatrician or general physician and a vascular surgeon.

### **Requirements for the interventional cardiologist**

The interventional cardiologist should be trained in accordance with the Cardiac Society of Australia and New Zealand (CSANZ) guidelines. The current generation of devices requires two operators (primary and secondary) and the recommendations should apply to both. A background in structural intervention is considered an important prerequisite for competency in TAVI.

### **Requirements for the cardiac surgeon**

The TAVI surgeon should be experienced in surgical aortic valve replacement (SAVR) with experience in operating on high-risk SAVR patients. The surgeon should have experience in obtaining access via transapical and less invasive routes such as hemi-sternotomy.

The applicant advised that it provides a comprehensive and hands-on training program. The whole team including: cardiac surgeons, interventional cardiologists, anaesthetists, echocardiographers, nurses and technicians are trained together.

Upon completion of this educational program, each participant is certified to perform TAVI (transfemoral and minimally invasive surgery) procedures successfully.

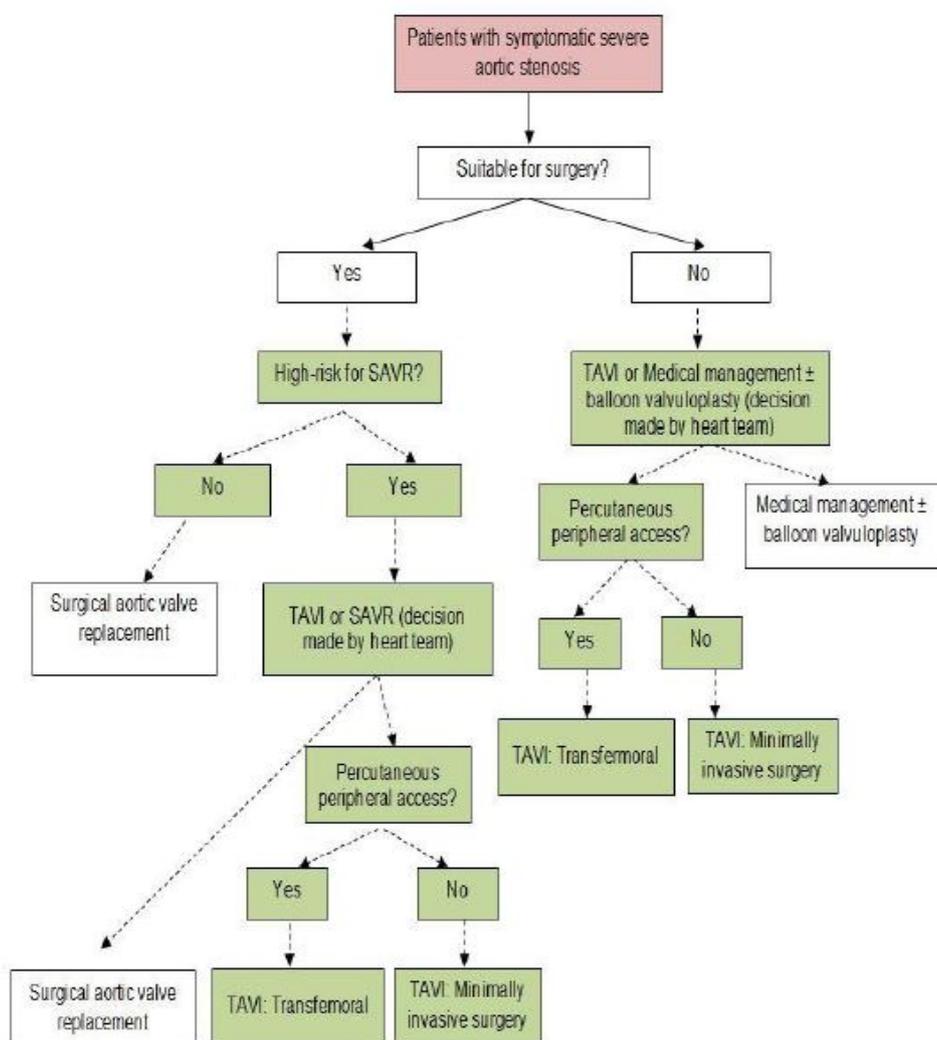
## 7. Summary of Public Consultation Feedback/Consumer Issues

No specific consumer impact statement was provided in the assessment. However ESC noted concerns of limited access to patients in rural and remote areas, the out of pocket costs currently incurred by patients paying for the service privately.

## 8. Proposed intervention's place in clinical management

The clinical management algorithm for the intended use of TAVI is presented below. The clinical management algorithm is based on the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (ECS-EACTS) 2012 guidelines for the management of severe aortic stenosis and concurs with the management algorithm of the main comparator.

Proposed clinical management pathway for patients with symptomatic severe aortic stenosis



Patients with symptomatic severe aortic stenosis would continue to require to be assessed as suitable or not suitable for SAVR. Once a patient with symptomatic severe aortic stenosis is assessed as suitable for SAVR, the proposed clinical management pathway requires that they then need further assessment to determine their surgical risks. Patients not considered high risk would continue along the treatment pathway to SAVR. Patient assessed as 'high risk' would, after assessment by and discussion with their clinician, be offered either TAVI or SAVR.

