



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### *Application 1347 – Transcatheter occlusion of the left atrial appendage (LAA) for patients with non-valvular atrial fibrillation*

**Applicant:** Boston Scientific Pty Ltd

**Date of MSAC consideration:** MSAC 62nd Meeting, 26 – 28 November 2014

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 MBS listing for transcatheter occlusion of left atrial appendage (LAA) for patients with non-valvular atrial fibrillation (NVAF) was received from Boston Scientific Pty Ltd by the Department of Health in January 2013.

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

After considering the available evidence in relation to safety, clinical effectiveness and cost-effectiveness, MSAC rejected the proposal to publically fund left atrial appendage closure (LAAC) for patients who are contraindicated for oral anticoagulant therapy (OAT) due to uncertain comparative safety and clinical effectiveness in the short and long term and uncertain cost-effectiveness.

The key area of uncertainty was the comparative safety and clinical effectiveness of LAAC compared to current standard of care with OAT or oral antiplatelet therapy (OAP). To address these uncertainties, MSAC advised that any reapplication should include results from the PREVAIL randomised trial.

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

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

MSAC noted that most strokes in NVAF are caused by thrombi of which over 90% originate in the LAA. Transcatheter closure of the LAA is a novel technique to augment current measures to reduce stroke risk in NVAF. The technique involves a transoesophageal echocardiogram (TOE) to assess eligibility. The placement of the closure device is performed under general

anaesthesia in a catheterisation lab with TOE and fluoroscopy. Follow-up TOEs occur at discharge, six weeks and six months.

Current management of NVAF focuses on oral anticoagulation therapy (OAT), such as warfarin, which is associated with a 60 – 70% reduction in stroke risk, but an increased risk of bleeding. However, anticoagulation is not a management option for patients with contraindications to oral anticoagulant medicines, which mostly arise when such patients already have an increased risk of bleeding.

MSAC noted that the proposed clinical indication was for patients with NVAF who are contraindicated for OAT and who have one or more risk factors for developing a stroke (these include prior stroke, transient ischaemic attack or non-central nervous system (CNS) systemic embolism, age 75 years and older, hypertension, diabetes mellitus or heart failure and/or left ventricular ejection fraction (LVEF) 35% or less). MSAC considered that, if implemented, the grounds for considering OAT to be contraindicated and the list of suitable risk factors would need to be more tightly defined, for example intolerance to therapy might simply reflect patient preference, and the list of risk factors should be limited to one or more of those listed. In relation to the second point, MSAC agreed with its ESC that allowing other possible risk factors would allow lower risk patients to become eligible, and considered that this would be associated with expected reduced effectiveness and less favourable cost-effectiveness.

MSAC expressed reservations over the proposed comparator of oral antiplatelet (OAP) therapy (specifically presented in the application as being aspirin plus clopidogrel). There were two issues noted by MSAC with regard to using this comparator for the assessment. First, the most common contraindication to OAT is increased risk of bleeding. However, OAP therapy is also associated with an increased risk of bleeding as indicated by both the ACTIVE-W randomised trial comparing clopidogrel plus aspirin against vitamin K antagonists such as warfarin (relative risk (RR) = 1.21; 95% CI 1.08 – 1.35, acknowledging that the statistically significant increase in risk of bleeding is driven mainly by minor bleeds: RR 1.23; 95% CI 1.09 – 1.39), and also the AVERROES randomised trial (Connolly et al. NEJM 2011;364:806-17) comparing aspirin against apixaban (a new oral anti-coagulant, (hazard ratio = 1.13; 95% CI 0.74 – 1.75). This increased risk of bleeding with OAP is likely to be driven by aspirin, but clopidogrel monotherapy is unlikely to be widely used in patients contraindicated to OAT because there is a lack of evidence to support its effectiveness in NVAF. This means that patients who are contraindicated to OAT are also highly likely to be unable to take OAP (especially dual OAP). Second, whilst MSAC noted that there are other reasons that patients may not be prescribed warfarin that are not related to increased risk of bleeding (eg. trouble maintaining a stable INR whilst taking warfarin), such patients may now be eligible for new oral anti-coagulants recently listed in the Schedule of Pharmaceutical benefits. However, these patients are not being considered in this application.

Overall, MSAC concluded the application could be rejected on the basis of nominating a comparator which should not be used in many patients contraindicated to OAT and so would leave best supportive care with no active intervention as the comparator for patients with elevated bleeding risk. No assessment was provided against this comparator. However, this was not specified in the Protocol. Furthermore, it is acknowledged that patients with a bleeding contraindication for OAT would often receive aspirin alone, despite the limited evidence for stroke prevention. Therefore, MSAC proceeded to consider the rest of the application as presented. MSAC acknowledged that this was not questioned across the pre-MSAC processes.

MSAC considered the evidence presented for the comparative safety and efficacy of LAAC in the proposed population. No direct randomised trial comparing OAP and LAAC had been

performed. For the purposes of the application, an indirect comparison was performed between the PROTECT-AF randomised trial that compared LAAC with warfarin, and the ACTIVE-W randomised trial that compared clopidogrel plus aspirin with vitamin K antagonists including warfarin.

The data on safety came directly from the PROTECT-AF trial, where there was a 9.1% rate of device placement failure (41/449). MSAC noted that there were no data presented on how these were managed. In addition, other adverse events occurred in less than 5% of patients. Against the nominated comparator of OAP therapy, the indirect comparison suggested a similar risk of bleeding across all types (RR 1.00; 95% CI 0.65 – 1.68). MSAC concluded that the evidence presented indicated that LAAC is probably less safe than OAP.

