Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1615 –Transcatheter occlusion of the left atrial appendage for patients with non-valvular atrial fibrillation

Applicant: **Abbott Australasia Pty Ltd and Boston Scientific Pty Ltd**

Date of MSAC consideration: **MSAC 81st Meeting, 31 March – 1 April 2021**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting amendment of Medicare Benefits Schedule (MBS) item 38276 for transcatheter occlusion of the left atrial appendage for patients with non-valvular atrial fibrillation (NVAF) was received from Boston Scientific Pty Ltd and Abbott Australasia Pty Ltd by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported amendment of MBS item 38276 to expand the list of absolute contraindications to oral anticoagulation therapy (Population 1). MSAC advised that the MBS item should require formal documentation of the absolute contraindication by an independent specialist/medical practitioner and recommended utilisation of this item be monitored to inform a review 2 years after this amendment is implemented.

The MSAC supported descriptor is below.

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support amendment of MBS item 38276 to include relative contraindications to oral anticoagulation therapy (Population 2). MSAC considered that the evidence did not demonstrate comparative safety and clinical effectiveness of left atrial appendage closure for stroke prevention in this population where there is an effective alternative treatment option.

Category 3 – Therapeutic procedures

MBS item 38276

Transcatheter occlusion of left atrial appendage, and cardiac catheterisation performed by the same practitioner, for stroke prevention in a patient who has non-valvular atrial fibrillation if the patient:

(a) is at increased risk of thromboembolism demonstrated by:

(i) a prior stroke (whether of an ischaemic or unknown type), transient ischaemic attack or non-central nervous system systemic embolism; or

(ii) at least 2 of the following risk factors:

(i) an age of 65 years or more;

(ii) hypertension;

(iii) diabetes mellitus;

(iv) heart failure or left ventricular ejection fraction of 35% or less (or both);

(v) vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque) **and**

(b) Where written documentation is provided from a medical practitioner, specialist or consultant physician outside the speciality of cardiology or cardiothoracic surgery confirming that the patient has an absolute and permanent contraindication to oral anticoagulation.

(H) (Anaes) (Assist)

Fee: $ 940.80 Benefit 75% = $ 705.60

Consumer summary

Abbott Australasia Pty Ltd and Boston Scientific Pty Ltd applied to amend the existing Medicare Benefits Schedule (MBS) item 38276, which provides public funding for left atrial appendage closure (LAAC) in a specific group of patients with non-valvular atrial fibrillation (NVAF).

NVAF is a common cause of irregular heartbeat. A blood clot can form when blood pools due to the irregular heartbeat. The left atrial appendage is the part of the heart where most clots come from in these patients. If the blood clot comes loose, it can travel along an artery to the brain, which may cause a stroke and lead to a large number of complications including paralysis, problems with speech or swallowing, and even death.

Anticoagulants are a type of medication given to patients to prevent the formation of blood clots, including patients with NVAF. However, some people have a medical reason that prevents them from being able to take the medication, this is called a contraindication. An absolute contraindication to anticoagulants means that taking the medication is not advisable because it could cause a life-threatening situation. A relative contraindication is where there may be a higher risk, but – depending on the situation – taking the medication may still be a good option.

LAAC is a procedure where a device is inserted into the heart to close the left atrial appendage so that clots can no longer form and dislodge. Currently, public funding for LAAC is available for a specific group of patients with NVAF who have a high risk of stroke but who cannot take anticoagulants.

The applicant wants more people to be eligible for LAAC through the MBS by expanding the list of absolute contraindications and including relative contraindications to anticoagulation. However, MSAC considered that in patients with a relative

Consumer summary
contraindication to anticoagulation, the clinical evidence did not show that LAAC is as safe or as effective as the alternative treatment option. **MSAC's advice to the Commonwealth Minister for Health** MSAC recommended expanding the list of absolute contraindications to anticoagulation (Population 1). MSAC did not recommend including relative contraindications to anticoagulation (Population 2) because the evidence did not show comparative safety and clinical effectiveness of LAAC to prevent stroke in this population where there is another effective treatment available.

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

Applicant hearing

The applicant was granted a hearing, during which it presented information to MSAC on the basis for the proposed amendments to MBS item 38276 for transcatheter occlusion of the left atrial appendage for patients with NVAF.

MSAC heard from the applicant that the objective for expanding the list of absolute contraindications to anticoagulation (Population 1) is to address a sub-group of patients who have an absolute contraindication to anticoagulation that is not currently captured in the definition within MBS item 38276. The applicant claimed these patients have no other available treatment options. The applicant's proposal to include relative contraindications (Population 2) is to provide an alternative treatment option for patients at high risk of bleeding complications before they sustain a major bleeding event while on anticoagulation.

MSAC heard the applicant's proposed amendments to the definition of a contraindication to oral anticoagulation were developed, in consultation with six experts in the management of stroke prevention, to align with the contraindications and precautions for use stated in the product information for direct oral anticoagulants (DOACs).

MSAC heard from an Australian clinician experienced in implanting LAAC devices for stroke prevention. The clinician presented real-world registry data, including data from the United States National Cardiovascular Data Registry (N=38,158) which reported a total complication rate of 2.1% and a fatality rate of 0.19%. Although an Australian registry has not yet been established, the clinician advised that the experience with the LAAC devices in Australia suggests there is a learning curve effect but that the overall adverse event rates are similar to that reported in the international registries. Overall, the clinician considered the published real-world data confirms the procedural safety and long-term safety of LAAC.

MSAC asked the clinician about patient selection guidance for clinicians managing patients with a short life expectancy (e.g. Child Pugh C liver disease) and whether the increased risk of infection observed for dialysis patients influences the risk of infection for LAAC. The clinician acknowledged that managing a patient with a short life expectancy is a delicate balance but considered the procedure should be offered if the patient has an adequate life expectancy. In regards to device infection, the clinician advised that the device becomes endothelialised and is not an intravascular device permanently in contact with the blood pool. Therefore, in their experience the LAAC device doesn't have the same infection risk over time.

MSAC asked the clinician about the ongoing clinical trials for Population 2 patients and the clinical equipoise to recruit patients with relative contraindications to anticoagulation, who could use an anticoagulant. The clinician reiterated that the proposed relative contraindication includes patients who have experienced 'a major bleeding complication without remedial cause'. The clinician indicated that if these patients with a high bleeding risk have a negative perception regarding their ability to safely take anticoagulants it can lead to non-compliance reducing the efficacy of DOACs. Therefore, the clinician considers there to be a need for LAAC as an alternative treatment for these patients.

MSAC asked the clinician about access to onsite cardiac surgery. The clinician indicated that based on their experience implanting LAAC devices, access to onsite cardiac surgery may not be necessary if there are well-established procedures in place for retrieval to a cardiac centre.

MSAC asked the clinician about the clinical implication of peri-device leakage and the implication of long-term identification of a clot on the device. The clinician indicated that there is no evidence of reduced efficacy due to peri-device leakage and that new LAAC device designs has reduced the occurrence of peri-device leakage. In regards to device-related thrombus, the clinician indicated that in their experience the LAAC device becomes endothelialised over time, and that where device-related thrombus occurs most are 'silent' and are identified incidentally during routine follow-up imaging.

MSAC discussion

MSAC noted that this application requested amendment of an existing MBS item 38276, for left atrial appendage closure (LAAC) for patients with NVAF with an absolute contraindication to oral anticoagulation, which was listed on the MBS in 2017 (MSAC Application 1347.1). The proposed amendments to the definition of contraindication to lifelong anticoagulation would expand the patient population eligible for the service.

In regards to Population 1, expanding the definition of absolute contraindications to anticoagulation, MSAC noted that the Applicant Developed Assessment Report (ADAR) did not present an assessment of the clinical evidence or an economic evaluation for this population. The ADAR claimed that the evidence base previously presented in MSAC application 1347.1 that formed the basis for recommendation of LAAC in patients with absolute contraindications in 2017, remains unchanged and is applicable to Population 1. That is, the same comparator (i.e. best supportive care), evidence and economic model still applies to Population 1. MSAC recalled that the evidence considered in 2017 for the use of LAAC in patients with absolute contraindications to anticoagulation relied on indirect comparisons to demonstrate LAAC had a reasonable safety profile and acceptable clinical and cost-effectiveness in the population with an unmet clinical need.

In regard to the clinical evidence for Population 2 (patients with relative contraindications to anticoagulation), MSAC noted that the ADAR identified one randomised controlled trial (RCT; PRAGUE-17) that directly compared LAAC to the main comparator for Population 2 (i.e. DOACs). MSAC noted concerns with risk of bias in the PRAGUE-17 trial and that the nominated non-inferiority margin (1.47) meant the device could be 47% worse than DOACs and still be considered non-inferior. MSAC noted the ADAR also included six RCT to provide an indirect treatment comparison (ITC) of LAAC versus DOACs via warfarin as the common comparator and a direct comparison between LAAC and warfarin. MSAC noted that the PRAGUE-17 trial primary outcome was a composite of safety and efficacy outcomes: stroke, transient ischaemic attack, systemic embolism, cardiovascular-related death, bleeding or procedure/device-related complications.

MSAC noted that the main limitation of the comparative safety assessment for Population 2 is the underlying differences in risks associated with LAAC, and DOACs or warfarin. MSAC noted the applicant's claim of superior safety for LAACs relative to DOACs was based on evaluation of two related outcomes: major bleeding and major gastrointestinal bleeding. However, this contrasted with the included studies, which used composite primary endpoints due to differences in risks associated with LAACs and anticoagulant therapy. LAAC has superior safety with respect to post-procedural bleeding (i.e. after 7 days of the procedure); however, there is no difference in bleeding risk between LAAC and DOACs when considering combined procedural and post-procedural bleeding (head-to-head: hazard ratio [HR]: 0.81; 95% CI 0.44–1.52; ITC odds ratio [OR]: 1.02: 95% CI 0.67–1.56).

MSAC noted that the main limitation of the comparative effectiveness assessment is the lack of direct comparative evidence for LAAC and NOACs. MSAC noted that the PRAGUE-17 trial indicated no difference between LAAC compared to DOACs for the outcomes: prevention of stroke, systemic embolism, cardiovascular mortality and all-cause mortality. However, the PRAGUE-17 trial was not powered to detect differences for individual outcomes.

Overall, MSAC considered that in patients with NVAF with a relative contraindication to anticoagulation, the evidence did not demonstrate that LAAC has superior safety to DOACs and the efficacy of LAAC compared to DOACs is uncertain from insufficient direct evidence. MSAC noted that there are a number of ongoing or planned RCTs comparing LAAC with anticoagulation, which will be needed to show superior safety and non-inferior efficacy of LAAC.

MSAC noted a cost utility analysis was provided in the ADAR to support the proposed benefit for LAAC relative to DOACs and warfarin in patients with a relative contradiction to anticoagulation (Population 2). MSAC noted that the modelled treatment efficacy was based on stroke and post-procedural bleeding rates from PRAGUE-17. MSAC agreed with ESC that the **REDACTED**. MSAC noted that the pre-MSAC response presented a revised base case with the utility values weighted to the Australian population as requested by ESC. MSAC noted that this increased the incremental cost-effectiveness ratio (ICER) from $**REDACTED** to $**REDACTED** per QALY. MSAC also noted the assumed rates of bleeding and stroke along with a range of utility values were tested in sensitivity analysis in the pre-MSAC response, which indicated the ICER remained below of $**REDACTED** /QALY, except when the All stroke risk was tested using the 95% confidence interval from the PREVAIL trial (RR=2.358; > $**REDACTED**/QALY).