Patients offered TAVI would require further assessment to indicate whether percutaneous access can be achieved through the femoral artery. If femoral artery access is not available, patients would require minimally invasive surgery for the TAVI procedure.

A patient with symptomatic severe aortic stenosis assessed as not suitable for SAVR would, under the proposed clinical management pathway, have further assessment to determine if they are suitable for TAVI or continue with medical management. For patients considered suitable for TAVI, further assessment would then be required to determine whether percutaneous access could be achieved through the femoral artery. If femoral artery access is not available, patients under the proposed clinical management pathway would require minimally invasive surgery for the TAVI procedure.

The critique noted that evidence in support of TAVI via minimally invasive surgery for inoperable patients was not provided in the submission-based assessment (SBA) of the application.

Severe aortic stenosis (AS) remains the most common indication for aortic valve replacement (AVR) with rheumatic heart disease and degenerative calcification the main causes of AS. Degenerative calcific AS is most common and typically occurs in individuals > 65 years of age. Typically, patients with AS are free from cardiovascular symptoms (e.g. angina, syncope and/or heart failure) until late in the course of the disease. The severity and progression of AS are best described as a continuum; however, once symptoms manifest, the prognosis is poor with the presence of congestive heart failure indicative of low survival. Survival analyses have demonstrated that the interval from the onset of symptoms to the time of death is approximately two years in patients with heart failure, three years in those with syncope, and five years in those with angina. Current treatments for severe AS include medical management or an aortic valve replacement.

The development of percutaneous bioprosthetic heart valves has provided a new surgical option for patients with severe aortic stenosis if the risk of open-heart surgery is prohibitively high or contraindicated. Two main percutaneous valves have become available—the Edwards SAPIEN valve (TGA-approved) and the Medtronic CoreValve ReValving System (not currently TGA-approved). The technical specifications for each valve and the main differences between them are summarised in the table below.

**Technical specification of the available percutaneous aortic valve prostheses**

	<b>Edwards SAPIEN Transcatheter Heart Valve</b>	<b>CoreValve ReValving System</b>
Valve specification	Balloon-expandable, tubular, slotted, stainless steel stent with an attached bovine pericardial trileaflet valve and fabric sealing cuff	Self-expandable 50 mm nitinol (nickel titanium alloy) frame sewn to three porcine pericardial leaflets; prosthesis has three separate structural elements (inlet, middle and outlet)
Delivery method	Valve is mechanically crimped onto a balloon catheter immediately before implantation	Preloaded valves; crimping to balloon is not required as it is a self-expanding valve
Rapid ventricular pacing requirement	To stabilise the prosthesis during balloon expansion, rapid pacing (220 beat/min) is needed for deployment	Not necessary for device deployment
Delivery sheath size	Most available data are for 22F (7.3 mm) and 24F (8 mm) devices;	Most available data are for the third-generation CoreValve, which is 18F (6 mm)
Methods of deployment	Antegrade, retrograde and transapical	Retrograde (transfemoral and subclavian); animal feasibility study for transapical delivery recently published
Potential advantages	Prosthesis can be re-expanded if under-deployed initially	More controlled deployment because stent is self-expanding; device can be retrieved with partial deployment

Source: Layland JJ et al, 2010

TAVI can be delivered via two different approaches: the percutaneous peripheral access approach (i.e. transfemoral delivery) or the minimally invasive surgical approach (transapical, transaortic or sub-clavian delivery). TAVI is usually performed under general anaesthesia; however, sedation and analgesia may suffice for transfemoral delivery.

The transfemoral procedure is performed by the retrograde femoral approach with fluoroscopic and transoesophageal echocardiographic guidance and without cardiopulmonary bypass.

Where peripheral access is not available, transapical, transaortic or sub-clavian delivery can provide an alternative method. For the transapical procedure, access to the aortic valve is achieved surgically via an anterolateral mini-thoracotomy placed in the fifth or possibly sixth intercostal space, followed by apical puncture of the left ventricle. The transaortic and sub-clavian procedures are alternative surgical approaches if the patient's anatomy prevents a transapical approach. The transaortic procedure involves either a transverse sub-clavian incision through an intercostal muscle or a mini-sternotomy where 2-3 cm of the sternum is removed. Access to the aortic valve is navigated through this incision to the aorta, which is punctured allowing direct access to implant the valve.

The proposed intervention is likely to substitute SAVR in patients not contraindicated for SAVR but who have a high risk of complications or death from SAVR. These patients can undergo SAVR or TAVI based on the assessment by the multidisciplinary team.

The proposed intervention would also be used in patients who are contraindicated for SAVR. Patients contraindicated for SAVR would usually, in the absence of TAVI have medical management. Some patients receiving medical management may undergo a minimally invasive balloon valvuloplasty.

The development of percutaneous bioprosthetic heart valves has provided a new surgical option for patients with severe aortic stenosis if the risk of open-heart surgery is prohibitively high.