In terms of comparative effectiveness, the indirect comparison suggested that, compared to LAAC, OAP therapy was associated with an increased relative risk of stroke (RR 2.5; 95% CI 1.3 – 4.8) and increased cardiovascular mortality (RR 2.8; 95% CI 1.5 – 5.5) with no difference in total haemorrhage. MSAC concluded that, based on these results, the LAAC technology may be more effective than OAP therapy.

However, MSAC noted there was some considerable uncertainty in the evidence presented, including that it was difficult to attribute the reported differences solely to the two compared interventions when other differences across the two trials may also contribute. In particular, MSAC questioned whether the populations in the study are similar to each other as well as to those identified by the proposed MBS item descriptor. Specifically, proposed MBS patients who would be contraindicated for OAT would have more complex medical histories and higher baseline risk of stroke. The comparative effectiveness of LAAC in this population may be overestimated by the indirect comparison, because the outcomes may be driven by comorbidities. In addition, the mean follow-up for the two trials was substantially different at 3.8 and 1.3 years. However, MSAC noted an analysis in the Pre-ESC response which varied the results according to different durations of follow-up in the PROTECT-AF trial, which suggested a similar indirect relative treatment effect compared with the original indirect comparison.

MSAC noted that there was insufficient basis to compare across available LAAC devices in terms of their comparative safety and comparative effectiveness.

MSAC considered the application's economic evaluation of LAAC for patients who are contraindicated for OAT, which estimated an incremental cost-effectiveness ratio (ICER) of \$16,844 per QALY over a lifelong time horizon. This increased to \$137,446 per QALY for a five-year time horizon, to \$33,082 per QALY for a lifelong time horizon without accruing additional benefit of stroke after 5 years, and to \$23,573 per QALY when re-analysed by the assessment group. The economic evaluation was based on several assumptions: that initial risk of procedural events with LAAC is similar to that seen in the PROTECT-AF study; that LAAC is associated with reduced risk of stroke and cardiac death compared with OAP; that there is no difference in bleeding events compared with OAP; and that the benefits of LAAC continue to diverge from those of OAP for the lifetime of the patient. The economic evaluation was also sensitive to the relative risks for stroke and cardiovascular death. When using the lower estimate of effectiveness (lower limit of the 95% confidence interval), the ICER increased to \$128,024 per QALY over a lifelong time horizon.

MSAC considered the comparative effectiveness estimated from the indirect comparison to be the major source of uncertainty, which is further exacerbated when it is assumed to increase constantly over a lifelong time horizon. MSAC noted that other concerns with the model had

been reasonably addressed in the pre-MSAC response, including: no utility decrements for age, the LAAC procedure, adverse events and procedure failures; the assumption of one LAAC device needed per patient; and the exclusion of longer-term costs of monitoring, complications and device failure.

MSAC considered the budgetary impacts of publically funding LAAC and accepted advice from its ESC that there was considerable uncertainty in the costs presented, in particular on the numbers of patients who would be eligible for the device and the costs associated with replacing devices that had failed. MSAC noted that these projections indicated that clopidogrel cost offsets would not be sufficient to cover increased costs of LAAC to the MBS, and that the greatest burden of cost for LAAC would fall to private health insurance for the device.

MSAC noted that the PREVAIL randomised trial, a follow-up trial to PROTECT AF, had already given equivocal results, but is only due for completion in 2017. The inclusion of these results in a reapplication would strengthen the evidence base and assist in generating a more robust economic evaluation.

#### 4. Background

MSAC has not previously considered this application.

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

Several devices are currently listed in the Australian Register of Therapeutic Goods (ARTG) and are in use at hospitals around Australia.

#### 6. Proposal for public funding

The proposed MBS item descriptor is provided below. The proposed fee is based on MBS item 38272 (atrial septal defect closure, with septal occluder or other similar device, by transcatheter approach).

TOE is performed by a different specialist (e.g. echocardiologist) and is claimed using a separate item.

Category 3 – THERAPEUTIC PROCEDURES
<p><b>MBS XXXXX</b>            Transcatheter occlusion of left atrial appendage, including any associated imaging and cardiac catheterisation performed by the same practitioner, for stroke prevention in a patient who:</p> <ul style="list-style-type: none"> <li>• has non-valvular atrial fibrillation;</li> <li>• has contraindications to oral anticoagulation therapy; and</li> <li>• has one or more risk factors for developing stroke.</li> </ul> <p>(Anaes.) (Assist.)            Fee: \$912.30 Benefit: 75%=\$684.25</p> <p>[Explanatory Notes]            Risk factors for developing stroke include, but not limited to:            (i) Prior stroke (ischaemic or unknown type), transient ischaemic attack or non-central</p>

### Category 3 – THERAPEUTIC PROCEDURES

nervous system (CNS) systemic embolism;  
(ii) age 75 years or older;  
(iii) hypertension;  
(iv) diabetes mellitus;  
(v) heart failure and/or left ventricular ejection fraction 35% or less.

Contraindications for oral anticoagulation therapy include adverse reactions, inability to tolerate therapy, failed therapy or intolerance to therapy. These include both absolute and relative contraindications.

The practitioner is required to undergo appropriate training and credentialing.

The procedure is performed as a hospital service.

The fee does not include the cost of the device.

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

Consumer input was concerned about impact to health costs for the community as this condition is associated with an ageing population with the majority of patients (70%+) being male.

Consumer feedback also noted that there would be limited out of pocket expenses regarding this intervention.