MSAC noted the financial estimates for Population 1 and 2 were presented separately. For Population 1, MSAC noted the estimates were based on current MBS data and **REDACTED** % eligibility expansion while assuming the same suitability and referral rates, which indicated over the five-year period, the MBS budget impact is $**REDACTED** to $**REDACTED** MSAC noted that the utilisation of MBS item 38276 for patients with absolute contraindications since inclusion on the MBS appears to be fairly stable. For Population 2, MSAC noted that the applicant estimated that the utilisation of LAAC would increase about **REDACTED**-fold. MSAC noted that the difficulty in defining Population 2 means that there is potential for significant budget impacts. MSAC noted the pre-MSAC response presented additional sensitivity analyses testing the eligible patient population, treatment uptake and the population overlap between Population 1 and 2, which indicated there is potential for significant additional costs to the MBS and the healthcare system (up to $**REDACTED** million).

MSAC considered that the proposed LAAC listing eligibility criteria for either or both the absolute contraindications population (Population 1) and relative contraindications population (Population 2) have the potential to "grow the market" for LAAC treatment, with potentially material financial implications for the MBS. However, the extent of any changes in LAAC treatment numbers and resulting financial impacts that would result from the proposed revisions of either population (or both) was unclear. MSAC also considered that costs maybe underestimated depending on whether the pre-intervention screening occurs as an in-patient or outpatient. MSAC noted that utilisation and costing are uncertain and that more robust estimates of population size for Population 2 with sensitivity analyses are required.

MSAC also noted that currently approximately **REDACTED** centres perform this intervention but that it may not be easily accessible for people living in remote and regional Australia.

MSAC reviewed the applicant's proposed amendments to MBS item 38276 to expand the absolute contraindications (Population 1) and include relative contraindications (Population 2) in the explanatory note. In regard to Population 1, after considering the evidence available, MSAC considered it was reasonable to extend the service to include patients with other absolute contraindications, if the population can be well defined. MSAC noted the consultation feedback on the list of contraindications provided by three clinical societies and a Neurologist/Neurointerventionist. MSAC deliberated on options for ensuring patients with a clinically valid absolute and permanent contraindication are defined and have access to LAAC while respecting the autonomy of clinicians and patients in the decision making. MSAC advised that the item descriptor should be amended to require formal written documentation that the patient has an absolute and permanent contraindication to oral anticoagulation from an independent specialist/medical practitioner (i.e. non-cardiologist).

In regard to Population 2, after considering the evidence available, MSAC did not support amending the definition to include relative contraindications to anticoagulation.

MSAC reviewed the applicant's proposal to create two new case conference MBS items for assessing patient eligibility to LAAC by a non-interventional and interventional physician. MSAC recommended the applicant's proposal for a case conference to assess patient eligibility be included in the item descriptor of the procedural item rather than creating two new case conference items. MSAC also recommended that the service should be amended to include all associated imaging (which includes catheter and contrast) to represent a complete medical service and the specific associated co-claiming restrictions for heart catheterisation.

MSAC discussed whether there is a need for an onsite cardiac surgeon where the LAAC procedure is being performed. MSAC requested the Department to ask the applicant to provide Registry data on emergency surgical intervention rates and compare onsite with no onsite cardiac surgery. The MSAC Executive can then review the data and advise an evidence-based decision prior to implementation.

4. Background

Transcatheter occlusion of the left atrial appendage for stroke prevention in patients with NVAF who have an increased risk of thromboembolism and have a contraindication to lifelong oral anticoagulant therapy has been listed on the MBS (item 38276) since 1 November 2017, following consideration and support by MSAC (see MSAC application 1347.1 Public Summary Document [PSD]).

The current explanatory note for MBS item 38276 defines a contraindication to lifelong anticoagulation as:

i) a previous major bleeding complication experienced whilst undergoing treatment with oral anticoagulation therapy,
ii) a blood dyscrasia, or
iii) a vascular abnormality predisposing to potentially life-threatening haemorrhage.

The application seeks to expand the patient population eligible for MBS item 38276, by modifying the definition of contraindication to lifelong anticoagulation to:

- expand the list of absolute contraindications to anticoagulation (Population 1), andinclude relative contraindications to anticoagulation (Population 2).Following consideration of the PICO[1] confirmation by the PICO Advisory Sub-Committee (PASC) at its April 2020 meeting, a budget impact analysis for Population 1 was referred to the MSAC executive for consideration. The MSAC Executive did not consider it appropriate to expand the previously supported patient population and amend the absolute list of contraindications currently stated in MBS item 38276 without further evaluation. The MSAC Executive advised that both proposed populations should progress through the full MSAC process.

The ADAR for MSAC Application 1615 subsequently lodged by the applicant pertains to both Population 1 and Population 2. However, the ADAR asserted that the clinical evidence and economic model previously reviewed and supported for MSAC Application 1374.1 remains unchanged and is applicable to Population 1 (absolute contraindication to anticoagulation). Therefore, for Population 1, the ADAR presented a review of the contraindication to DOAC to inform the proposed amended list of absolute contraindications to anticoagulation, along with a budget impact analysis to estimate the cost to the MBS as a consequence of expanding the list of absolute contraindications to anticoagulation. A full assessment of the safety, effectiveness and cost-effectiveness of LAAC against the nominated comparator was provided for Population 2 (relative contraindication to anticoagulation).

5. Prerequisites to implementation of any funding advice

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

[1] Population, Intervention, Comparator, Outcomes

Table 1 LAA occluders and associated delivery kits listed on the ARTG

ARTG no.	GMDN/ Product category	Product name	Sponsor
340173	45418 cardiac occluder/ Medical Device Class III	WATCHMAN FLX™ LAA Closure Device with Delivery System - Cardiac occluder	Boston Scientific Pty Ltd
216434	45418 cardiac occluder/ Medical Device Class III	Watchman Left Atrial Appendage Closure Device Delivery System - Cardiac occluder	Boston Scientific Pty Ltd
216435	45419 Cardiac occluder delivery kit/ Medical Device Class III	Watchman Access System - Cardiac occluder delivery kit	Boston Scientific Pty Ltd
310680	45419 Cardiac occluder delivery kit/ Medical Device Class III	WATCHMAN™ TruSeal™ Access System - Cardiac occluder delivery kit	Boston Scientific Pty Ltd
216398	45418 Cardiac occluder/ Medical Device Class III	AMPLATZER Amulet Left Atrial Appendage Occluder - Cardiac occluder	Abbott Medical Australia Pty Ltd
162137	45418 Cardiac occluder/ Medical Device Class III	AMPLATZER Cardiac Plug - Cardiac occluder	Abbott Medical Australia Pty Ltd
230575	45418 Cardiac occluder/ Medical Device Class III	Coherex WaveCrest™ Left Atrial Appendage Occlusion System - Cardiac occluder	Johnson & Johnson Medical Pty Ltd
230576	45419 Cardiac occluder delivery kit/ Medical Device Class III	Coherex WaveCrest™ LAA Occlusion System Delivery Sheath - Cardiac occluder delivery kit	Johnson & Johnson Medical Pty Ltd

Source: Table 9, p. 45-47 of the ADAR and ARTG website (accessed on 21 January 2021).
Abbreviations: ARTG = Australian Register of Therapeutic Goods; GMDN = Global Medical Device Nomenclature; LAA = left atrial appendage

6. Proposal for public funding

The applicant proposed amendments to the explanatory note for MBS item 38276, to expand the list of absolute contraindications to anticoagulation (Population 1) and to include relative contraindications to anticoagulation (Population 2), are shown in red and green text respectively in Table 2. The proposed amendments are based on the applicant's review of the 'contraindications' and 'precautions for use' listed in the TGA approved product information (PI) for DOACs on the ARTG (Attachment 3 of the ADAR).

The applicant also proposed amendment of the descriptor for MBS item 38276 to specify that patient eligibility for LAAC to be assessed by a non-interventional and interventional physician, shown in blue text in Table 2. The applicant also proposed two new case conference items (Table 3) for eligibility for LAAC to be assessed by a non-interventional and an interventional physician, which the applicant modelled on MBS items 6080 and 6081 for the transaortic valve implantation (TAVI) case conference.

The applicant did not propose changes to the fee for MBS item 38276.

The commentary noted that MSAC may wish to consider whether MBS item 38276 should be amended to include Population 2 or whether Population 2 should be a separate MBS item. MSAC did not support creating a new MBS item or amending MBS item 38276 to include population 2 – patients with relative contraindications to anticoagulation. MSAC considered it reasonable to expand the definition of an absolute contraindication to anticoagulation and advised that the item descriptor should be amended to require formal written documentation that the patient has an absolute and permanent contraindication to oral anticoagulation from an independent specialist (i.e. non-cardiologist), which could include a General Practitioner (as shown in Section 2 of this PSD).

Table 2 Applicant proposed amendment to MBS item for LAAC – Population 1 and 2

Category 3 – Therapeutic procedures
MBS item 38276 Transcatheter occlusion of left atrial appendage, and cardiac catheterisation performed by the same practitioner, for stroke prevention in a patient who has non-valvular atrial fibrillation and assessed by a non-interventional and interventional physician as having a contraindication to life-long oral anticoagulation therapy, and is at increased risk of thromboembolism demonstrated by: (a) a prior stroke (whether of an ischaemic or unknown type), transient ischaemic attack or non-central nervous system systemic embolism; or (b) at least 2 of the following risk factors: (i) an age of 65 years or more; (ii) hypertension; (iii) diabetes mellitus; (iv) heart failure or left ventricular ejection fraction of 35% or less (or both); (v) vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque) Fee: $ 940.80 Benefit 75% = $ 705.60
TN.8.132 Transcatheter occlusion of left atrial appendage for stroke prevention (item 38276) Explanatory Note: A contraindication to life-long oral anticoagulation therapy is defined as: i. A previous major bleeding complication ~~experienced whilst undergoing treatment with oral anticoagulation therapy~~, or ii. History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding, or iii. Long-term or recurrent gastrointestinal bleeding without a reversible cause (eg, radiation proctitis or gut angiodysplasia), or iv. A blood dyscrasia, or v. A vascular abnormality predisposing to potentially life threatening haemorrhage, or vi. Hepatic disease with coagulopathy and clinically relevant bleeding risk (Child Pugh B and C), or vii. Receiving concomitant medications with strong inhibitors of both CYP3A4 and P-glycoprotein (P-gp), or viii. Severe renal impairment defined as creatinine clearance (CrCL) < 15 ml/min or undergoing dialysis and where warfarin is inappropriate, or ix. Known hypersensitivity to the direct oral anticoagulant (DOAC) or to any of the excipients. The procedure is performed as a hospital service.

Source: Table 1, p22 of the ADAR
Abbreviations: LAAC = left atrial appendage closure; MBS = Medicare Benefits Schedule; DOAC = direct oral anticoagulant
Note:
Amendments to expand the list of 'absolute' contraindications (Population 1) and to include 'relative' contraindications (Population 2) are shown in red and green text respectively.
Amendment to the item descriptor to specify that patient eligibility for LAAC to be assessed by a non-interventional and interventional physician is shown in blue text.
To align with the definition provided by the International Society on Thrombosis and Haemostasis (ISTH)(Barnes, Ageno, Ansell, & Kaatz, 2015) the applicant proposed descriptor has been updated to use DOAC (direct oral anticoagulant) instead of NOAC (novel oral anticoagulant).