The most common approach to percutaneous aortic valve replacement is the retrograde approach (transfemoral), because it is a simpler technique and has procedural similarity to coronary angiography. The transapical approach is an alternative minimally invasive surgical approach and is far more invasive, requiring direct puncture of the left ventricle. Edwards SAPIEN aortic valve can be inserted by either the transfemoral or transapical approach.

It was proposed that TAVI be used in patients with symptomatic aortic stenosis (aortic valve area  $< 1.0 \text{ cm}^2$ ) and who have been assessed by a specialist medical team to have high risk for operative mortality, or are 'non-operable'.

## **9. Comparator**

Consistent with the final Protocol, the SBA nominated two comparators:

- 1) SAVR in patients not contraindicated for SAVR, but assessed as at 'high risk' for complications or death; and
- 2) medical management (with or without balloon valvuloplasty) in patients who are assessed as 'inoperable' for surgical aortic valve replacement.

The arguments provided in support were that:

- SAVR is the current treatment for 'high risk' patients with symptomatic aortic stenosis;

and

- medical management (with or without balloon valvuloplasty) is the only treatment available for patients with symptomatic aortic stenosis who are considered too high risk to undergo SAVR.

SAVR is listed on the MBS.

**Current MBS item descriptors for surgical aortic valve replacement (SAVR)**

Category 3 – Therapeutic Procedures	
MBS: 38488	
VALVE REPLACEMENT with BIOPROSTHESIS OR MECHANICAL PROSTHESIS	
Multiple Services Rule (Anaes.) (Assist.) Fee: \$1,909.60	
Explanatory note: T8.68 Cardiac and Thoracic surgical items (Items 38470 to 38766) Items 38470 to 38766 must be performed using open exposure or minimally invasive surgery which excludes percutaneous and transcatheter techniques unless otherwise stated in the item.	
MBS: 38489	
VALVE REPLACEMENT with allograft (subcoronary or cylindrical implant), or unstented xenograft	
Multiple Services Rule (Anaes.) (Assist.) Fee: \$2,271.05	
Explanatory note: T8.68 Cardiac and Thoracic surgical items (Items 38470 to 38766) Items 38470 to 38766 must be performed using open exposure or minimally invasive surgery which excludes percutaneous and transcatheter techniques unless otherwise stated in the item.	

**Medical management (with or without balloon valvuloplasty)**

The SBA did not specify a treatment regimen for patients with symptomatic severe aortic stenosis who are treated by medical management (with or without balloon valvuloplasty). The SBA stated that ACE inhibitors, antiarrhythmic medication, beta-blockers, calcium channel blockers, diuretic and vasodilator are being used in medical management. Some patients receiving medical management may undergo a minimally invasive balloon valvuloplasty for symptomatic relief.

**Current MBS item descriptor for balloon valvuloplasty**

Category 3 – Therapeutic Procedures	
MBS 38270	
BALLOON VALVULOPLASTY OR ISOLATED ATRIAL SEPTOSTOMY, including cardiac catheterisations before and after balloon dilatation	
Multiple Services Rule (Anaes.) (Assist.) Fee: \$912.30 Benefit: 75% = \$684.25 85% = \$833.90	

Correspondence from three other TAVI suppliers and evidence provided in the SBA did not draw any clear conclusions regarding the comparative efficacy of other valves.

**10. Comparative safety**

The evidential basis of the SBA consisted of results from:

- the superiority trial of TAVI (Edwards SAPIEN valve) versus medical management in inoperable patients (Cohort B of the PARTNER trial, Leon, 2010); and
- the non-inferiority trial of TAVI (Edwards SAPIEN valve) versus SAVR in patients considered at high surgical risk (Cohort A of the PARTNER trial, Smith, 2011) and the non-inferiority trial of TAVI (Medtronic CoreValve system) versus SAVR in high surgical risk patients (Adams, 2014).

For the assessment of long-term safety, the SBA relied on observational non-randomised studies from registry data records. The majority of studies were identified in a recent review by Pera et al (2014) and Cao et al (2013).

The table below shows the results of the safety outcomes observed at 1 year in the pivotal trials.

#### Safety outcomes at one year in the PARTNER trial and Medtronic CoreValve trial

Safety outcomes at 1 year Cohort B	ITT population n (%*) Cohort A			ITT population n (%*) Medtronic CoreValve trial						As-treated population n (%*)		
	TF-TAVI n=179	MM n=179	P*** value	TF-TAVI n=244	TF-SAVR n=248	P*** value	TA-TAVI n=104	TA-SAVR n=103	P** value	TAVI ** n=390	SAVR n=357	P*** value
Stroke or TIA	19 (11.2)	8 (5.5)	0.06	15 (6.4)	6 (2.8)	0.07	12 (13.0)	7 (8.0)	0.28	39 (10.4)	47 (14.2)	0.10
MI	1 (0.8)	1 (0.7)	1.00	1 (0.5)	1 (0.4)	0.91	0 (0.0)	1 (1.0)	0.31	7 (1.9)	5 (1.5)	0.7
Vascular complications	58 (32.4)	13 (7.3)	<0.001	57 (23.5)	9 (3.8)	<0.001	5 (5.1)	7 (7.3)	0.52	24 (6.2)	7 (2.0)	0.004
Acute kidney injury Creatinine >3mg/dl	2 (1.1)	5 (2.8)	0.45	12 (5.4)	6 (2.8)	0.17	0 (0.0)	2 (2.4)	0.16	23 (6.0)	54 (15.1)	<0.001
Major bleeding	42 (24.2)	21 (14.9)	0.04	38 (16.2)	58 (24.5)	0.02	11 (11.0)	27 (28.5)	0.006	114 (29.5)	130 (36.7)	0.03

Source: Leon, 2010; Makkar, 2012; Smith, 2011; Adams, 2014.