Consumer input was concerned with the limited public health campaigns targeting men's health, especially since studies show that men's attitude to their health is not as good as women's attitude to their health.

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

The LAA Closure Device is intended for patients with NVAF who require treatment for potential thrombus formation and are eligible for long-term oral anticoagulation therapy, or who have a contraindication to anticoagulation therapy. The procedure aims to prevent ischemic stroke and systemic thromboembolism by closing off the LAA permanently to avoid the migration of emboli (clots) to the brain.

The LAA Closure Device is a self-expanding nitinol frame structure with fixation anchors and a permeable polyester fabric that covers the atrial facing surface of the device. The access sheath and delivery catheter permit device placement in the LAA via femoral venous access and inter-atrial septum crossing into the left atrium.

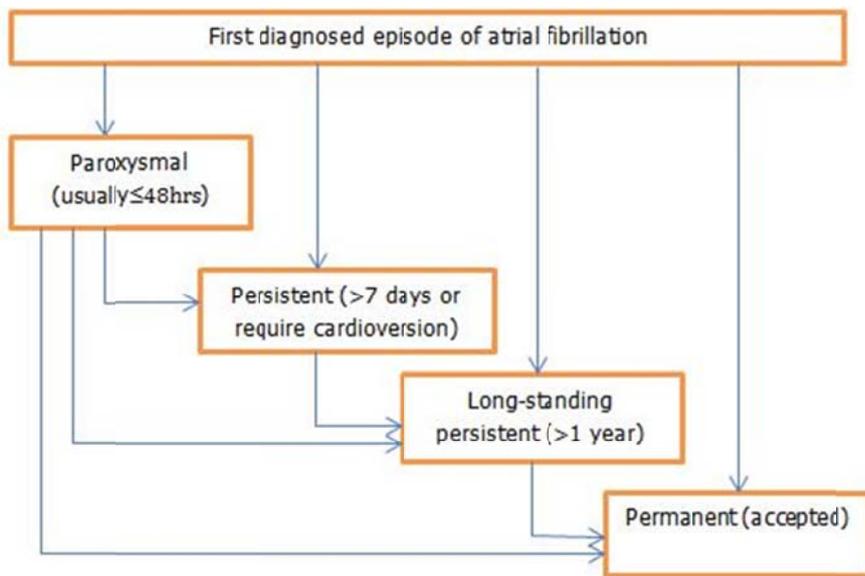
The procedure takes approximately 60 minutes, and is performed under general anaesthesia by an interventional cardiologist or electrophysiologist in a catheterisation lab under fluoroscopy and transoesophageal echocardiogram (TOE).

The proposed service is a new intervention that provides an additional option to the currently available stroke prevention options (i.e. antiplatelet therapy) in this population.

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia and a key risk factor for ischaemic strokes. A thrombus can form when blood becomes trapped in the LAA due to fibrillation. When the thrombus becomes dislodged it migrates through the arterial system, resulting in vascular occlusion from thromboembolism which may occur in vital organs including the brain (resulting in an ischemic stroke). Ischemic strokes can lead to a large number of complications including hemi-paralysis, speech deficits, dysphasia, and even death.

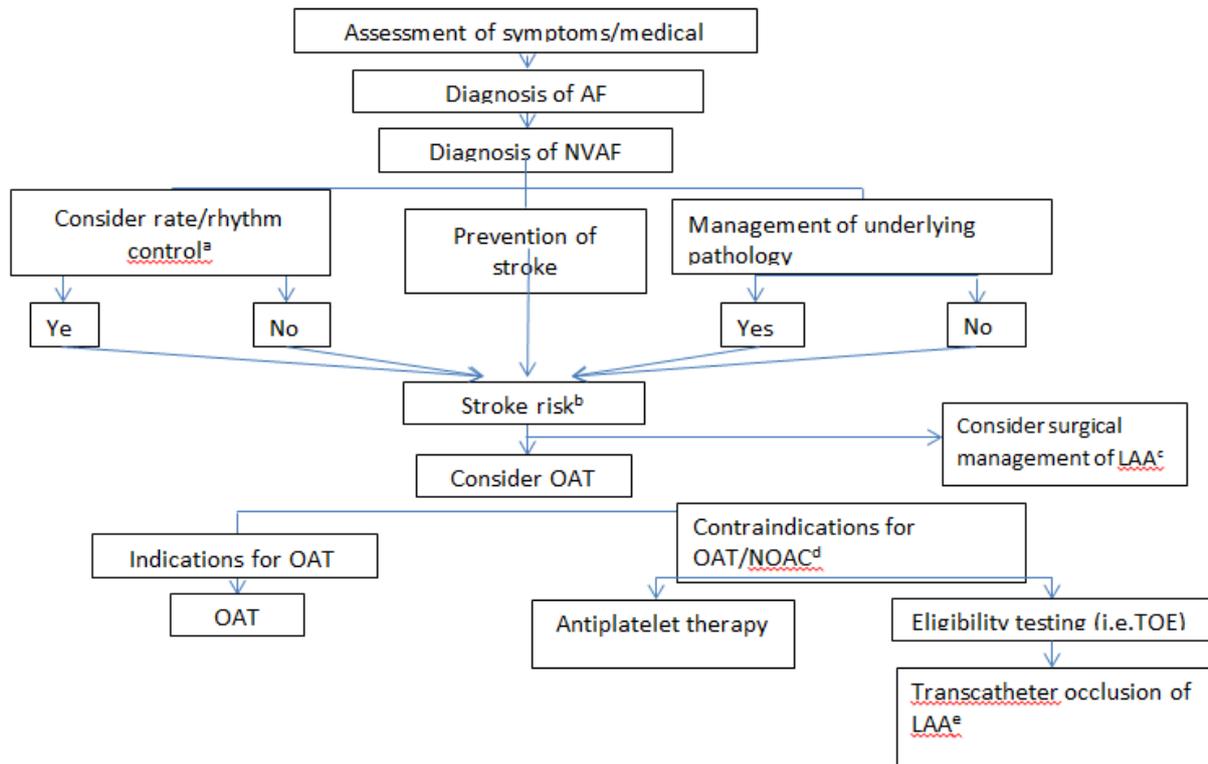
The current guidelines of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology provide a classification of AF based on arrhythmia progression, shown in Figure 1 below:

Figure 1: Classification of AF based on arrhythmia progression



The proposed service provides an additional option to the currently available stroke prevention options (i.e. antiplatelet therapy) in this population.

Figure 2: Proposed clinical decision algorithm



AF: atrial fibrillation; NVAf: non-valvular atrial fibrillation; OAT: oral anticoagulant therapy (currently includes warfarin, rivaroxaban, apixaban and dabigatran); LAA: left atrial appendage; TOE: trans-oesophageal echocardiography.

a: Rate control strategies may include antiarrhythmic drugs such as beta-blockers, and AV node ablation with implant of permanent pacemaker. Rhythm control strategies may include left atrial catheter ablation and antiarrhythmic drugs, which are used in conjunction with cardioversion.

b: Stroke risk can be assessed by CHADS1, CHADS2 or CHA2DS2-VASc scoring system. Based on CHADS2, risk factors for stroke are history of stroke or transient ischaemic attack, cardiac failure and/or LVEF assessed by CHADS1, CHADS2 or CHA2DS2-VASc scoring system. Based on CHADS2, risk factors for stroke are history of stroke or transient ischaemic attack, stroke risk, once they have any of these risk factors for stroke.

c: Surgical closure of LAA may be performed concomitantly with other open or percutaneous surgical procedures (e.g. mitral valve replacement). Devices, such as AtriClip may be used for LAA exclusion; however, these procedures are performed under direct visualisation.

d: Contraindications to warfarin include absolute and relative contraindications (see Table 2)

e: Patients receive x-ray and/or TOE prior to discharge from hospital. At 6 weeks to 6 months post-implantation, another TOE is performed. Some patients may require repeated imaging, if post procedural adverse events are suspected.

## 9. Comparator

The submission based assessment (SBA) nominated combination treatment with the antiplatelet agents aspirin and clopidogrel as the main comparator. The main arguments provided in support of this nomination were:

- that RCT evidence (2009) has demonstrated that combination therapy with aspirin and clopidogrel has superior efficacy in the prevention of stroke compared to either clopidogrel or aspirin taken alone; and,
- that according to expert advice, most Australian patients with NVAf who are identified as moderate to high risk for stroke, but in whom OAT is contraindicated, receive combination treatment with aspirin and clopidogrel for stroke prevention.

The main comparator specified in the final protocol was antiplatelet therapy. This is a broader definition of the comparator than is used in the SBA. A comparison to “antiplatelet therapy” could include comparisons to combined clopidogrel and aspirin, comparison to clopidogrel and aspirin as single agents, and comparisons to other available antiplatelet agents.

## **10. Comparative safety**

The SBA presented an indirect comparison of LAAC versus aspirin plus clopidogrel via warfarin. Two randomised controlled trials (RCTs) are used to construct the indirect comparison:

- PROTECT-AF, a RCT comparing LAAC with warfarin; and
- ACTIVE –W, a RCT comparing aspirin plus clopidogrel with OAT

The primary safety outcome in PROTECT-AF was a composite outcome that included device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitates an operation. There was no significant difference in the composite outcome between LAAC and warfarin.

LAAC device placement was not attempted for 14 of the 463 randomised patients (3.0%) and, of the 449 patients with attempted placement, 41 placements were failures (9.1%). The SBA did not describe how LAAC device implantation failures were managed, for example, whether a second implantation was attempted and whether any other surgical or medical management was required. This information is important for assessing the comparative safety of the LAAC procedure and is also important for the economic evaluation of LAAC. Adverse events related to the LAAC procedure occurred in fewer than 5% of patients and included cardiac perforations requiring surgical repair (1.6%), pericardial effusion with tamponade (2.9%) and procedure-related ischemic stroke (1.1%).

The SBA section on the extended assessment of comparative harms repeats the data from PROTECT-AF on procedure-related adverse events and no further evidence of the safety of LAAC is presented.

## **11. Comparative effectiveness**

The results of the indirect comparison are presented below in Table 1. Compared with LAAC, combination aspirin and clopidogrel therapy was associated with significant increase in the risk of all stroke (RR 2.50; 95% CI 1.31 to 4.77) and cardiovascular mortality (RR 2.81; 95% CI 1.45 to 5.47), and no increased risk of total haemorrhage (RR 1.002; 95% CI 0.65 to 1.68).