Table 3 Applicant proposed, associated MBS items relevant for determining eligibility for LAAC

Category 3 – Therapeutic procedures
MBS item #### Coordination of a LAAC Case Conference by a Practitioner where the LAAC Case Conference has a duration of 10 minutes or more. (Not payable more than once per patient in a five year period.) Fee: $52.50 Benefit: 75% = $39.40 85% = $44.65
Category 3 – Therapeutic procedures
MBS item #### Attendance at a LAAC Case Conference by a specialist or consultant physician who does not also perform the service described in item #### for the same case conference where the LAAC Case Conference has a duration of 10 minutes or more. (Not payable more than once per patient in a five year period.) Fee: $39.15 Benefit: 75% = $29.40 85% = $33.30
Notes: Item #### and #### apply to a LAAC Case Conference organised to discuss a patient's suitability to receive the service described in Item 38276 for left atrial appendage closure (LAAC). For item #### and #### a LAAC case Conference is a process by which: a. There are two participants, where one is an interventional physician that performs LAAC procedures and one is a specialist or consultant physician who does not perform a service described in item 38276. b. The interventional and non-interventional physicians assess a patient's eligibility to receive the service described in item 38276, taking into account: i. The patient's risk of thromboembolism ii. The patient's contraindication(s) to direct oral anticoagulant (DOAC) as per the Therapeutic Goods Administration (TGA) approved product information for DOACs registered for use in stroke prevention. c. The result of the assessment is that a recommendation about whether or not the patient is suitable to receive the service described in Item 38276; and d. The particulars of the assessment and recommendation are recorded in writing.

Source: Table 13, p51 of the ADAR
Abbreviations: LAAC = left atrial appendage closure; MBS = Medicare Benefits Schedule; DOAC = direct oral anticoagulant
Note: To align with the definition provided by the International Society on Thrombosis and Haemostasis (ISTH)(Barnes, Ageno, Ansell, & Kaatz, 2015) the applicant proposed descriptor has been updated to use DOAC (direct oral anticoagulant) instead of NOAC (novel oral anticoagulant).

7. Summary of public consultation feedback/consumer Issues

Consultation feedback was received from a consumer group, a health care funding body and from a specialist organisation. The consumer group was supportive of the proposed service, noting it is a once off procedure that would reduce bleeding risks associated with daily oral anticoagulants for high risk patients, and would benefit patients who may "have trouble taking or staying on medicines for stroke prevention". The health care funding body considered a key issue with the proposed service was the cost of the prosthesis ($11,400) relative to the cost of one of the common medications for AF, which they stated as $21 as per the PBS list price; along with risk of over-servicing. The specialist organisation (members of the Australasian Stroke Academy (ASA)) were supportive of the proposed amendment to MBS item 38276 as it would allow another alternative in the management of patients with atrial fibrillation where life-long oral anticoagulants are contraindicated or unsafe. It supported aligning the restriction with Australian DOAC product information to minimise misinterpretation.

Following consideration by ESC, the Department undertook targeted consultation to seek clinical expert opinion on the proposed definition of a contraindication to lifelong

anticoagulation therapy. Responses were received from three clinical societies (Australian and New Zealand Society for Vascular Surgery, Gastroenterological Society of Australia, and Thrombosis & Haemostasis Society of Australia and New Zealand) and a Neurologist/Neurointerventionist. The feedback noted that while some of the proposed contraindications are not always an absolute contraindication to anticoagulation, it was also noted that assessment of the bleeding risks and the overall risk-benefit balance is determined on an individual basis.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention
The proposed intervention is percutaneous insertion of a left atrial appendage closure (LAAC) device, to occlude the left atrial appendage (LAA) in patients with NVAF. The left atrial appendage is the primary source for thromboembolism in patients with NVAF. The percutaneous insertion of an implantable device to occlude the LAA may be performed to reduce thromboembolism in patients with NVAF. The procedure aims at preventing stroke and systemic thromboembolism, by closing off the LAA permanently to avoid formation and migration of emboli to the brain.

Description of Medical Condition(s)
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 AF. When the thrombus becomes dislodged it migrates through the arterial system towards the brain, resulting in vascular occlusion from the thromboembolism which may cause an ischemic stroke. Ischemic strokes can lead to a large number of complications including hemi-paralysis, speech deficits, dysphasia, and even death.

The clinical management of patients with absolute contraindications (Population 1) is unchanged as per MSAC 1347.1 PSD.

The proposed clinical management algorithm with introduction of LAAC in patients with relative contraindications (Population 2) to anticoagulation is presented in Figure 1. Patients with an increased risk of thromboembolism (CHA2DS2-VA score of ≥ 2) and with a relative contraindication to anticoagulation may receive treatment with DOAC (preferred) or warfarin, and for these patients LAAC may provide an alternate, one-procedure option.

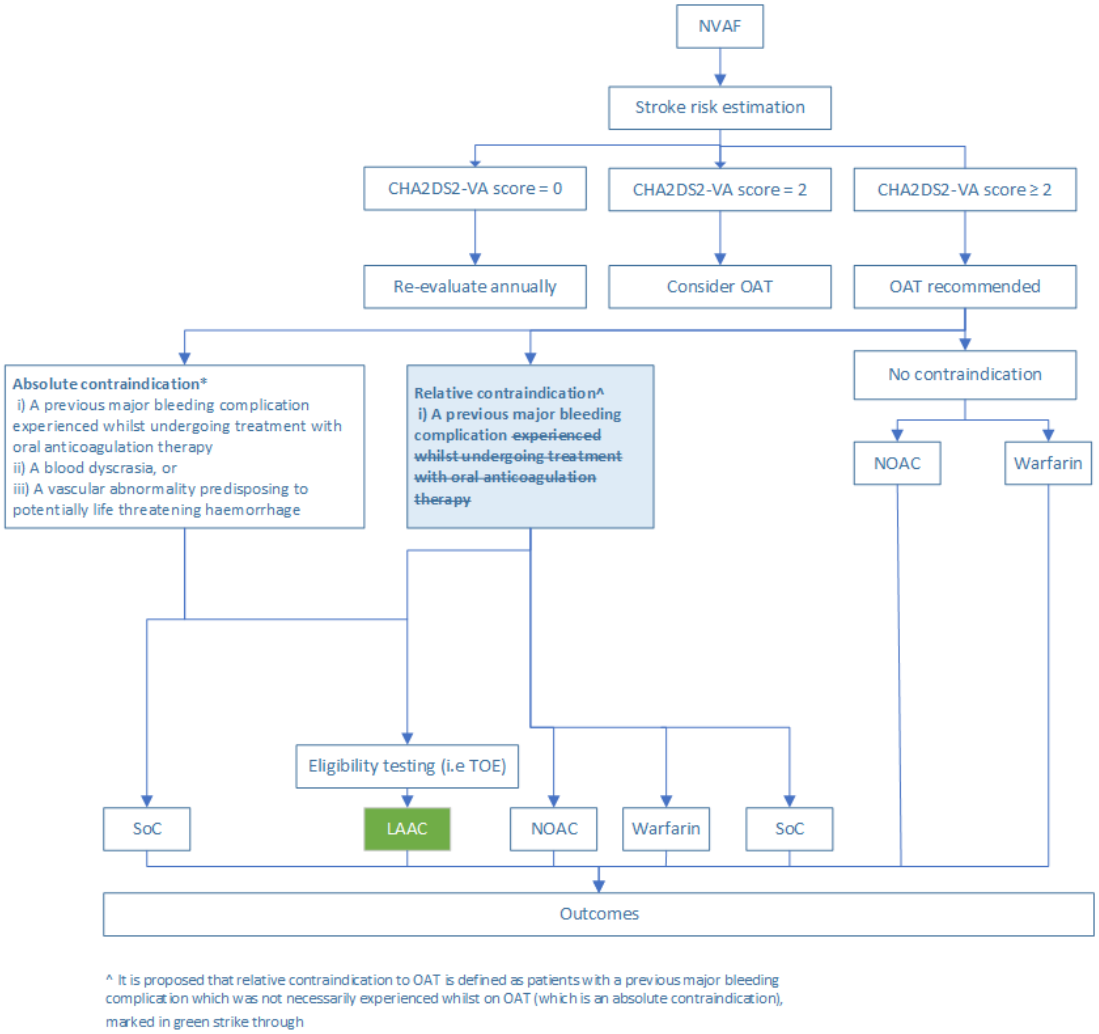

Figure 1 Proposed clinical management algorithm with introduction of LAAC in the proposed population

Source: Figure 5, p19 of MSAC 1615 Ratified PICO.
Abbreviations: LAAC = of left atrial appendage closure; NOAC = novel oral anticoagulants; NVAF = non-valvular atrial fibrillation; OAT = oral anticoagulant therapy; SoC = standard of care; TOE = transoesophageal echocardiogram
*Medications affecting haemostasis; P-glycoprotein (P-gp) inhibitors; thrombolytic agents; selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs); non-steroidal anti-inflammatory drugs (NSAIDs)

9. Comparator

Population 1
Unchanged, best supportive care as per MSAC 1374.1 PSD.

Population 2
The main comparator for LAAC in patients with NVAF with relative contraindication to anticoagulation is DOACs as these agents are the preferred treatment option in the proposed patient population. Warfarin is an alternate treatment option in these patients, thus is included as an additional comparator.

Warfarin has a general listing on the pharmaceutical benefits scheme (PBS) whereas the DOACs are restricted to stroke prevention in NVAF patients with CHA2DS2-VA ≥ 1. There are three DOACs listed on the PBS for stroke prevention in NVAF: apixaban, dabigatran and rivaroxaban, restriction provided in Table 4.

Table 4 PBS restriction for DOACs for prevention of stroke

PBS restriction for DOACs
Prevention of stroke or systemic embolism Patient must have non-valvular atrial fibrillation Patient must have one or more risk factors for developing stroke or systemic embolism: i. Prior stroke (ischaemic or unknown type), transient ischaemic attack or non-central 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.

Source: Table 22, p16 of the commentary

10. Comparative safety

Population 1
Unchanged, as per MSAC 1374.1 PSD.

Population 2
Seven randomised clinical trials (RCT) were included in the ADAR **(**Table 5). One randomised, unblinded, non-inferiority trial directly compared LAAC to DOAC (PRAGUE-17, Osmancik 2020[2]) and specifically targeted patients with NVAF with relative contraindications to anticoagulation. The PRAGUE-17 study primary outcome was a composite of benefit and harm endpoints: stroke, transient ischemic attack, systemic embolism, cardiovascular-related death, bleeding, or procedure/device-related complications.

The remaining six RCT were included to allow an indirect treatment comparison (ITC) of LAAC versus DOACs via warfarin as the common comparator and a direct comparison between LAAC and warfarin.

The commentary noted that in the PREVAIL, J-ROCKET-AF and ROCKET-AF trials 91-100% of the participants had a $CHADS_2$ score ≥2 in the warfarin arm, compared to the PROTECT-AF, ARISTOTLE and RE-LY trials where 66-73% of the participants had a $CHADS_2$ score ≥2 in the warfarin arm. Of note are the J-ROCKET-AF and ROCKET-AF trials where majority of participants (63.6% and 54.6% respectively) had a history of stroke or transient ischemic attach (TIA), compared to other four trials where not more than 30% patients had a previous stroke. Given this variation in the risk of stroke among the participants who were allocated warfarin in the six included trials, the commentary considered that the common comparator arm was not exchangeable across the included trials.