TIA = transient ischaemic attack; MI = myocardial infarction; MM = medical management +/- balloon valvuloplasty

\*All percentages are Kaplan-Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number in the study group.

\*\* includes combined results for TF-TAVI and TAVI using subclavian delivery

\*\*\* P-values are for between-group comparisons of the frequency of the event at each time point (log-rank test)

In inoperable patients (Cohort B of the PARTNER trial), the rate of stroke (K-M estimates) was higher in the TAVI group than in the medical management group both at 1 year (11.2% vs. 5.5%,  $P = 0.06$ ) and at 2 years (13.8 vs. 5.5%,  $P = 0.01$ ) (Makkar, 2012) (data not in table). TAVI was also associated with the higher rate of vascular complications at one year, 32.4% vs 7.3% in the medical management group ( $P < 0.001$ ); and with the higher rate of major bleeding (24.3% and 14.9% in TAVI and medical management arms respectively, K-M estimates,  $P = 0.04$ ). MSAC noted that the recently published 5-year results for the PARTNER Cohort B trial (Kapadia et al. Lancet, 2015) confirmed that the risk of stroke following TAVI did not increase over time.

In high surgical risk patients (Cohort A of the PARTNER trial), rates of major stroke were 3.8% in the combined TF-and TA-TAVI group and 2.1% in the SAVR at 30 days ( $P = 0.20$ ) and 5.1% and 2.4%, respectively, at one year ( $P = 0.07$ ). Rates of all neurologic events were higher in the TAVI group than in the surgical group at 30 days (5.5% vs. 2.4%,  $P = 0.04$ ) and at one year (8.3% vs. 4.3%,  $P = 0.04$ ). This was also true when the rates of all neurologic events observed in the TF-TAVI group were compared with the rates in TF-SAVR

comparator group (6.4% vs. 2.8%,  $P = 0.07$ ). TF-TAVI was also associated with a higher rate of vascular complications at one year than in the TF-SAVR group (23.5% vs 3.8%,  $P < 0.001$ ). Major vascular complications and major bleeding events were frequent procedure-related complications in the TAVR and surgery groups, respectively, but after 1 year, these events were uncommon and did not differ significantly between the groups. MSAC noted that the recently published 5-year results for the PARTNER Cohort A trial (Mack et al. Lancet, 2015) suggested that any signal of an increased risk of stroke diminished over time.

## 11. Comparative effectiveness

The primary effectiveness and safety endpoint for the PARTNER trial (Cohort A and Cohort B) was all-cause mortality at 12 months, in the ITT population. Cohort A included patients considered to be at high surgical risk. Depending on whether the percutaneous access can be achieved through the femoral artery (peripheral access), patients had either TAVI via a transfemoral access (TF-TAVI) or a transapical TAVI (TA-TAVI), the only type of minimally invasive surgery practiced in the PARTNER trial. Cohort B included patients considered to be inoperable. All patients from Cohort B had peripheral access and underwent TF-TAVI. Another pivotal trial presented in the SBA was the US Medtronic CoreValve trial in high surgical risk patients. Patients who had peripheral access underwent TF-TAVI, otherwise subclavian delivery was used. Results of this trial were not reported by the type of delivery. The results are presented in the tables below.

Rate of death from any cause in inoperable patients (TF-TAVI), ITT population

PARTNER (Cohort B)	TF-TAVI, N=179 n (%)	MM (+/- BAV), N=179 n (%)	P-value
Death at 30 days	9 (5.0)	5 (2.8)	0.41
Death at 12 months	55 (30.7)	89 (49.7**)	<0.001
Death at 24 months*	77 (43.3)	117 (68.0)	<0.005***

Source: Leon (2010); Makkar (2012). BAV = balloon valvuloplasty; MM = medical management; TF= transfemoral access

\*cross-over to TAVI after 12 months was allowed

\*\*different from the Kaplan–Meier analysis estimate of 50.7%, presented elsewhere

\*\*\*P-value is for between-group comparison of the frequency of the event (point-in-time analysis)

Rate of death from any cause in high surgical risk patients, ITT population

PARTNER (Cohort A)	TF-TAVI, N=244 n (%**)	TF/TA-SAVR*, N=248 n (%**)	P-value***
Death at 30 days	8 (3.3)	15 (6.2)	0.13
Death at 12 month	54 (22.2)	62 (26.4)	0.29
Death at 24 months	74 (30.9)	80 (34.6)	0.38