Table 1: Results from the indirect comparison presented in the submission

	PROTECT-AF			ACTIVE-W			Indirect comparison RR (95% CI)	P-value
	Treatment Effect RR (95% CI)	LAAC n with event/N (%)	OAT n with event/N (%)	OAT n with event/N (%)	Aspirin plus clopidogrel n with even/N (%)	Treatment Effect RR (95% CI)		
All-Stroke	0.685 (0.39, 1.20)	26/463 (5.6)	20/244 (8.2)	59/3371 (1.8)	100/3335 (2.99)	1.713 (1.25, 2.36)	2.50 (1.31, 4.77)	0.005
Cardiac Mortality	0.407 (0.22, 0.75)	17/463 (3.7)	22/244 (9.0)	106/3371 (3.1)	120/3335 (3.6)	1.144 (0.89, 1.48)	2.81 (1.45, 5.47)	0.002
Total Haemorrhage	1.096 (0.77, 1.56)	79/463 (17)	38/244 (15.6)	574/3371 (17.0)	669/3335 (20.0)	1.178 (1.07, 1.30)	1.002(0.65, 1.68)	0.993

*Note that in the PROTECT-AF study the follow-up time is 3.8 years mean follow up while in the ACTIVE-W study there is a median of 1.28 years of follow up.*

It should be noted that the results used are derived from a mean of 3.8 years of follow-up in PROTECT-AF and a median of 1.28 years of follow-up in ACTIVE-W trials. This difference in trial duration may overestimate the effect of LAAC compared to aspirin plus clopidogrel. The SBA did not include a discussion of the suitability of the PROTECT-AF and ACTIVE-W trials for use in an indirect comparison. In particular, the rate of vascular death was considerably lower in OAT arm of ACTIVE-W (2.87%) than in PROTECT-AF (9.0%). The higher mortality rate in PROTECT-AF may be due to the inclusion of “unexplained deaths” with cardiovascular deaths. In this case, an indirect comparison that did not also include the “unexplained deaths” in ACTIVE-W would be incomplete and inappropriate. Alternatively, the difference may be due to an underlying difference between the study populations that may reduce the comparability of the trials. In either case, the results of the indirect comparison should be interpreted with caution.

The SBA did not provide any justification for the outcomes selected for the indirect comparison. The SBA should have presented separate indirect comparisons for ischaemic and haemorrhagic stroke, particularly as these were specified in the final protocol and the data were available. An independent analysis of the results for ischaemic and haemorrhagic stroke was performed during the evaluation and found a reduced risk of both types of stroke, but neither estimate reached statistical significance (although it is noted that the indirect comparison was probably underpowered for the separate endpoints).

#### Premodelling studies:

The SBA included the following premodelling studies:

1. Applicability: a comparison of patient characteristics from the PROTECT-AF trial and other studies of LAAC in patient who are contraindicated to OAT

The SBA concluded that patients in PROTECT-AF are similar to NVAf patients who are contraindicated to OAT, and thus that the results of the indirect comparison are applicable to the MBS population. However, the results presented suggest that NVAf patients who are contraindicated to OAT have more complex medical histories and may have a higher baseline risk of stroke, and that the comparative effectiveness of LAAC in this population may be overestimated.

2. Transformation and extrapolation: yearly probability rates for stroke, bleeding, and cardiovascular death were calculated from the trial data and were assumed to be maintained for the duration of the model.

The base case economic analysis assumed a constant comparative effectiveness for LAAC over aspirin plus clopidogrel, which may not be appropriate. The SBA included a supplementary analysis in which the benefits from LAAC are limited to the 5-year trial duration.

3. Utility values: preference-based utility estimates for the health states in the economic model were identified through a structured literature search.

Overall, the utility values selected for use in the economic model were appropriate. However, the model did not include any utility decrement for age, for the overall LAAC procedure, for an unsuccessful LAAC procedure or for adverse events following a successful LAAC.

## **12. Economic evaluation**

The SBA presented a stepped economic evaluation based on the indirect comparison of the two randomised trials. The types of economic evaluation presented were a cost-utility analysis and a cost-effectiveness analysis. Two versions of the model were provided: one following the base case ITT analysis and another following the per-protocol analysis.

The SBA presented a Markov cohort model that compares LAAC with aspirin plus clopidogrel in patients with NVAF who are contraindicated to OAT.

The model takes the perspective of the Australian health system and includes the costs of the compared interventions, costs for procedure-related complications, costs for subsequent bleeding and stroke events, and long term costs of disability and aged care following disabling stroke events. Both costs and effects are discounted at 5% per annum and the effect of discounting is explored in sensitivity analyses

The time horizon used in the base case is lifetime, which was approximately 35 years. An analysis with a time horizon of five years was included as a part of the stepped analysis, to reflect the duration of the key LAAC trial PROTECT-AF. The cycle length used in the model was one year. The time horizon selected was considered appropriate. The cycle length is considerably longer than the cycle length used in the published economic evaluations of LAAC and the economic evaluations used in the SBA as sources of AF utility estimates, all of which used cycle lengths of one month.

Table 2 below summarises the results of the economic evaluation of LAAC compared to aspirin plus clopidogrel.

Table 2: Results of the economic evaluation

Resource item description	LAAC implantation	Aspirin plus clopidogrel	Incremental
<b>Step 1: Trial-based evaluation (5 years)</b>			
Cost	\$21,492.65	\$3,008.46	\$18,484.19
Effect (LYs)	4.234	4.094	0.139
<i>Cost per LYG</i>	-	-	<b>\$132,754.62</b>
Effect (QALYs)	4.075	3.940	0.134
<i>Cost per QALY gained</i>	-	-	<b>\$137,446.41</b>
<b>Step 2: Extrapolated lifetime evaluation (base case)</b>			
Cost	\$22,723.90	\$5,568.76	\$17,155.14
Effect (LYs)	9.400	8.509	0.890
<i>Cost per LYG</i>	-	-	<b>\$19,271.84</b>
Cost	\$22,723.90	\$5,568.76	\$17,155.14
Effect (QALYs)	8.771	7.753	1.018
<i>Cost per QALY gained</i>	-	-	<b>\$16,844.12</b>

Using a lifetime time horizon, the incremental cost-effectiveness ratio (ICER) for LAAC was \$19,300 per LYG and \$16,800 per QALY gained. When the time horizon was limited to the duration of the trial (5 years), the ICER for LAAC was \$132,755 per LYG and \$137,446 per QALY gained.