[2] Osmancik et al. (2020) *Journal of the American College of Cardiology*. 75(25):3122

Table 5 Key features of the included evidence in the RCTs

Trial/Study (publication)	N	Design/ follow-up / country	Risk of bias	Key outcome(s)	Result used in economic model
LAAC vs. DOAC					
PRAGUE-17 (Osmancik 2020)	LAAC=201 DOAC=201	RCT, P, MC, Czech Republic (2015–2019), OL / median 19.9 months	Low	Stroke, Systemic embolism, Major and non-major bleeding events, CV mortality, All-cause mortality, Significant peri-procedural or device-related complications	Yes
LAAC vs. warfarin					
PROTECT-AF (Holmes 2009, Reddy 2013, Reddy 2014)	LAAC=463 Warfarin=244	RCT, P, MC, USA/Europe (2005–2008), OL / mean 47.6 months	Low	Stroke (any type), Systemic embolism, CV/unexplained mortality, Device/procedure-related events, Major bleeding events	No
PREVAIL (Holmes 2014)	LAAC=269 Warfarin=138	RCT, P, MC, USA (2010–2012), OL / median 2.8 years	Low	Stroke (any type), Systemic embolism, CV/unexplained mortality, Device/procedure-related events, Major bleeding events	No
DOAC vs. warfarin					
J-ROCKET AF (Hori 2014)	Rivaroxaban=639 Warfarin=639	RCT, P, DB, DD, MC, Japan / expected study duration, were 30 months	Low	Stroke, Systemic embolism, CV mortality, All-cause mortality, Major and non-major clinically relevant bleeding events	No
ROCKET AF (Patel 2011, Pokorny 2016)	Rivaroxaban=7131 Warfarin=7133	RCT, DB, DD, MC, 45 countries (2006–2009) / median 707 days	Low	Stroke, Systemic embolism, CV mortality, All-cause mortality, Major and non-major clinically relevant bleeding events	No
RE-LY (Connolly 2009)	Dabigatran=12091 Warfarin=6022	RCT, SB, OL, MC, 44 countries (2005–2007) / median 2.0 years	Low	Stroke, Systemic embolism, CV mortality, All-cause mortality, Major bleeding	No
ARISTOTLE (Granger 2011)	Apixaban=9120 Warfarin=9081	RCT, DB, DD, MC, 39 countries (2006–2010) / median 1.8 years	Low	Stroke, Systemic embolism, CV mortality, All-cause mortality, Major bleeding and non-major bleeding	No

Source: Adapted from Table 29, Page 102-103 of the ADAR
Abbreviations: AF = atrial fibrillation; AS = aortic stenosis; CEP = cerebral protection device; CV = cardiovascular; DB = double-blind; DD = double dummy; DOAC = direct oral anticoagulant; MC = multicentre; MI = myocardial infarction; NVAF = non-valvular atrial fibrillation; OL = open label (unblinded); SAVR = surgical aortic valve replacement; SB = single-blind; SC = single centre; STS = Society of Thoracic Surgeons; TAVI = transcatheter aortic valve implantation; TOE = transesophageal echocardiography; TIA = transient ischaemic attack; TMVI = transcatheter mitral valve repair; USA = United States of America.

LAAC versus DOAC

Nine patients implanted with LAAC experienced a procedural / device related complication, with a total incidence of 4.5% within 30 days in the PRAGUE-17 trial (Table 6).

Table 6 Device and procedural complications with LAAC in PRAGUE-17

Study ID	Early (≤ 7 days) occurrence	Late (>7 days) occurrence	Total
Pericardial effusion	0	2[a]	2
Device embolization	1[b]	0	1
Device-related death	0	1[c]	1
Procedure-related death	1[d]	0	1
Vascular complications	2[e]	0	2
Other complications	0	2[f]	2
Total	4/201 (2.0)	5/201 (2.5)	9/201 (4.5)

Source: Table 36, p123 of the ADAR based on PRAGUE-17, Osmancik 2020 table 4.

a. Late pericardial effusions occurred at 89 and 194 days after implantation with the Amulet device. One was treated with pericardiocentesis and the other conservatively; both patients had good outcomes.
b. Acute device embolization during the procedure, requiring surgical removal.
c. A groin bleed occurred that required vascular surgery, in turn complicated by a large myocardial infarction with unsuccessful resuscitation.
d. Device-related pericardial tamponade.
e. One femoral pseudoaneurysm and one large groin hematoma, both treated with vascular surgery
f. One device malposition at the left inferior pulmonary vein, with successful removal and reimplantation. One large device-related thrombus was diagnosed by TOE imaging 113 days after implantation. The thrombus was considered potentially malignant (although no embolic event had occurred), so surgical removal was successfully performed.

In the PRAGUE-17 trial, the bleeding rates were similar between the LAAC (10.9%) and DOAC (9.0%) arms during a mean follow up of 21.1 months and 19.3 months, respectively (Table 7). However, the ADAR noted that when procedure-related bleeding events were excluded, the incidence of major/non-major clinically relevant bleeding in the LAAC arm was lower relative to the DOAC arm (6.0% versus 10.9%, respectively). The ADAR claimed this trend showed a 48% reduction in the odds of experiencing major/non-major clinically relevant bleeding with LAAC relative to DOAC with the confidence interval marginally crossing one (OR [95% CI]: 0.52 [0.25, 1.07]). The ADAR suggested that, with continued follow up of patients in PRAGUE-17, the difference in bleeding would reach statistical significance in favour of LAAC, given the divergence of lines in the Kaplan Meier curve.

Table 7 Clinically significant major / non-major bleeding (defined based on ISTH criteria): PRAGUE-17

Outcome	LAAC			NOAC			RD [95% CI]; p value	sHR [95% CI]; p value
	n/N (%)	Events	Event rate/yr	n/N (%)	Events	Event rate/yr		
Clinically significant major/non-major bleeding	18/201 (9.0)	19 (major, 13; non-major, 6)	5.5	22/201 (10.9)	26 (major, 14, non-major, 12)	7.42	-0.02 [-0.08, 0.04]; p=0.50	0.81 [0.44–1.52]; NR
Clinically significant major/non-major bleeding – not related to device	12/201 (6.0)	13	3.76	22/201 (10.9)	26	7.42	-0.05 [-0.10, 0.00]; p=0.07	0.53 [0.26–1.06]; NR

Source: Table 38, p63 of the commentary

Abbreviations: CI = confidence interval; RD = risk difference; sHR = subdistribution Hazard Ratio.

The ADAR claimed the results from the ITC of LAAC versus DOACs, via warfarin supported the claim of superior safety in favour of LAAC. The ADAR claimed the results demonstrated statistically significant differences in favour of LAAC relative to DOAC with respect to major bleeding and major GI bleeding, when considering bleeding events occurring

> 7 days after the LAAC procedure. The ADAR also noted the treatment effect observed in favour of LAAC was similar in the direct (0.52) and ITC (0.54).

The commentary noted uncertainty with only considering major bleeding after the procedure and noted that if bleeding events related to the procedure and other procedure-related complications were considered, the safety of LAAC relative to DOAC may be considered non-inferior based on the current evidence base. Due to differences in the risks associated with LAAC and DOAC, the commentary considered it challenging to draw safety conclusions.

LAAC versus warfarin
With respect to safety, there was no statistically significant difference in the proportions of subjects experiencing a major bleeding event in subjects treated with LAAC compared to warfarin (OR [95% CI]: 0.87 [0.60, 1.27]; p=0.47). There was no significant heterogeneity in this analysis. However, in the post-procedure analysis (excluding events occurring within the first 7 days of the procedure), the ADAR reported that LAAC was associated with significantly fewer bleeding events relative to warfarin (OR [95% CI]: 0.46 [0.30, 0.70]; p=0.0003). A pooled analysis of PROTECT-AF and PREVAIL of bleeding outcomes including individual patient level data indicated that the reduced risk of gastrointestinal bleeding in the LAAC group relative to those treated with warfarin was the main driver of the difference in post-procedural major bleeding events.

The ADAR's meta-analysis indicated LAAC to be superior to warfarin on the basis of a statistically significant reduction in major bleeding events and major GI bleeding events relative to DOAC, when considering events occurring > 7 days post procedure (6.6% vs 13.1%; and 4.1% vs 7.9% respectively). On this basis, the ADAR suggested that in the longer-term, LAAC is the superior treatment option relative to warfarin, on the basis of preventing bleeding events.

The commentary considered there to be some uncertainty around the superior safety claim. The commentary noted that there is low quality evidence showing that LAAC is superior to warfarin on the basis of a statistically significant reduction in major bleeding events and major GI bleeding events. However, the evidence for the conclusion of superior safety of LAAC versus warfarin was downgraded due to low certainty, predominantly due to the populations in the evidence base not reflecting patients with relative contraindication to anticoagulation.

11. Comparative effectiveness

Population 1
Unchanged, as per MSAC 1374.1 PSD.

Population 2
LAAC versus DOAC

In terms of all stroke, in the PRAGUE-17 trial, eight (4.0%) and seven (3.5%) LAAC and DOAC patients experienced a stroke during the follow up of the study (OR: 1.15; 95% CI: 0.41, 3.23; p=0.79), none of which were procedure related, supporting non-inferiority. The results from the ITC of LAAC versus DOACs, via warfarin indicated no difference in prevention of any stroke, when all events are considered with and without PREVAIL (OR: [95% CI]; 1.09 [0.48, 2.48]; and 0.78 [0.4, 1.5], respectively) and when considering post-procedure events only with and without PREVAIL (0.97 [0.33, 2.86]; and 0.59 [0.3, 1.17], respectively).

With respect to ischaemic stroke, the results from the ITC indicated no statistically significant differences were observed between LAAC and DOAC patients, suggesting there are no differences between LAAC and DOAC with respect to long term risk of ischaemic stroke.

In terms of haemorrhagic stroke, in the PRAGUE-17 trial, a treatment benefit was observed in favour of LAAC with respect to haemorrhagic stroke, with LAAC associated with a 67% reduction in the odds of experiencing a haemorrhagic stroke compared with DOAC (OR [95% CI]: 0.33 [0.01 to 8.19]). However, the number of events were few, making the results difficult to interpret. The ITC similarly demonstrated a protective benefit with respect to haemorrhagic stroke with LAAC relative to DOAC, at a similar magnitude of effect. The analysis including only PROTECT-AF produced results that were borderline statistically significantly in favour of LAAC (OR: [95% CI]; 0.22 [0.05, 1.02]; p=0.05). When including PREVAIL the confidence interval crossed one to a greater extent (OR: [95% CI]; 0.37 (0.11, 1.27); p=0.1). That is, LAAC is nominally superior to DOACs with respect to haemorrhagic stroke.

In terms of cardiovascular (CV) mortality, there was no statistically significant difference in rates between groups in the PRAGUE-17 trial (subdistribution hazard ratio [sHR]: 0.75; 95% CI:0.34, 1.62), with the treatment effect numerically in favour of LAAC. The results from the ITC showed that LAAC is statistically superior with respect to post-procedural CV mortality when only PROTECT-AF is included (OR: [95% CI]; 0.46 [0.24, 0.88]; p= 0.0198). When both trials are included, the upper bound of confidence interval marginally exceeds one (0.79 [0.56, 1.11; p=0.17]. As the magnitude of effect from the ITC (OR=0.46–0.79) and the PRAGUE-17 study (OR=0.75) were similar, the ADAR claimed this suggested a treatment benefit in favour of LAAC with respect to CV death.

The commentary noted that there was no difference in all stroke, ischaemic stroke, all-cause mortality, and systemic embolism between LAAC and DOAC as such the claim of non-inferior effectiveness may be reasonable. Although the ADAR stated that there were some advantages of LAAC over DOAC with respect to haemorrhagic stroke and CV mortality, the commentary noted that this conclusion was drawn largely from the ITC. Although the ADAR suggested that PRAGUE-17 trial showed a treatment benefit with LAAC for reduction of haemorrhagic stroke, the commentary noted that as there was only a single haemorrhagic event across the two study arms (in the warfarin group) as such, no conclusions of treatment effectiveness can be made from this study.

The balance of clinical benefits and harms of LAAC compared with DOACs, (direct) and via warfarin ITC are presented in Table 8 and Table 9 respectively.