Source: Smith (2011); Kodali (2012). TA = transapical access; TF= transfemoral access

\*The TF and TA control groups in the SAVR arm of the trial include the patients who at the pre-randomisation stage were categorised as eligible for TF or TA procedures respectively

\*\*All percentages are Kaplan-Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number in the study group

\*\*\*P-values are for between-group comparisons of the frequency of the event at each time point (log-rank test)

Rate of death from any cause TAVI in high surgical risk patients, ITT population

Medtronic CoreValve trial	TAVI, N=390 n (%**)	SAVR, N=357 n (%**)	P-value***
Death at 30 days*	13 (3.3)	16 (4.5)	0.43
Death at 12 months (ITT)	NR (13.9)	NR (18.7)	< 0.001 for non-inferiority; 0.04 for superiority

Source: Adams (2014). NR = not reported

\*as-treated population

\*\*All percentages are Kaplan-Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number in the study group.

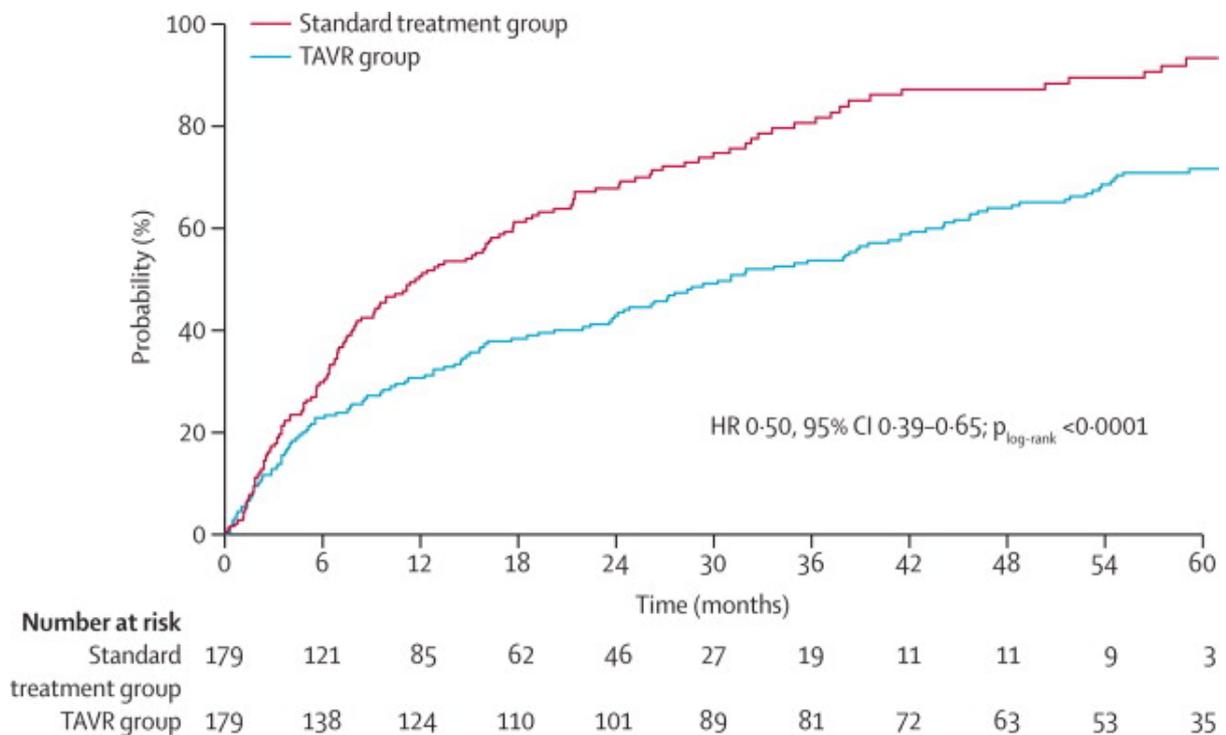
\*\*\*P-values are for between-group comparisons of the frequency of the event at each time point (log-rank test).

The critique stated that, in the “inoperable” population, TAVI using transfemoral delivery was associated with significant improvement in patient survival at one and two years, and an increased risk of neurological events, major vascular complications and major bleeding when compared with patients receiving medical management.