The ICER for LAAC compared to aspirin plus clopidogrel is highly dependent on extrapolation of the clinical effects from the trial duration to lifetime duration. As the long-term safety and efficacy of LAAC is uncertain, the results of this extrapolation should be interpreted with caution.

#### Independent cost-effectiveness analyses

A number of errors or omissions were identified during the critique of the economic model. In order to assess the impact of these errors; a revised base case analysis was generated. Using this revised model, the effect of uncertainty in the clinical effect estimates was explored and a selection of the results is presented in Table 3.

Table 3: Results of revised economic analysis

**(Table redacted)**

The additional QALYs experienced by those patients in the LAAC arm of the economic model are driven by the relative risks for cardiovascular death and all-stroke obtained from the indirect comparison of the PROTECT-AF and ACTIVE-W randomised trials. Analyses using the lower bound of the 95% confidence interval for both parameters resulted in an ICER of \$128,024 per QALY with the ITT analysis and \$460,382 per QALY with the per protocol analysis.

### 13. Financial/budgetary impacts

#### Estimated financial impact of the proposed intervention:

##### Estimates of patient numbers

The SBA presented two estimates for the number of patients who will receive LAAC. The calculations use two estimates for the prevalence of AF in Australia and two estimates for the proportion of patients contraindicated to OAT to generate upper and lower estimates of the patient population.

Estimates of the proportion of patients contraindicated for OAT vary considerably, and may be as high as 40% (Kirley et al 2012). A revised upper estimate was generated using 40% for the proportion of patients contraindicated to OAT (see Table 4). Given the substantial uncertainty surrounding the epidemiological data for NVAF, the number of patients who would be eligible to receive LAAC is highly uncertain.

Table 4: Estimated uptake of the LAAC procedure

-	2015	2016	2017	2018	2019
Uptake estimate	5%	10%	15%	20%	25%
Lower estimate	-	-	-	-	-
Anticipated number of LAAC procedures per year	109	211	291	338	348
Total LAAC procedures and patients no longer requiring clopidogrel	109	320	611	949	1297
Upper estimate	-	-	-	-	-
Anticipated number of LAAC procedures per year	531	1027	1416	1644	1695
Total LAAC procedures and patients no longer requiring clopidogrel	531	1558	2974	4618	6312
<i>Revised upper estimate</i>	-	-	-	-	-
<i>Anticipated number of LAAC procedures per year</i>	<i>969</i>	<i>1876</i>	<i>2586</i>	<i>3003</i>	<i>3095</i>
<i>Total LAAC procedures and patients no longer requiring clopidogrel</i>	<i>969</i>	<i>2845</i>	<i>5431</i>	<i>8434</i>	<i>11529</i>

Abbreviations: LAAC, left atrial appendage closure

##### Total cost to the MBS of the requested listing

The SBA did not include a disaggregated analysis of MBS costs and did not provide an estimate of the cost of the requested MBS item. The total cost to the MBS per patient, including the LAAC procedure costs, was estimated to be \$2,802.90. A number of errors were identified with the costs included. A revised analysis was performed and the revised total cost was estimated to be \$3,006 per patient.

The total cost to the MBS, as calculated in the SBA is presented in Table 5. An additional analysis was performed using the revised total cost per patient. With the lower estimate of patient numbers, the revised total cost to the MBS was \$0.3 million in 2015. With the upper estimate of patient numbers, the revised total cost to the MBS was \$1.6 million in 2015. When the revised upper estimate of patient numbers was used, the total estimated cost to the MBS was \$2.9 million in 2015.

**Table 5: Estimated cost of proposed intervention to the MBS for Year 1 to Year 5**

-	2015	2016	2017	2018	2019
Uptake estimate	5%	10%	15%	20%	25%
<i>Lower estimate</i>					
Anticipated number of LAAC procedures per year	109	211	291	338	348
Total additional cost to MBS	\$305,565	\$591,573	\$815,421	\$946,944	\$975,957
<i>Revised total additional cost to MBS</i>	<i>\$320,749</i>	<i>\$620,970</i>	<i>\$855,942</i>	<i>\$994,001</i>	<i>\$1,024,455</i>
<i>Upper estimate</i>					
Anticipated number of LAAC procedures per year	531	1027	1416	1644	1695
Total additional cost to MBS	\$1,487,082	\$2,878,990	\$3,968,384	\$4,608,462	\$4,749,657
<i>Revised total additional cost to MBS</i>	<i>\$1,560,979</i>	<i>\$3,022,056</i>	<i>\$4,165,586</i>	<i>\$4,837,471</i>	<i>\$4,985,682</i>
<i>Revised upper estimate</i>					
Anticipated number of LAAC procedures per year	969	1876	2586	3003	3095
Total additional cost to MBS	\$2,716,131	\$5,258,429	\$7,248,191	\$8,417,281	\$8,675,173
<i>Revised total additional cost to MBS</i>	<i>\$2,851,104</i>	<i>\$5,519,737</i>	<i>\$7,608,376</i>	<i>\$8,835,563</i>	<i>\$9,106,269</i>

Abbreviations: MBS = Medicare Benefits Schedule

The SBA did not consider the cost of managing any long-term complications of LAAC. As there are no clinical data to inform estimates of the frequency of the necessity for later removal or replacement of LAAC devices, the potential impact of these events is uncertain.