Table 8 Balance of clinical benefits and harms of LAAC, relative to DOAC, and as measured by the critical patient-relevant outcomes in the key studies: PRAGUE-17

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE)a	OR (95%CI)	Risk with DOAC	Risk with LAAC	Comments
All stroke	402 (1 RCT)	⊕⊕⊕⊙	OR 1.15 (0.41 to 3.20)	35 per 1,000	40 per 1,000 (15 to 104)	LAAC likely results in little to no difference in all stroke when considering all events.
All stroke - Post-procedure analysis	402 (1 RCT)	⊕⊕⊕⊙	OR 1.15 (0.41 to 3.20)	35 per 1,000	40 per 1,000 (15 to 104)	LAAC likely results in little to no difference in all stroke - Post-procedure analysis.
Ischemic stroke	402 (1 RCT)	⊕⊕⊕⊙	OR 1.35 (0.46 to 3.96)	30 per 1,000	40 per 1,000 (14 to 109)	LAAC likely results in little to no difference in ischaemic stroke when considering all events.
Ischemic stroke – post procedure analysis	402 (1 RCT)	⊕⊕⊕⊙	OR 1.35 (0.46 to 3.96)	30 per 1,000	40 per 1,000 (14 to 109)	LAAC likely results in little to no difference in ischaemic stroke - Post-procedure analysis
Haemorrhagic stroke	402 (1 RCT)	⊕⊕⊕⊙	OR 0.33 (0.01 to 8.19)	30 per 1,000	40 per 1,000 (14 to 109)	~~Numerical difference in favour of LAAC; yet wide CIs, due to few events.~~ *LAAC likely results in little to no difference in haemorrhagic stroke*
CV mortality	402 (1 RCT)	⊕⊕⊕⊙	OR 0.72 (0.32 to 1.60) sHR 0.75 (0.34, 1.62)	75 per 1,000	55 per 1,000 (25 to 114)	~~LAAC probably reduces cardiovascular mortality slightly.~~ *LAAC likely results in little to no difference in CV mortality*
MNMCRB – All events	402 (1 RCT)	⊕⊕⊕⊙	OR 0.80 (0.42 to 1.54) sHR 0.81 (0.44, 1.52);	109 per 1,000	90 per 1,000 (49 to 159)	~~LAAC likely reduces major/non-major clinically relevant bleeding slightly.~~ *LAAC likely results in little to no difference in MNCRB when all events are considered*
MNMCRB - Excluding procedure-related events	402 (1 RCT)	⊕⊕⊕⊙	OR 0.52 (0.25 to 1.07) sHR 0.53 (0.26, 1.06)	109 per 1,000	60 per 1,000 (30 to 116)	LAAC likely reduces major/non-major clinically relevant bleeding when excluding procedure-related events.

Source: Table 2, p26-27 of the ADAR with commentary in *italics*
Abbreviations: CI = confidence interval; MNMCRB = major/non-major clinically relevant bleeding; CV = cardiovascular; DOAC = direct oral anticoagulant LAAC = left atrial appendage closure; NR = not reported; OR = odds ratio; RCT = randomised controlled trial; sHR = subdistribution hazard ratio.

[a] GRADE Working Group grades of evidence (Guyatt et al., 2013); ⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 9 Balance of clinical benefits and harms of LAAC, relative to DOAC via warfarin ITC, and as measured by the critical patient-relevant outcomes in the key studies

Outcomes (units) Follow-up	**Participants (studies)**	**Quality of evidence (GRADE)[a]**	**LAAC vs warfarin OR (95%CI)** OR < 1 favours LAAC	**DOAC vs warfarin OR (95%CI)** OR < 1 favours DOAC	**IEE: OR (95%CI)** OR < 1 favours LAAC	**Comments**
All stroke	ITC of LAAC vs warfarin k=2; N=1114 / DOAC vs warfarin k=4; N=51,731	⊕⊙⊙⊙[b] VERY LOW	0.94 (0.43, 2.06) PROTECT-AF only: 0.67 (0.36, 1.22)	0.86 (0.68, 1.09)	1.09 (0.48, 2.48) PROTECT-AF only: 0.78 (0.4, 1.5)	No significant difference. Numerical difference in favour of LAAC in the analysis including only PROTECT-AF
All stroke – post procedural	ITC of LAAC vs warfarin k=2; N=1114 / DOAC vs warfarin k=4; N=51,731	⊕⊙⊙⊙[b] VERY LOW	0.83 (0.29, 2.42) PROTECT-AF only: 0.51 (0.27, 0.96)	0.86 (0.68, 1.09)	0.97 (0.33, 2.86) PROTECT-AF only: 0.59 (0.3, 1.17)	No significant difference. Numerical difference in favour of LAAC in the analysis including only PROTECT-AF
Ischaemic stroke	ITC of LAAC vs warfarin k=2; N=1114 / DOAC vs warfarin k=4; N=51,731	⊕⊕⊙⊙[c] LOW	1.56 (0.84, 2.92) PROTECT-AF only: 1.28 (0.6, 2.72)	0.91 (0.8, 1.04)	1.71 (0.91, 3.24) PROTECT-AF only: 1.41 (0.66, 3.02)	No significant difference, whether PREVAIL is included or excluded
Ischaemic stroke – post procedural	ITC of LAAC vs warfarin k=2; N=1114 / DOAC vs warfarin k=4; N= N=51,731	⊕⊕⊙⊙[c] LOW	1.34 (0.58, 3.09) PROTECT-AF only: 0.95 (0.43, 2.08)	0.91 (0.8, 1.04)	1.47 (0.63, 3.43) PROTECT-AF only: 1.04 (0.47, 2.32)	No significant difference, whether PREVAIL is included or excluded; OR when excluded close to 1.
Haemorrhagic stroke	ITC of LAAC vs warfarin k=2; N=1114 / DOAC vs warfarin k=4; N=51,731	⊕⊕⊙⊙[d] LOW	0.17 (0.05, 0.54) PROTECT-AF only: 0.1 (0.02, 0.47)	0.46 (0.32, 0.66)	0.37 (0.11, 1.27) PROTECT-AF only: 0.22 (0.05, 1.02)	No significant difference, when PREVAIL is included, when excluded the approaching significance (p=0.05). LAAC likely results in a reduction in haemorrhagic stroke.
CV mortality	ITC of LAAC vs warfarin k=2; N=1114 / DOAC vs warfarin k=4; N=51,759	⊕⊕⊙⊙[c] LOW	0.64 (0.25, 1.68) PROTECT-AF only: 0.51 (0.26, 0.98)	0.9 (0.83, 0.98)	0.71 (0.27, 1.85) PROTECT-AF only: 0.57 (0.29, 1.11)	No significant difference, whether PREVAIL is included or excluded; OR in favour of LAAC
CV mortality – post procedural	ITC of LAAC vs warfarin k=2; N=1114 / DOAC vs warfarin k=4; N=51,759	⊕⊕⊙⊙[c] LOW	0.71 (0.51, 0.99) PROTECT-AF only: 0.41 (0.21, 0.78)	0.9 (0.84, 0.96)	0.79 (0.56, 1.11) PROTECT-AF only: 0.46 (0.24, 0.88)	No significant difference when PREVAIL is included, a statistically significant difference in favour of LAAC when excluded. LAAC likely results in a reduction in CV mortality.

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE)[a]	LAAC vs warfarin OR (95%CI) OR < 1 favours LAAC	DOAC vs warfarin OR (95%CI) OR < 1 favours DOAC	IEE: OR (95%CI) OR < 1 favours LAAC	Comments
Major bleeding	ITC of LAAC vs warfarin k=2; N=1114 / DOAC vs warfarin k=4; N=51,767	⊕⊙⊙⊙[b] VERY LOW	0.87 (0.6, 1.27) PROTECT-AF only: 0.9 (0.55, 1.46)	0.85 (0.7, 1.03)	1.02 (0.67, 1.56) PROTECT-AF only: 1.06 (0.63, 1.79)	No significant difference whether PREVAIL is included or not
Major bleeding – post procedural	ITC of LAAC vs warfarin k=2; N=1114 / DOAC vs warfarin k=4; N=51,767	⊕⊙⊙⊙[e] VERY LOW	0.46 (0.3, 0.7) PROTECT-AF only: 0.41 (0.23, 0.71)	0.85 (0.7, 1.03)	0.54 (0.34, 0.86) PROTECT-AF only: 0.48 (0.27, 0.88)	Statistically significant difference in favour of LAAC. LAAC is likely to reduce major bleeding events vs DOAC over the longer term.

Source: Table, 3, pg 27-28 of the ADAR
Abbreviations: AF = atrial fibrillation; CI = confidence interval; CV = cardiovascular; DOAC = direct oral anticoagulant; IEE = indirect estimate of effect; ITC = indirect treatment comparison; k = number of studies; LAAC = left atrial appendage closure; N = number of participants; NR =not reported; OR = odds ratio; RCT = randomised controlled trial; sHR = subdistribution hazard ratio.

[a]GRADE Working Group grades of evidence (Guyatt et al., 2013); ⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.;
[b] On the basis of ITC of two sets of data of LOW quality, graded down from LOW to VERY LOW for indirectness;
[c] On the basis of ITC of two sets of data, of which one is LOW quality and one is MODERATE quality, where the MODERATE quality dataset was derived from the largest body of evidence; graded down from MODERARE to LOW for indirectness;
[d] On the basis of ITC of two sets of data of MODERATE quality, graded down from MODERATE to LOW for indirectness;
[e] On the basis of ITC of two sets of data, of which one is LOW quality and one is MODERATE quality, where the MODERATE quality dataset was derived from the smaller body of evidence; graded down from LOW to VERY LOW for indirectness;

LAAC versus warfarin

The ADAR reported that the results from the meta-analysis demonstrated LAAC to be non-inferior to warfarin with respect to stroke when including all events (OR [95% CI]: 0.94 [0.43 to 2.06] and when only considering post-procedure events. (0.83 [0.29 to 2.42]). Similarly, the analysis of ischaemic stroke demonstrated non-inferiority, although the warfarin arm of PREVAIL is considered an anomaly in that the stroke rate was significantly lower than predicted based on the risk score, thus influencing the meta-analysis.

With respect to haemorrhagic stroke, a statistically significant difference was observed in favour of LAAC relative to warfarin (OR [95% CI]: 0.17 [0.05 to 0.54]), showing that LAAC was associated with an 83% reduction in the odds of experiencing a haemorrhagic stroke compared with warfarin. In the meta-analysis of LAAC versus warfarin for CV/unexplained mortality, there were no statistically significant difference observed between LAAC and warfarin in the analysis including all events and in the post-procedure analysis, however, both analyses numerically favoured LAAC (OR [95% CI]: 0.66 [0.27, 1.63]; p=0.37; and 0.64 [0.25, 1.68]; p=0.37, respectively). A significant difference in favour of LAAC relative to warfarin was observed with respect to all-cause mortality.

The commentary noted that LAAC also appeared to be superior in reducing the rates of haemorrhagic stroke and all-cause mortality relative to warfarin, and as such the claim that, relative to warfarin, LAAC has superior safety on the bases of haemorrhagic stroke may be

reasonable. However, the evidence for the conclusion of superior efficacy of LAAC versus warfarin was downgraded due to low certainty, predominantly due to the populations in the evidence base not reflecting patients with relative contraindication to anticoagulation.

Clinical claim

Population 1
Unchanged, as per MSAC 1374.1 PSD.

Population 2
The ADAR claimed that:

- relative to DOAC, LAAC has superior safety with respect to bleeding and non-inferior effectiveness, noting some advantages with LAAC with respect to haemorrhagic stroke and CV mortality.
- relative to warfarin, LAAC has superior safety on the basis of major bleeding events and superior effectiveness on the basis of haemorrhagic stroke.

12. Economic evaluation

Population 1
Unchanged, as per MSAC 1374.1 PSD.

Population 2
A cost-utility analysis was presented to estimate the expected costs and health outcomes associated with LAAC implantation compared to DOACs in patients with NVAF who have an increased risk of thromboembolism (CHA2DS2-VA score of ≥ 2) and with a relative contraindication to anticoagulation (Table 11). Warfarin was tested in a sensitivity analysis using the same structure as per the DOAC mode.