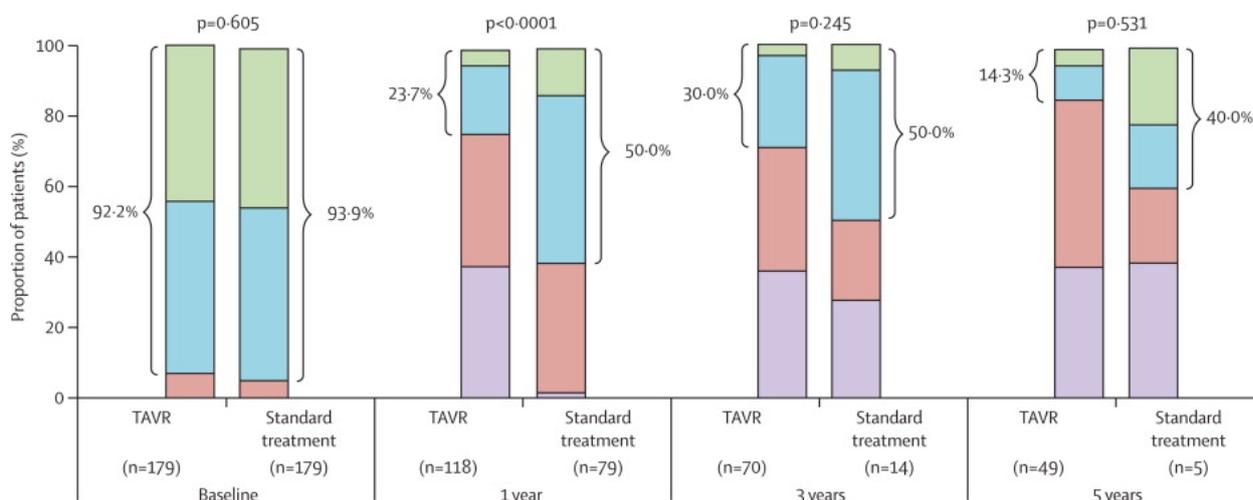
In the “high surgical risk” population, TAVI using transfemoral delivery was associated with the similar patient survival at one and two years, and an increased risk of neurological events and major vascular complications when compared with patients receiving SAVR. Conversely, the incidence of major bleeding was less frequent in TAVI group than in SAVR group.

The critique considered that there was insufficient evidence to estimate clinical effectiveness and safety outcomes for the high surgical risk/inoperable patients not suitable for transfemoral delivery in TAVI.

MSAC noted that the recently published 5-year results for the PARTNER Cohort B trial (Kapadia et al. Lancet, 2015) demonstrated continuing superior all-cause mortality for TAVI over medical management (at 2 years: 57% alive on TAVI vs 32% alive on medical management; at 5 years: 28% alive on TAVI vs 6% alive on medical management):



MSAC also noted that these recently published results also provided some evidence suggesting more favourable NYHA functional class in surviving trial participants:



Similarly, MSAC noted that the recently published 5-year results for the PARTNER Cohort A trial (Mack et al. Lancet, 2015) demonstrated a continuing non-inferior all-cause mortality between TAVI via transfemoral delivery and SAVR (at 5 years: 37% alive on TAVI vs 36% alive on SAVR; hazard ratio 1.01; 95% CI: 0.86-1.24, log rank P = 0.76).

## 12. Economic evaluation

A modelled economic evaluation, in the form of a cost-utility analysis, was presented with the time horizon of 10 years. Two separate models were presented to estimate costs and health outcomes associated with TAVI in two populations (i) inoperable patients and (ii) 'high surgical risk' patients with severe aortic stenosis. Each modelled analysis was conducted twice; firstly for TAVI using transfemoral delivery (TF-TAVI) and secondly for TAVI using transapical delivery (TA-TAVI). MSAC noted that the clinical evidence-base was derived primarily from the PARTNER trial, rather than the Medtronic CoreValve trial.

The results of the economic evaluation are presented in the table below.

### Results of the economic evaluation

High-risk patients	SAVR	TAVI-TF	Incremental	SAVR	TAVI-TA	Incremental
Cost	\$128,557	\$101,453	(\$27,104)	\$129,226	\$115,802	(\$13,425)
QALYs	2.02	2.19	0.16	1.93	2.19	0.27
ICER			TAVI is dominant (\$164,540)			TAVI is dominant (\$50,545)
Inoperable patients	MM+/-BAV	TAVI-TF	Incremental	MM+/-BAV	TAVI-TA	Incremental
Cost	\$77,276	\$105,130	\$27,853	\$63,216	\$119,502	\$56,286
QALYs	1.01	1.67	0.66	0.75	1.68	0.93
ICER			\$42,179			\$60,584

Source: Table 63, p127 of the submission-based assessment

BAV = balloon valvuloplasty; ICER = incremental cost effectiveness ratio; MM = medical management; QALY = quality-adjusted life year; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; TA = transapical; TF = transfemoral

The SBA claimed that, for high-risk patients, both transfemoral and transapical TAVI are dominant strategies compared to SAVR, that is, improved health outcomes and saved costs. For inoperable patients, both transfemoral and TAVI-TA procedures were claimed to be cost

effective, that is, transfemoral TAVI had an ICER of \$42,179 and transapical TAVI had an ICER of \$60,584.

The SBA presented the final ICER for each procedural approach as the weighted average across the population cohorts (high-risk and inoperable), see table below. The proportional split between high risk and inoperable patients was expected to be 20:80 (i.e. 20% high risk and 80% inoperable).