Total cost to Government of the requested listing

Table 6 below outlines the total net costs to Government health budgets. Over time, the total net cost per patient decreases as the cost savings from the reduced use of clopidogrel accumulate.

Additional analyses were performed using the revised total MBS cost estimates and the revised upper estimate of patient numbers. The analysis found that the estimated total cost to Government was \$2.6 million in 2015, increasing to \$6.0 million in 2019.

**Table 6: Total net cost to Government of LAAC**

-	2015	2016	2017	2018	2019
Uptake estimate	5%	10%	15%	20%	25%
<i>Lower estimate</i>					
Anticipated number of LAAC procedures per year	109	211	291	338	348
Total cost per patient	\$2,531	\$2,391	\$2,232	\$2,040	\$1,791
Total additional cost to Australian Government	\$275,973	\$504,692	\$649,573	\$689,391	\$623,890
<i>Revised total cost to Government</i>	<i>\$291,158</i>	<i>\$534,089</i>	<i>\$690,094</i>	<i>\$736,448</i>	<i>\$672,388</i>
<i>Upper estimate</i>					
Anticipated number of LAAC procedures per year	531	1,027	1,416	1,644	1,695
Total cost per patient	\$2,531	\$2,391	\$2,232	\$2,040	\$1,791
Total additional cost to Australian government	\$1,343,069	\$2,456,169	\$3,161,254	\$3,355,036	\$3,036,263
<i>Revised total cost to Government</i>	<i>\$1,416,967</i>	<i>\$2,599,235</i>	<i>\$3,358,456</i>	<i>\$3,584,045</i>	<i>\$3,272,288</i>
<i>Revised upper estimate</i>					
Anticipated number of LAAC procedures per year	969	1876	2586	3003	3095
Total additional cost to Australian government	\$2,453,094	\$4,486,153	\$5,773,981	\$6,127,920	\$5,545,685
<i>Revised total cost to Government</i>	<i>\$2,588,067</i>	<i>\$4,747,461</i>	<i>\$6,134,166</i>	<i>\$6,546,202</i>	<i>\$5,976,782</i>

Sensitivity analyses

The SBA did not present any additional sensitivity analyses. The justification for this was that the key uncertainty is the size of the eligible patient population and the analyses presented include the consideration of a range of values using upper and lower estimates.

The financial impact analyses presented in the SBA did not consider the costs of adverse events related to the LAAC procedure. The SBA stated that 1.6% (7/449) of LAAC patients experience cardiac perforations requiring surgical repair and 2.9% (13/449) of LAAC patients experience pericardial effusion with tamponade requiring percutaneous drainage.

The costs for the management of LAAC-related adverse events were calculated using the National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2011-2012 as per the costs included in the economic model. Using the lower estimate of patient numbers, the total cost of adverse events was estimated to be \$97,604 in 2015, increasing to \$311,740 in 2019. Using the revised upper estimate of patient numbers, the total cost of adverse events was estimated to be \$867,587 in 2015, increasing to \$2,771,025 in 2019.

The inclusion of costs for the management of adverse events related to LAAC will considerably increase the net cost to Government of the LAAC procedure. Using the revised costs calculated for this critique, the total net cost to Government in 2015 would be \$0.45 million with the lower estimate of patient numbers, \$2.17 million with the upper estimate of patient numbers and \$3.96 million with the revised upper estimate of patient numbers.

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

ESC noted that the timing of the SBA compared with finalisation of the protocol had led to some divergence. Text regarding systemic ischaemic embolism had been removed from the protocol, and text specifying that the service be performed by an interventional cardiologist or cardiac electrophysiologist had been retained. This text was removed from the final protocol and text relating to training and credentialing was added in its place.

The SBA also added:

- Risk factors for stroke “not limited to”;
- Absolute and relative contraindications; and
- Specifying that the service is a hospital service.

In relation to the first dot point, ESC also advised against accepting these other risk factors because they would increase the eligible population to include lower risk patients and there is no evidence to support this.

ESC suggested that dual antiplatelet therapy would be a more appropriate comparator than aspirin alone, although did question whether dual antiplatelet therapy would be prescribed in patients at increased risk of bleeding.

ESC noted that reasons for contraindications to oral anticoagulants specified in the descriptor may potentially cause leakage to a larger population.

ESC noted that the population specified in the descriptor is potentially broad, as it includes, but does not limit risk factors for developing a stroke. The item would therefore be sufficiently broad to capture any advances in factors associated with stroke risk. ESC suggested that the descriptor be more specific regarding risk factors for AF-related embolic episodes so as to align the indications for the procedure more closely with the current scoring system for risk used in clinical practice.

ESC noted that the device could not prevent all clots as clots also form in other parts of the heart and vascular system.

ESC noted that the claims of superior efficacy and non-inferior safety are primarily based on a single randomised trial (PROTECT-AF) that was not carried out in the proposed MBS population. Whether the efficacy observed in PROTECT-AF is applicable to the proposed MBS population is uncertain.

Applicability:

ESC noted that the SBA concludes that patients in PROTECT-AF are similar to NVAF patients who are contraindicated to OAT, and the results of the indirect comparison are applicable to the MBS population. However, the results presented suggest that NVAF patients who are contraindicated to OAT have more complex medical histories and may have a higher baseline risk of stroke, and the comparative effectiveness of LAAC in this population may be overestimated.