Table 10 Summary of the economic evaluation

Perspective	Healthcare system
Comparator	DOACs (primary), warfarin (secondary)
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Trial based (PRAGUE-17, ARISTOTLE, ROCKET, see Section C.2) Literature based (see Section C. 4-7 for details) PBS scripts analysis (see Section C.3)
Time horizon	Lifetime
Outcomes	Quality-adjusted life years
Methods used to generate results	Markov cohort
Health states	LAAC, no stroke, no major bleeding LAAC, no stroke, major bleeding LAAC, non-disabling stroke, no major bleeding LAAC, non-disabling stroke, major bleeding LAAC, disabling stroke, no major bleeding LAAC, disabling stroke, major bleeding DOAC, no stroke, no major bleeding DOAC, no stroke, major bleeding DOAC, non-disabling stroke, no major bleeding DOAC, non-disabling stroke, major bleeding DOAC, disabling stroke, no major bleeding DOAC, disabling stroke, major bleeding SOC, no stroke, no major bleeding SOC, no stroke, major bleeding SOC, non-disabling stroke, no major bleeding SOC, non-disabling stroke, major bleeding SOC, disabling stroke, no major bleeding SOC, disabling stroke, major bleeding Death
Cycle length	1 year
Discount rate	5%
Software packages used	TreeAge

Source: Table 7, pXXIII of the commentary
Abbreviations: DOAC = direct oral anticoagulants; PBS = Pharmaceutical Benefits Scheme; LAAC,= left atrial appendage closure; SOC = standard of Care

The commentary considered that the ADAR appropriately demonstrated that the PRAGUE-17 trial was applicable to the Australian setting; and that the structure of the model for economic evaluation was appropriate and reflected the treatment algorithm used for the intervention. The time horizon of the model is lifetime from 73 years of age, which roughly ends after 40 years with an annual cycle length. The commentary considered this appropriate noting the cycle length and time horizon of the model reflects the natural history of the medical condition post treatment with intervention and comparator, and is long enough to capture important clinical events.

The model assumes the distribution of stroke disability and fatality for LAAC and DOAC patients are equal. The commentary considered this assumption to be valid as the only demonstrated difference between DOACs and LAAC in the ADAR was major bleeding after 7 days.

The baseline patient characteristics, treatment efficacy of LAAC versus DOACs, baseline stroke and major bleeding rates, and proportion of patients that initiate LAAC versus SoC

after a major bleeding event, were derived from the PRAGUE-17 trial. The proportion of strokes resulting in disability or fatality were derived from pooled ARISTOTLE and ROCKET data. Other clinical and economic inputs in the model, including 'real-world' DOAC compliance derived from PBS scripts analysis, treatment efficacy of SOC/PBO relative to LAAC and DOACs, extrapolation of event rates, utility values and cost inputs, were derived from the literature.

The commentary highlighted several limitations of the ADAR's model. The treatment efficacy of standard of care/placebo (SOC/PBO) relative to LAAC and DOACs was based on a review of the ITC of LAAC and SOC/PBO. The relative risk (RR) of SOC/PBO versus DOAC/LAAC in terms of major bleeding was assumed to be equal to LAAC and the model applied a hazard ratio (HR) of 3.45 (Arauz 2017)[3]. The commentary noted that while the risk of bleeding decreases over time, this risk is distinctly different in the treatment and post-treatment phases, with the risk (possibly) roughly double in the LAAC arm during the procedure phase. The differences in interventions are clinically advantageous to the patient by either avoiding surgery (DOACs) and the potential harms of surgery, or by mitigating non-compliance to therapies (LAAC) as LAAC is a "one-off" treatment. However, the ADAR quantified non-compliance but not surgical related outcomes. Therefore, biases any modelled outcome in favour of LAAC.

The relative treatment effect of LAAC versus DOACs for clinically significant major/non-major bleeding – not related to device (sHR=0.53) reported in PRAGUE-17 was applied in the economic model. The commentary noted that while the sHR for clinically significant major/non-major bleeding not related to the device was 0.53, the overall odds ratio (OR) for major bleeding was 1.02 (0.67-1.56). Assuming the OR is similar to the RR, the OR for procedural bleeding may be approximately 1.51 [(1.51+0.53)/2 = 1.03], or approximately 50% greater in the LAAC arm, and this increase in procedural bleeding has not been considered. Although this additional risk is only attributed in the first 7 days, and the impact of post-procedural bleeding may be greater than procedural bleeding, this increased risk suggests the model may overestimate the benefit of LAAC.

Further, while the rates of procedural bleeding were not considered in the economic model, the ADAR estimated cost of procedural bleeding was included in the model and therefore may overestimate the incremental benefit of LAAC. While the impact of procedural bleeding may be marginal, the impact may be significant if the incremental difference in benefit is small.

A utility value of 0.998 for the 'No stroke' health state, derived from the Gage et al 1996[4] study was applied in the model. The model assumed that 32% of patients had a history of stroke (based on the baseline patient characteristics in the PRAGUE-17 trial) and therefore, the baseline utility value for 'No stroke' was adjusted to 0.918 (0.998*0.68 +0.75*0.32). The commentary noted that based on the Australian population norms on health-related quality of life by Norman (2013)[5], the mean SF-6D utility value in the age group of 71 years and above is 0.703 (SD 0.129). The commentary considered the utility value of 0.998 to be too high and unreasonable as the baseline age in the model is 73 years with an indication of NVAF. The commentary considered that this would overestimate the health outcomes of patients in the 'No stroke, no bleed' and 'No stroke, bleed' health state.

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[3] Arauz et al. (2017) *Journal of Vascular and Interventional Neurology*. 9(6):5
[4] Gage et al. (1996) *Archives of internal medicine*. 156:1829
[5] Norman et al. (2013) *Australian and New Zealand journal of public health*. 37(1):17

LAAC versus DOACs

The overall costs and outcomes, and incremental costs and outcomes as calculated for LAAC and DOACs, using the base case assumptions are presented in Table 11. The commentary presented revised calculations that incorporated correction of the costs and utility inputs. The cost for LAAC increased to $**REDACTED** and cost of DOACs increased to $**REDACTED**. When the utility values were revised (ADAR utility value multiplied by 0.703 from Norman 2013), the QALYs reduced to **REDACTED** and **REDACTED** for LAAC and DOACs, respectively. Based on the revised inputs, the ICER changed from $**REDACTED** to $**REDACTED** (Table 11).

Table 11 Incremental cost-effectiveness for LAAC versus DOACs

Outcome	LAAC	DOACs	Incremental
Base case			
Costs	$**REDACTED**	$**REDACTED**	$**REDACTED**
QALYs	**REDACTED**	**REDACTED**	**REDACTED**
ICER			**REDACTED**
Commentary revised base case			
Costs	$**REDACTED**	$**REDACTED**	$**REDACTED**
QALYs	**REDACTED**	**REDACTED**	**REDACTED**
ICER			**REDACTED**

Source: Adapted from Table 128, p228 of the ADAR and Table 83, p145 of the commentary
Abbreviations: DOAC = direct oral anticoagulants; ICER = incremental cost effectiveness ratio; LAAC = left atrial appendage closure; QALYs = quality adjusted life years.

The ADAR presented several one-way sensitivity analyses as well as two-way sensitivity analysis. The key drivers of the model for LAAC versus DOACs, based on the ADAR sensitivity analyses, are presented in Table 12. However, the commentary noted that the applicant may wish to provide updated sensitivity analyses based on the revised inputs (LAAC procedure costs and utility values).

Table 12 Key drivers of the economic model (LAAC versus DOACs)

Parameter	Impact
Costs	The cost of disease related events in the model including major bleeding and stroke, and the cost of treatments were increased and decreased by 50% respectively. The univariate analyses did not exceed an ICER of $**REDACTED**
Population and model time horizon	Reducing the time horizon of the economic model to 5 ($**REDACTED**) and 10 ($**REDACTED**) years had the largest impact on cost-effective ness of all univariate analyses.
Major Bleeding	Univariate analyses measured the impact of altering the overall probability of bleeding events, applying age and prior bleeding as a risk factor in the model, the RR of major bleeding events between LAAC/SoC and DOAC (HR=1 in sensitivity) and the probability of fatal bleeding. The univariate analyses did not exceed an ICER of $ **REDACTED**.
DOAC Compliance	Univariate analysis measured the effect of assuming DOAC adherence of 100% medication persistence ratio (MPR). Applying 100% adherence to the DOAC arm had little effect on the ICER ($**REDACTED**).
Stroke	The univariate analyses measured the impact of applying age as a risk factor for disabling and fatal stroke outcome in the model, altering the overall probability of stroke events, applying a constant probability of stroke based on PRAGUE-17 and altering the relative treatment effect of SoC versus LAAC and DOACs. This analysis resulted in an ICER of $ **REDACTED**
Utilities	The disutility of stroke and a major bleeding events were altered and resulted in ICERs that did not exceed $**REDACTED**.

Source: Table 6, p31 of the ADAR.
Abbreviations: DOAC = direct oral anticoagulant; ICER = incremental cost effectiveness ratio; LAAC = left atrial appendage closure; SoC = standard of care.

LAAC versus warfarin

The cost-effectiveness of warfarin was tested in a sensitivity analysis using the same structure as per the DOAC model. The commentary's revised utility estimates resulted in a change in the QALYs for LAAC and warfarin. Based on the revised estimates, LAAC generates **REDACTED** QALYs and warfarin generates **REDACTED** QALYs with an incremental gain of **REDACTED** for LAAC. The incremental QALY gains with LAAC reduced based on the revised inputs.

Based on the revised cost and utility inputs, the results of incremental cost-effectiveness are provided in Table 13. The ICER changed from $**REDACTED** to $**REDACTED**.

Table 13 Revised incremental cost-effectiveness for LAAC versus warfarin

Outcome	LAAC	warfarin	Incremental
Costs	**$REDACTED**	**$REDACTED**	**$REDACTED**
QALYs	**REDACTED**	**REDACTED**	**REDACTED**
ICER			**$REDACTED**

Source: Table 10, pXXV of the commentary
Abbreviations: LAAC = left atrial appendage closure; QALYs = quality adjusted life years; ICER = incremental cost effectiveness ratio

The pre-MSAC response stated that economic model applied a 2.23% risk of procedural bleeding for all patients implanted with an LAAC device. After this initial procedural risk, patients in both arms of the model are exposed to a continued risk of bleeding (LAAC at a placebo rate of 3.93% per annum and NOAC at a higher rate of 7.42% based on the hazard ration of 0.53). The pre-MSAC response also presented a revised economic analysis in which the base case was revised using utility values weighted to the Australian population as requested by ESC (Table 14), along with additional sensitivity analyses testing the assumed rates of bleeding and stroke along with a range of utility values (Table 15).