**Weighted average ICER for TAVI by procedural approach**

	High Risk (20%)			Inoperable (80%)			Weighted average		
TF	SAVR	TAVI	Δ	MM	TAVI	Δ	SAVR / MM	TAVI	Δ
Cost	\$128,475	\$101,453	(\$27,104)	\$77,276	\$105,130	\$27,853	\$87,532	\$104,394	\$16,862
QALY	2.02	2.19	0.16	1.01	1.67	0.66	1.21	1.77	0.56
ICER	TAVI is dominant			\$42,179			\$30,047		
TA	SAVR	TAVI	Δ	MM	TAVI	Δ	SAVR / MM	TAVI	Δ
Cost	\$129,226	\$115,802	(\$13,425)	\$63,163	\$119,502	\$56,286	\$76,418	\$118,762	\$42,344
QALY	1.93	2.19	0.27	0.75	1.68	0.93	0.98	1.78	0.80
ICER			TAVI is dominant			\$61,367			\$53,169

MM = medical management; QALY = quality-adjusted life year; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; TA = transapical; TF = transfemoral; Δ = incremental difference

The SBA claimed that the ICER/QALY for transfemoral TAVI procedures was \$30,047 and \$53,169 for transapical TAVI procedures (representing all minimally invasive surgical approaches).

**13. Financial/budgetary impacts**

In 2014, the unit cost of a TAVI device was \$33,348 compared to the cost of a valve implant used in SAVR of \$5,925.

The TAVI procedure was estimated to cost \$4,277 per patient, including co-payments (\$3,208 excluding co-payments). The comparator, SAVR, was estimated to cost \$5,092

including co-payments and \$3,819 excluding co-payments. The comparator of medical management with balloon valvuloplasty was estimated to cost \$2,143 including co-payments and \$1,607 without co-payments. Medication was estimated to cost \$76.85 per month.

It was estimated that 720 patients in 2015 would receive TAVI. This included patients who are 'high risk' but would have TAVI instead of SAVR and patients who are currently medically managed who would be offered and accepted to have TAVI.

The tables below present net financial implications to the MBS and across all government health and private health insurance budgets, respectively.

#### Net financial implications to the MBS

Variable	2015	2016	2017	2018	2019
Total cost of TAVI to the MBS	\$2,309,681	\$2,386,670	\$2,463,660	\$2,543,857	\$2,624,054
Total cost offsets to the MBS from substitution of SAVR / BAV	\$1,030,207	\$1,064,524	\$1,101,052	\$1,134,791	\$1,169,623
Net cost of TAVI to the MBS	\$1,048,506	\$1,084,763	\$1,118,808	\$1,155,642	\$1,194,592

#### Total financial implications to other government and private health insurance budgets

Variable	2015	2016	2017	2018	2019
Net cost of TAVI prosthesis	\$23,258,085	\$24,034,737	\$24,805,464	\$25,615,464	\$26,425,464
Net cost of TAVI hospital costs	\$9,336,572	\$9,693,418	\$9,950,848	\$10,308,594	\$10,651,027
Net cost (saving) to PBS	(\$290,689)	(\$300,493)	(\$309,807)	(\$320,101)	(\$330,395)
Net cost for other budgets	\$32,303,968	\$33,427,662	\$34,446,505	\$35,603,957	\$36,746,096
Net cost of TAVI to the MBS	\$1,048,506	\$1,084,763	\$1,118,808	\$1,155,642	\$1,194,592
Net costs to all budgets	\$33,352,474	\$34,512,425	\$35,565,313	\$36,759,599	\$37,940,688

The main area of uncertainty was the number of patients in Australia with severe symptomatic AS who may be being medically treated (+/- balloon valvuloplasty) for this condition. Using prevalence estimates from a meta-analysis indicated that the likely number of patients who are being medically managed and eligible for TAVI may be 4,117 in 2015; a number 7 times greater than the 593 patients estimated by the SBA. This number was calculated for patients > 75 years of age and with severe AS. If the criteria were to be relaxed to > 65 years of age and with less severe AS, then the potential unmet demand for TAVI would be greater again. However, MSAC agreed with the applicant that uptake may be most limited by the capacity of the specialist cardiac centres to perform the procedure.

#### 14. Key issues from ESC for MSAC

ESC noted that the SBA described a population that, in terms of a measure of severity of aortic stenosis (AS), differed from the population for whom TGA listing was requested (aortic valve area < 0.8 cm<sup>2</sup>) and from the population in the pivotal trials (aortic valve area < 0.8 cm<sup>2</sup>) by describing a population with aortic valve area < 1.0 cm<sup>2</sup>. ESC advised that the relevant clinical practice guidelines have changed over the last decade to now limit symptomatic severe AS to a mean transaortic gradient of > 40 mmHg and an aortic valve area of < 0.8 cm<sup>2</sup> (for example, see the 2014 valvular heart disease practice guidelines from the American College of Cardiology and the American Heart Association<sup>1</sup>). The SBA's intended population, by this measure, would include patients with less severe disease.

<sup>1</sup>page 44, <http://circ.ahajournals.org/content/early/2014/02/27/CIR.0000000000000031.full.pdf>

The proposed MBS item descriptor was less specific in characterising the target population with symptomatic severe aortic stenosis than the proposed indication. ESC agreed that this potentially allowed for less severe patients to be eligible for TAVI. ESC was concerned about this, as the harm/benefit trade-off has not been established in a lower risk population.