The safety data from the PROTECT-AF trial represent a mean of 3.8 years of patient follow-up. The longer-term safety of LAAC devices remains uncertain.

An independent indirect comparison analysis found no statistically significant difference in haemorrhagic stroke or ischaemic stroke with LAAC compared to aspirin plus clopidogrel. As ischaemic stroke prevention is the purpose of the LAAC procedure, the true extent of the efficacy of LAAC remains uncertain and the claim of superior efficacy may not be supported. ESC noted that the SBA does not include a discussion of the suitability of the PROTECT-AF and ACTIVE-W trials for use in an indirect comparison. The rate of vascular death was considerably lower in the OAT arm of ACTIVE-W (2.87%) than in PROTECT-AF (9.0%). ESC noted that the higher mortality rate in PROTECT-AF may be due to the inclusion of “unexplained deaths” with cardiovascular deaths. In this case, an indirect comparison that did not also include the “unexplained deaths” in ACTIVE-W would be incomplete and inappropriate.

Alternatively, the difference may be due to an underlying difference between the study populations that may reduce the comparability of the trials. In either case, the results of the indirect comparison should be interpreted with caution.

ESC noted that the results used are derived from a mean of 3.8 years of follow-up in PROTECT-AF and a median of 1.28 years of follow-up in ACTIVE-W trials. This difference in trial duration may overestimate the effect of LAAC compared to aspirin plus clopidogrel. However, an analysis provided by the applicant suggests that the clinical effectiveness based upon the indirect comparison was similar for different follow-up periods in PROTECT-AF.

ESC noted recent developments in the evidence for the clinical efficacy of the intervention. The FDA has identified a number of important weaknesses in the PROTECT-AF trial. In 2010, FDA requested the company to perform another clinical trial to demonstrate long-term safety and effectiveness. The PREVAIL trial was then designed to supplement PROTECT AF. PREVAIL is still recruiting participants. The 18 month follow-up data are currently under review by FDA as part of their assessment for the same device (Watchman, Boston Scientific). The trial has a complicated trial design; three co-primary endpoints and a novel and difficult-to-understand Bayesian trial design. The current review indicates that eight additional ischemic strokes occurred in the Watchman group, while there were no additional events in the control group. The results are no longer positive for either of the two co-primary endpoints assessing efficacy. New strokes occurred more than one year after device implantation, “raising questions about long-term device effectiveness.” (The third co-primary endpoint, assessing the safety of the implantation procedure, remains positive.)

Extrapolation:

ESC noted that yearly probability rates for stroke, bleeding, and cardiovascular death were calculated from the trial data and were assumed to be maintained for the duration of the model.

ESC was concerned that the base case economic analysis assumes a constant comparative effectiveness for LAAC over aspirin plus clopidogrel, which may not be appropriate. The SBA includes a supplementary analysis in which the benefits from LAAC are limited to the 5-year trial duration.

Transformation:

ESC noted that preference-based utility estimates for the health states in the economic model were identified through a structured literature search.

The model does not include any utility decrement for age, for the overall LAAC procedure, for an unsuccessful LAAC procedure or for adverse events following a successful LAAC.

ESC noted that four key areas of economic uncertainty:

- whether the clinical effects calculated in the indirect comparison can be applied to the MBS population, who may have more complex medical histories and be at higher risk of stroke;
- whether the relative benefits of LAAC can be extrapolated beyond the trial duration of 5 years, and, if so, for how long the benefit would be maintained. In this regard, the follow-up data from the current PREVAIL trial are concerning;
- the true values for the key drivers of the economic model (risk of stroke and risk of cardiovascular death). These estimates were obtained from an indirect comparison using only two RCTs conducted in patients who do not match the MBS population;
- the effects of long-term potential complications, such as late device failure requiring removal, on the cost-effectiveness of LAAC are uncertain.
- When the number of LAAC devices is set to 1.5 per patient and the number of post-operative TOE procedures (with associated consultations and anaesthesia) is set to three, the total cost for the LAAC procedure increases to \$26,701; and
- The model also assumes that all LAAC device implantation failures occur at the time of initial implantation. The model does not include any costs for LAAC follow-up monitoring after 6 months, or costs for the removal of the device if failure occurs at a later point in time. As the long-term safety of LAAC devices remains uncertain, there is a potential for additional monitoring and maintenance costs to be accrued over the long-term, which would reduce the cost-effectiveness of LAAC.

ESC suggested that it would be useful for MSAC to consider a plot of ICER over time.

ESC noted that the overall budget impact of the intervention is highly uncertain. The number of patients who would receive LAAC is highly uncertain and the costs of the management of procedure-related adverse events were not included in the SBA. The SBA also does not consider the cost of managing any long-term complications of LAAC as there are insufficient clinical data to inform on the necessity for later removal or replacement of LAAC devices.

**15. Other significant factors**

Nil.

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

The applicant acknowledges MSAC's consideration of the proposed listing of left atrial appendage closure (LAAC) on the MBS. The intent of the proposed listing is to address an area of high unmet clinical need because patients contraindicated to OAT are not receiving sufficient anticoagulation and therefore remain at a high risk of stroke. Some areas of uncertainty presented in this PSD were addressed in the applicant's response to the evaluation report, pre-ESC report, and indeed the SBA itself. The applicant accepts that there are areas that require further consideration and will seek to work with all stakeholders to ensure a reapplication for the proposed service is clinically and financially responsible and meets the needs of clinicians to treat patients who may otherwise remain at high risk of stroke.

## **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).