Table 14 Revised pre-MSAC base case for the economic evaluation

Model Inputs	ICER
ADAR Base Case *(Total cost of LAAC: $21,900.45; Health state utility values: No stroke=0.998, Non-disabling stroke=0.75, Disabling stroke=0.39; Rates of disabling stroke in NOAC/LAAC arm: 23/75)*	**$REDACTED**
Pre-ESC response's Revised Base Case (Total cost of LAAC: $23,171; Health state utility values: No stroke=0.998, Non-disabling stroke=0.75, Disabling stroke=0.39; Rates of disabling stroke in NOAC/LAAC arm: 0.23)	**$REDACTED**
Pre-MSAC response's Revised Base Case *(Total cost of LAAC: $23,171; Health state utility values: No stroke = 0.86826; Non-disabling stroke= 0.6525; Disabling stroke= 0.3393; Rates of disabling stroke in NOAC/LAAC arm: 0.23)*	**$REDACTED**

Source: Table 1, p6 of the pre-MSAC response

Table 15 Pre-MSAC revised base case - sensitivity analyses requested by ESC

Parameter/ Base case value	Sensitivity	ICER
Base Case		**$REDACTED**
Relative risk of post-procedural major bleeding LAAC/SOC versus NOACs		
Relative treatment effect LAAC versus NOACs = HR 0.53 (PRAGUE-17- clinically significant bleeding (excluding procedural related bleeding) endpoint)	Lower 95% CI reported in PRAGUE-17: RR = 0.26	**$REDACTED**
	Upper 95% CI reported in PRAGUE-17: RR = 1.06	**$REDACTED**
Relative risk of stroke LAAC versus NOACs		
Relative treatment effect LAAC versus NOACs = 1 based on claim of non-inferior efficacy	Lower 95% CI (RR) based on All stroke ITC (PROTECT-AF only); RR = 0.438	**$REDACTED**
	Lower 95% CI (RR) based on All stroke ITC (PROTECT-AF + PREVAIL); RR = 0.507	**$REDACTED**
	Decrease RR of stroke in LAAC arm by 20%; RR = 0.8	**$REDACTED**
	Increase RR of stroke in LAAC arm by 20%; RR = 1.2	**$REDACTED**
	Upper 95% CI (RR) based on All stroke ITC (PROTECT-AF only); RR = 1.469	**$REDACTED**
	Upper 95% CI (RR) based on All stroke ITC (PROTECT-AF + PREVAIL); RR = 2.358	**$REDACTED**
Disutility of stroke		
No stroke = 0.86826; Non-disabling stroke= 0.6525; Disabling stroke= 0.3393	Reduce disutility by 25%; Non-disabling = 0.678; Disabling utility = 0.443	**$REDACTED**
	Increase disutility by 25%; Non-disabling = 0.62; Disabling utility = 0.235	**$REDACTED**

Source: Table 2, p6 of the pre-MSAC response

13. Financial/budgetary impacts

The ADAR estimated the financial implications of Population 1 and Population 2 separately. The ADAR claimed that estimation of the combined financial implications of Population 1 and Population 2 is not necessarily the sum of the two separate estimates claiming there is likely to be overlap between the two patient populations due to patient co-morbidity.

The commentary noted there appeared to be an interdependency between the two populations and their financial implications analyses, however the extent of this was unclear. Therefore, it was unclear what the total combined financial implications for both proposed revisions would be.

Population 1
A mixed market share and epidemiological approach has been used to estimate the financial implications of modifying the definition of contraindication to lifelong anticoagulation to expand the list of absolute contraindications to anticoagulation (Population 1) and thereby expanding the patient population eligible for MBS item 38276, summarised in Table 16.

The ADAR estimated the per patient cost to the MBS for the procedure as $1,843.35, and that an additional **REDACTED** patients in the first year, increasing to **REDACTED** patients by year five, and assumed DOAC treatment would not be used after a patient experienced an absolute contraindication. The estimated financial impact was $**REDACTED** in year one, increasing to $ **REDACTED** in year five.

The commentary considered the approach used to estimate additional patients was plausible. However, the commentary considered that the MBS cost of the LAAC procedure was underestimated; accounting for estimated procedural resource utilisation saw this revised upwards to $**REDACTED**. The commentary noted that revision to correct calculation errors

resulted in the annual MBS costs increasing from $**REDACTED** in year one to $**REDACTED** in year five, resulting in the five-year MBS impact being revised from $**REDACTED** to $**REDACTED** (Table 16).

Table 16 Financial implications for the government health budget for the proposed expansion of the list of absolute contraindications to anticoagulation for LAAC (Population 1)

Parameter	Year 1 (2021)	Year 2 (2021)	Year 3 (2023)	Year 4 (2024)	Year 5 (2025)	Source/ Calculation
Additional LAAC procedures reimbursed on the MBS	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	Table 16
Total cost to the MBS	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	Table 15.
Total cost to the PBS	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	Table 15.
Total cost to the Australian Government	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	Table 15.
Total cost to private health funds	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	Table 15

Source: Table 17, p34 of the ADAR Attachment 1 with commentary in *italics*
Abbreviations: LAAC = left appendage atrial closure; MBS, Medical Benefits Schedule; PBS = Pharmaceutical Benefits Scheme
Note:
1. Original table had six years of estimates. The table above represents the relevant excerpt of the first five years.
2. Table sources refer to ADAR Attachment 1.

Population 2

An epidemiological approach was used to estimate the financial implications of modifying the definition of contraindication to lifelong anticoagulation to include relative contraindications to anticoagulation (Population 2) and thereby expanding the patient population eligible for MBS item 38276, are summarised in Table 15.

The ADAR provided an estimated MBS cost of service for the LAAC procedure of $**REDACTED**, with accumulated PBS cost offsets (over the five-year analysis period) of at minimum $**REDACTED**. The ADAR estimated the inclusion of relative contraindications for LAAC would result in an estimated additional **REDACTED** patients in the first year, increasing to **REDACTED** patients by year five. The estimated financial impact is $**REDACTED** in year one, increasing to $**REDACTED** in year five.

The commentary noted that after accounting for minor revisions to assumed patient eligibility rates, assumed mortality and calculation errors, this resulted in a revised estimate of **REDACTED** patients forecast in year one, increasing to **REDACTED** patients by year five. The commentary also considered that the incremental financial impact over five years was understated due to ADAR errors in calculating the assumed total MBS costs per LAAC procedure (revised upwards to $**REDACTED**). Revisions to correct the MBS costs per LAAC procedure and the estimated incremental number of LAAC resulted in the five-year MBS impact increasing from $**REDACTED** to $**REDACTED** (Table 17).

Table 17 Financial implications for the government health budget for the proposed inclusion of relative contraindications to anticoagulation for LAAC (Population 2)

Row	Parameter	Year 1 (2021)	Year 2 (2021)	Year 3 (2023)	Year 4 (2024)	Year 5 (2025)	Source/ Calculation
A	Additional LAAC procedures reimbursed on the MBS (RCI population)	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	Table 148 of the ADAR
B	Total cost to the MBS	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	A x **REDACTED**
C	Total cost to the PBS for LAAC	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	A x $**REDACTED**
D	Cost-offsets to the PBS for DOACs	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	Table 149 of the ADAR
E	Net cost to the PBS	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	C – D
F	Total cost to the Australian government	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	B - E
G	Total cost to private health funds	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	A x $**REDACTED**

Source: Table 150, p376, of the ADAR with commentary in *italics*
Abbreviations: LAAC = left atrial appendage closure; MBS = Medical Benefits Schedule; RCI = relative contraindication
Note:
1. Original table had six years of estimates. The table above represents the relevant excerpt of the first five years.

The commentary considered the financial implications estimates for both populations to be subject to uncertainty, the extent of which is unclear. The commentary recommended additional analysis should be undertaken to consider:

- The potential future burden of AF in Australia. While the ADAR acknowledges growth in AF prevalence, the exact extent may be uncertain, particularly given AF is often asymptomatic.
- The likely eligible patient populations – it is unclear what proportion of high-risk non-NVAF patients would be eligible under the respective revised eligibility criteria proposed for Populations 1 and 2 by the ADAR. For example:
    - The extent of any overlap in the proposed eligible patient populations 1 and 2 is unclear,
    - For Population 2, the estimates of the rate of bleeding events (the proposed revised eligibility criteria by the ADAR) presented in the ADAR varied considerably.
    - Further, it is unclear how the resulting proposed revision to Population 2 eligibility criteria will differ from the original proposed eligibility criteria for this population in terms of resulting patient numbers in practice.
    - The populations proposed by the ADAR have the potential to 'bring forward the market' for LAAC, as patients who would otherwise not be eligible (at least with present eligibility criteria) may now become eligible for LAAC earlier than they otherwise would, or when they otherwise may not have.
    - Current rates of LAAC uptake as a proportion of DOAC treated patients. This also makes unclear the likely incremental effects of the proposed expansions of eligibility criteria for the respective populations.

- Treatment uptake:
    - Patient referral rates – the proportion of patients who will subsequently be referred for a conference of an interventional and non-interventional physician for a decision on LAAC treatment eligibility.
    - The proportion of referred patients deemed suitable for LAAC by the physician conference.
    - Potential health care capacity, including the number of suitable treatment facilities and available physicians trained in the procedure.
    - Rates of market uptake aside from capacity. For example, ADAR analysis of population 1 assumes **REDACTED**% uptake from year one of analysis.
    - The proportion of LAAC patients having the procedure in a private hospital, or 'MBS setting'. This may be higher than that indicated by the ADAR.

The pre-MSAC response reiterated that the expanded listing for LAAC is considered to represent good value for money, as demonstrated in the cost-effectiveness analyses, and addresses an unmet clinical need. The pre-MSAC response also presented additional sensitivity analyses that indicated the total costs to the MBS over six years ranges from $**REDACTED** to $**REDACTED** million with corresponding net cost savings to the PBS ranging from $**REDACTED** to $**REDACTED** million (Table 18).

Table 18 Financial implications - sensitivity analyses requested by ESC

Parameters	Sensitivity Value	Number of LAAC procedures reimbursed on the MBS			Financial implications (expanded ACI and RCI populations): 2021 to 2026			
		Expanded ACI population	RCI population	LAAC uptake as a proportion of DOAC treated patients[a]	Additional cost to the MBS	Additional cost to the PBS for LAAC	Additional cost to private health funds	Additional cost to Australian healthcare system
Base case		**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
Eligible patient population (Base Case: ACI = **REDACTED** % of current LAAC market; RCI = **REDACTED**% eligibility rate in high risk NVAF patient population)								
Decrease eligibility rate in ACI and RCI population by 50%	ACI = **REDACTED**% RCI = **REDACTED**%	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
Increase eligibility rate in ACI and RCI population by 50%	ACI = **REDACTED**% RCI = **REDACTED**%	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
Treatment uptake (Base case: ACI = **REDACTED** % year 1-6; RCI = **REDACTED** % year 1, **REDACTED** % year 2, **REDACTED** % year 3, **REDACTED** % year 4, **REDACTED** % year 5, **REDACTED** % year 6)								
Decrease uptake rates in ACI and RCI population by 50%	ACI = **REDACTED** % year 1-6 RCI = **REDACTED** % year 1, **REDACTED** % year 2, **REDACTED** % year 3, **REDACTED** % year 4, **REDACTED** % year 5, **REDACTED** % year 6,	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
Increase uptake rates in RCI population by 50%	RCI = **REDACTED** % year 1, **REDACTED** % year 2, **REDACTED** % year 3, **REDACTED** % year 4, **REDACTED** % year 5 **REDACTED** % year 6,	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
Increase uptake rates in RCI population by 100%	RCI = **REDACTED** % year 1, **REDACTED** % year 2, **REDACTED** % year 3, **REDACTED** % year 4, **REDACTED** % year 5, **REDACTED** % year 6,	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
Overlap between ACI and RCI population (Base case presented populations separately)								
REDACTED % of ACI population double counted in RCI population	Reduce ACI patient numbers by **REDACTED** %	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**

REDACTED % of ACI population double counted in RCI population	Reduce ACI patient numbers by **REDACTED** %	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**

Source: Table 3, p7 of the pre-MSAC response

a. In these calculations LAAC procedures include all projected LAAC procedures to take place over the next six years under the current MBS listing (4,097) in addition to procedures conducted in the expanded ACI and RCI populations. The number of DOAC treated patients over the next 5 years was estimated to be 600,000 patients. This estimate is derived by factoring the prevalent NOAC treated patients reported in the 2016 DUSC review of NOAC utilisation (approx. 200,000 patients in 2015 based on 2 million scripts dispensed that year) by the annual number of scripts expected to be dispensed between 2021 and 2026 (5.3 million scripts dispensed in 202o, projected to be approximately 6 million annually between 2021 and 2026