ESC advised that there should be a non-brand-specific generic approach to the assessment and also to the item descriptor.

ESC agreed that the assessment of patients by a ‘heart’ multidisciplinary team be included in the descriptor as a prerequisite for TAVI. This would allow for the use of clinical judgment rather than a formal risk score.

ESC considered that a restriction of eligibility for patients judged by this team to have less than 12 months to live is appropriate because it would remove patients who are not suitable for TAVI, such as patients in a palliative state.

ESC advised that TAVI should be performed in institutions where immediate surgery for adverse events is available, and that MSAC should consider whether this should be specified in the item descriptor.

ESC could not estimate clinical safety outcomes for the high surgical risk/inoperable patients not suitable for transfemoral delivery of TAVI. This was due to a lack of evidence available.

However, ESC was concerned about safety of transapical delivery of TAVI and suggested that the MBS item descriptor could be re-worded to explicitly state that the minimally invasive approach is only to be done on ‘high surgical risk’ patients where transfemoral delivery is not possible.

ESC noted that use of the device might lead to problems with high risk patients requiring pacemaker insertion.

As with clinical safety, there was insufficient evidence for ESC to estimate clinical effectiveness outcomes for the high surgical risk/inoperable patients not suitable for transfemoral delivery TAVI.

ESC was concerned that the methods used to extrapolate the observed outcomes beyond the clinical trials might not be appropriate. For example, no justification was provided to use constant rather than time-dependent transition probabilities. This was particularly important for the economic evaluation of SAVR vs. TAVI as it could lead to the results potentially favouring TAVI.

ESC considered the SBA’s economic model, which involved the cycling of patients through a series of Markov health states to examine costs and outcomes for TAVI or SAVR. The cohort entered the Markov model in the “procedure” health state, which could result in a successful, no complication outcome, or be associated with complications. Complications included death, pacemaker, major bleeding, stroke, heart failure/vascular complication, and “other CV complications”.

The critique highlighted several issues with the economic evaluation. ESC noted that, whilst the applicant did make some changes to the model in its pre-ESC response document, there were many areas that the applicant should have ideally revised.

ESC noted that there was inappropriate pooling of patients experiencing a wide variety of events of differing severity into a single health state of “other complications” with differentials in the proportions across TAVI and its comparators.

ESC noted that there were discrepancies that patients experiencing the same events could transit to different health states across the different interventions.

ESC noted that the economic model failed to include all relevant health states, which had implications for survival outcomes.

ESC noted that most of the transition probabilities were artificially derived without a proper justification or supporting clinical evidence and so were considered invalid.

ESC noted that the economic evaluation applied unadjusted utility values obtained from two different multi-attribute utility instruments.

ESC noted the main area of financial uncertainty was the number of patients in Australia with severe symptomatic AS who may be being medically treated (+/- balloon valvuloplasty) for this condition. ESC noted that using prevalence estimates from a meta-analysis indicated that the likely number of patients who are being medically managed and eligible for TAVI may be 4,117 in 2015; a number 7 times greater than the 593 patients estimated by the SBA. ESC also noted that this number was calculated for patients > 75 years of age and with severe AS. If the criteria were relaxed to be > 65 years of age and with less severe AS, then the potential unmet demand for TAVI will be greater again. However, this estimate may be limited by the capacity of the existing specialist cardiac centre to perform the procedure.

ESC advised that data relating to first generation devices may overestimate some adverse events, for example, the high rate of pacemaker insertion required in patients who have undergone TAVI may be reduced with new generation devices.

## **15. Other significant factors**

MSAC discussed whether the rule of rescue might apply in this context and decided against this primarily because TAVI is not intended to be restricted to inoperable patients only and so other alternatives (eg SAVR) are available.

## **16. Applicant’s comments on MSAC’s Public Summary Document**

The applicant acknowledges MSAC’s consideration of the proposed listing of transcatheter aortic valve implantation (TAVI) on the MBS. The areas of uncertainty presented in this PSD were addressed in the applicant’s response to the evaluation report, to the ESC Report, to the MSAC request, and to the critique of post-MSAC. Specifically, the applicant notes that transapical and other minimally invasive TAVI procedures are no longer considered as part of the submission. The applicant notes that further justification was provided regarding the structure of the model, the costs of hospitalisations, the transitions probabilities, and the utility values in the response to the critique of post-MSAC. Further, the applicant notes that multivariate analyses have been provided to show that the economic model is robust. Finally, the applicant notes that the model was calibrated against the 5-year published PARTNER data in the response to the critique of post-MSAC. The 5-year PARTNER data were published 5 days before the MSAC meeting. However, the applicant reiterates that the Australian mortality rates would better represent the proposed patient population. The intent of the proposed listing is to address an area of high unmet clinical need for TAVI, particularly by patients deemed as high risk for SAVR or otherwise inoperable. The applicant

notes that MSAC considered that the 5-year results from the PARTNER trial strengthened the clinical case for public funding of TAVI.

#### **17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website at: [www.msac.gov.au](http://www.msac.gov.au).