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
"Relative contraindication" group almost impossible to define	The relative contraindication, "previous major bleeding complication" without the requirement to be experienced while undergoing treatment with anticoagulation, would be open to interpretation and poses a significant risk for the service to be used outside of the intended population.
Whether the proposed absolute contraindications are appropriate	It is unclear if the proposed contraindications are in fact an absolute contraindication that would prevent a patient from commencing or recommencing lifelong anticoagulation for stroke prevention. Targeted consultation with clinical societies is required to seek their clinical experience on how patients with these conditions are currently managed in clinical practice when they require anticoagulation for stroke prevention.
No evidence from RCT to support superior safety	The one trial (PRAGUE-17) directly comparing LAAC and DOACs demonstrated no difference in the overall bleeding risk (i.e. procedural + post-procedural bleeding rates). The applicant's clinical claim of superior safety is based on post-procedural bleeding rates only, biasing in favour of the device.
No evidence from RCT to support non-inferior efficacy	The primary outcome of the PRAGUE-17 trial was a composite outcome of safety and efficacy endpoints that was underpowered for individual efficacy endpoints.
Unknown long term safety profile	Extensive trial and clinical experience with DOACs and their adverse events profile is well understood; however, the long-term complications with LAAC devices are unknown.
Whether LAAC results in under-treatment of patients with relative contraindications	MSAC may wish to consider whether the lack of anticoagulation in patients with high CHA_2DS_2-VASc scores may put these patients at risk of other, non LAA ischaemic events.
The economic model overestimated safety of LAAC	The PRAGUE-17 trial showed no difference in the overall bleeding risk between LAAC and DOACs (i.e. combined procedural and post-procedural bleeding) however, the model did not include the procedural bleeding events (of which one bleed led to a participant death in PRAGUE-17) and applied a hazard ratio of 0.53 based on post-procedural bleeding events only. The exclusion of procedural bleeding rates creates significant uncertainty in the model
Utility values were unrealistically high	The utility values in the model were too high and were not weighted to the Australian population indicating the patient population in the model has a higher quality of life than the Australian population.
The ICER estimates are uncertain	ESC recommends the applicant revise the economic analysis to include: • the risk of procedural bleeding. • use the alternative utility values from McCaffrey 2016 ESC recommends the applicant conduct additional sensitivity analyses to: • test the 95% confidence interval of the assumed rates of bleeding and stroke • test a range of utility values.
Financial estimate uncertainty	The proposed amendments to the definition of a contraindication to anticoagulation have the potential to grow the market for LAAC procedures. However, the financial implications for the proposed changes are highly uncertain. ESC suggests the applicant revise

ESC key issue	ESC advice to MSAC
	financial estimates, which address the additional analyses recommended by the commentary, including consideration of: the likely eligible patient population and treatment uptake; the extent of any overlap between two populations; whether patient referral rates may increase; the proportion of referred patients deemed suitable for LAAC; and current rates of LAAC uptake as a proportion of DOAC treated.

ESC discussion

ESC noted that this application seeks to amend an existing MBS item 38276, for left atrial appendage closure (LAAC) for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) who have an absolute contraindication to lifelong oral anticoagulation therapy. The application proposes to expand the existing definition of absolute contraindication (Population 1) and to include relative contraindication (Population 2) to anticoagulation, thus expanding the population eligible for the service. ESC noted that the MSAC Executive had considered a budget impact analysis for Population 1 and advised that both proposed populations should progress through the full MSAC process.

ESC noted that consultation feedback from consumers was supportive of the application due to concerns that maintaining adherence to anticoagulation for stroke prevention can be difficult for patients and would provide clinicians with another option when managing the risk of clots with the risk of bleeds in these patients.

ESC noted that that the applicant reviewed the product information for direct oral anticoagulants (DOAC) to define the proposed expanded list of absolute contraindications (Population 1) to anticoagulation. ESC questioned whether some of the proposed contraindications would in fact prevent a patient from commencing or recommencing anticoagulation in clinical practice. ESC also noted that the applicant proposed to include relative contraindications (Population 2) by removing the requirement for a major bleeding event to be experienced whilst undergoing treatment with anticoagulation, thereby effectively including any previous bleeding event. ESC considered the change to a “previous major bleeding complication” without the requirement to be experienced while undergoing treatment with anticoagulation to be open to interpretation and poses a risk for the service to be used outside of the intended population. ESC considered that “relative contraindication” to anticoagulation needs to be more clearly defined. ESC advised that the Department should undertake targeted consultation with clinical societies to seek their advice on the clinical practice for managing patients with these conditions when they require anticoagulation for stroke prevention.

ESC noted that the PICO included warfarin as an alternative comparator for Population 2, but considered DOACs to be the primary informative comparator for Population 2.

ESC noted that the Applicant Developed Assessment Report (ADAR) identified only one randomised, non-inferiority trial (PRAGUE-17) that directly compared LAAC to DOACs and specifically targeted patients with NVAF. Two randomised clinical trials (RCT) comparing LAAC with warfarin and four RCT comparing DOACs with warfarin were also included in an indirect treatment comparison meta-analysis that was used to further inform safety and effectiveness of LAAC compared to DOACs.

ESC noted that the PRAGUE-17 trial primary outcome was a composite of safety and efficacy outcomes: stroke, transient ischaemic attack, systemic embolism, cardiovascular-

related death, bleeding or procedure/device-related complications. ESC queried whether combining benefits and harms in a composite endpoint creates a bias to the null. If so, then non-inferiority would be expected. ESC also noted that the device could be 47% worse than DOACs and still be considered non-inferior, due to the trial being designed with a non-inferiority margin of 1.47. ESC did not agree that the PRAGUE-17 trial had low risk of bias, noting potential selection and performance bias in the trial design, along with attrition bias with 12 patients lost to follow up in the LAAC arm compared to only 1 patient lost to follow up in the NOAC arm (due to consent).

In regards to comparative safety, ESC noted that the PRAGUE-17 trial reported nine procedural complications that included two procedural-related deaths, and 18 non-major bleeding events in the LAAC arm. In comparison, zero procedural complications and 22 non-major bleeding events were reported in the DOAC arm. ESC also noted that there is no difference in bleeding risk between LAAC and DOAC when considering combined procedural and post-procedural bleeding.

In regards to comparative efficacy, the PRAGUE-17 trail showed no difference between LAAC compared with DOACs in the prevention of stroke, systemic embolism, cardiovascular mortality and all-cause mortality. However, ESC noted that the trial was not powered to detect differences between LAAC and DOAC for individual outcomes. ESC noted that the indirect meta-analysis showed no difference between LAAC and DOACs, and had wide confidence intervals. ESC also noted that eight LAAC patients in the PRAGUE-17 trial had a stroke during follow-up, and that in the PREVAIL trial LAAC did not meet the predetermined non-inferiority endpoint due higher rates of strokes within the LAAC arm. ESC queried whether the lack of anticoagulation in patients with high CHA2DS2-VASc scores may put these patients at risk of other, non LAA ischaemic events.

ESC considered that overall, the evidence did not demonstrate that LAAC has superior safety to DOACs, and that the efficacy of LAAC compared to DOACs was uncertain as there was insufficient direct evidence.

ESC reviewed the cost-utility analysis comparing the cost-effectiveness of LAAC with DOAC in patients with NVAF with relative contraindications to anticoagulation (Population 2). ESC noted that the modelled treatment efficacy was based on stroke and post-procedural bleeding rates from the PRAGUE-17 trial.

ESC noted that although the PRAGUE-17 trial showed no difference in the overall bleeding risk between LAAC and DOACs (i.e. combined procedural and post-procedural bleeding), the model did not include the procedural bleeding events and applied a hazard ratio of 0.53 based on post-procedural bleeding events only. ESC considered that the exclusion of procedural bleeding rates created significant uncertainty in the model. ESC also noted the commentary estimated the odds ratio for procedural bleeding to be approximately 50% greater in the LAAC arm. ESC acknowledged that this additional risk is only attributed in the first 7 days, and the impact of post-procedural bleeding may be greater than procedural bleeding. However, ESC was uncertain whether any benefits in post-procedural bleeding were not offset by procedural bleeding. ESC agreed with the commentary that the exclusion of this increased risk suggests that the model may overestimate the benefit of LAAC and that any marginal gains in incremental benefit may be questionable.

ESC agreed with the commentary that the utility values for the health states should be weighted to the Australian population norms. ESC disagreed with the pre-ESC response that it was inappropriate to apply utility weights from a different normative health-related quality of life (HRQoL) instrument (i.e SF-6D) to that used in the ADAR (i.e. EQ-5D). However,

ESC noted the pre-ESC response clarified that the average utility value of the model cohort is proportional to the percentage of patients that are in the non-disabling and disabling health states over the course of the modelled time horizon. On this basis, ESC considered that while the utility values in the ADAR are too high, the utility values proposed by the commentary may be too low.

ESC noted the incremental cost-effectiveness ratios (ICERs) in the applicant's base case estimates and the commentary's revised estimates ranged from $**REDACTED to** $**REDACTED**, respectively. ESC noted the pre-ESC response provided a revised estimate assuming the same bleeding rates between LAAC and DOACs (i.e. procedure + post-procedural) which estimated the ICER to be $**REDACTED**. ESC noted that the model applied the published prices for DOACs and that when the weighted average effective price for DOACs was applied to the commentaries re-estimates the ICER increased to $**redacted**. Although, ESC noted that the ICER appears to remain within acceptable cost-effectiveness thresholds, ESC also noted the major drivers of the model, **REDACTED**, could have a significant impact on the ICER. Overall, ESC considered the ICER to be uncertain. ESC advised that the applicant should provide MSAC with revised estimates that include the risk of post-procedural bleeding and use the utility values from the alternative reference noted in the pre-ESC response (i.e. McCaffery 2016[6]), along with sensitivity analyses testing a range of utility values and the assumed rates for bleeding and stroke.

ESC noted that the applicant presented separate financial impact estimates for Population 1 and Population 2. ESC noted that for Population 1, the estimated uptake was based on current MBS data and **REDACTED**% eligibility expansion while assuming the same suitability and referral rates which, as noted for the previous application (MSAC 1347.1), there is some uncertainty regarding the ultimate uptake. ESC noted that based on the estimated additional utilisation for Population 1, the MBS budget impact is estimated to be $**REDACTED**.

For Population 2, ESC noted that the applicant estimated the utilisation of LAAC will increase approximately **REDACTED**-fold with the proposed addition of the relative contraindications to anticoagulation. ESC noted that the costs maybe under-estimated depending on whether the pre-intervention screening is conducted as an in-patient or out-patient procedure. ESC noted that these uncertainties makes utilisation and costing difficult to predict. ESC considered that more robust estimates of population size with sensitivity analyses are required.

ESC noted that the proposed LAAC listing eligibility criteria for either or both of the populations have the potential to grow the market for LAAC treatment. However, the extent of any changes in LAAC treatment numbers and resulting financial impacts that would result from the proposed revisions of either population (or both) are unclear. ESC also noted that there is a potential overlap of eligible patients for Population 1 and Population 2 and therefore adding the budget impact estimates for the two populations would overestimate the combined budget impact. ESC noted that the extent of this overlap is unclear and therefore the overall budget impact of expanding the absolute contraindications and including relative contraindications to anticoagulation is unclear. ESC agreed with the additional analyses recommended by the commentary, including reconsideration of the financial estimates to consider: the likely eligible patient population and treatment uptake, the extent of any overlap between two populations, whether patient referral rates may increase, the proportion of

[6] McCaffrey et al. (2016) *Health Qual Life Outcomes*. 14(1):133

referred patients deemed suitable for LAAC and current rates of LAAC uptake as a proportion of DOAC treated patients.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

The Applicants are pleased with MSAC's recommendation to expand the listing of absolute contraindications to OAT (population 1) allowing access to LAAC in patients who currently do not meet the eligibility and hence are left untreated and at high risk of stroke. However, the Applicants are disappointed that MSAC rejected listing of LAAC in patients with relative contraindications to OAT (population 2) and maintain that the totality of evidence support use of LAAC in these patients. Notably, MSAC did not appear to recognise the high rate of discontinuation of NOACs in Australian clinical practice, meaning any effectiveness of NOACs in clinical trial is likely overstated relative to real world usage.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website