

MSAC Application 1825

Transcranial Doppler bubble test for patent foramen ovale

**Applicant: Australian and New Zealand Stroke
Organisation Ltd.**

PICO Confirmation

Summary of PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PPICO for transcranial Doppler bubble test as a triage test within the diagnostic pathway for suspected PFO-associated stroke

Component	Description
Population	Individuals with prior cryptogenic ischaemic stroke or embolic stroke of undetermined source (ESUS) who are undergoing evaluation for a potential patent foramen ovale (PFO) as an underlying cause
Prior tests	Standard stroke work-up including: brain imaging (e.g. magnetic resonance imaging [MRI]); vascular imaging to exclude extracranial and intracranial arterial stenosis; cardiac rhythm monitoring to exclude atrial fibrillation; blood tests (e.g. for vasculitis and thrombophilia); and other investigations as clinically indicated
Intervention	Transcranial Doppler (TCD) bubble test (with provocative manoeuvre) used as a first-line triage test to detect right-to-left shunting and identify patients for confirmatory testing with transoesophageal echocardiography (TOE), performed using: • a conventional transcranial Doppler (TCD) system, or • a transcranial colour-coded duplex sonography (TCCD) system
Comparator	Transthoracic echocardiography (TTE) with bubble contrast (with provocative manoeuvre) used as an alternative first-line triage test to detect right-to-left shunting and identify patients for confirmatory testing with TOE
Reference standard	Higher-order anatomical reference standard (where evidence available): right heart catheterisation with documentation of guidewire passage across the atrial septum Pragmatic reference standard: TOE with bubble contrast (with provocative manoeuvre)
Outcomes	Safety • harms from the triage test procedure • harms associated with false positive (FP) and false negative (FN) results, including complications from potentially avoidable TOE and missed or delayed identification of a causally related PFO • harms associated with TOE with bubble contrast • downstream harms associated with subsequent treatment decisions, including inappropriate, delayed or foregone treatment, and adverse events related to PFO closure or medical management Clinical effectiveness Test performance • diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) • concordance of TCD vs TCCD and TCD/TCCD vs TTE • rate of inconclusive or technically inadequate studies Impact on clinical management: • proportion of patients referred for confirmatory TOE and other downstream investigations • appropriateness of referral for confirmatory testing • time to diagnosis and definitive classification (i.e. presence or absence of a causally related PFO) • appropriateness of classification and subsequent management Patient health outcomes: • stroke recurrence • mortality • health-related quality of life

Component	Description
	Health care resource use • cost of initial triage testing (TCD/TCCD versus TTE) • number and cost of subsequent investigations (e.g. TOE) • procedures avoided or incurred, including: ○ TOE ○ repeat or duplicate testing • costs associated with adverse events, including: ○ complications from triage testing (TCD/TCCD versus TTE) ○ complications from confirmatory TOE ○ consequences of FP (additional procedures) and FN (missed treatment) • costs associated with subsequent treatment (PFO closure or medical therapy) • costs associated with stroke recurrence and hospitalisation Cost-effectiveness • incremental cost per quality-adjusted life year (QALY) gained Health system costs • total costs to the Medicare Benefits Schedule (MBS) • total costs to the Pharmaceutical Benefits Scheme (PBS) • hospital and private sector costs (including procedures and admissions) • overall Australian healthcare system costs
Assessment questions	What is the safety, effectiveness and cost-effectiveness of TCD/TCCD bubble testing versus TTE with bubble contrast, when used as a triage test before confirmatory TOE with bubble contrast in individuals with prior cryptogenic ischaemic stroke undergoing evaluation for a causally related PFO? Direct evidence 1. In patients with prior cryptogenic ischaemic stroke or ESUS undergoing evaluation for a causally related PFO, does the use of TCD/TCCD bubble testing followed by TOE with bubble contrast, compared with TTE with bubble contrast followed by TOE with bubble contrast, result in superior health outcomes? Indirect evidence 2. Does the use of TCD/TCCD bubble testing, compared with TTE with bubble contrast, reduce the time to final classification of the presence or absence of a causally related PFO, and to subsequent clinical decision-making? 3. a) What is the comparative diagnostic accuracy of bubble testing using a TCD system compared with a TCCD system? b) What is the comparative diagnostic accuracy of TCD/TCCD bubble testing compared with TTE with bubble contrast against the reference standard (TOE with bubble contrast)? What is the concordance of TCD bubble testing compared to TTE with bubble contrast? c) What are the clinical consequences of a false-negative triage test (i.e. TCD/TCCD bubble testing or TTE with bubble contrast) result? 4. Does the use of TCD/TCCD bubble testing, compared with TTE with bubble contrast, alter the proportion of patients referred for TOE? 5. Does the use of TCD/TCCD bubble testing (followed by TOE with bubble contrast) result in the same classification (i.e. presence or absence of a causally related PFO) compared with TTE with bubble contrast (followed by TOE with bubble contrast)? 6. Do differences in the diagnostic performance of TCD/TCCD bubble testing and TTE with bubble contrast translate into differences in treatment selection (e.g. PFO closure or medical management) and subsequent health outcomes? 7. a) What are the direct harms associated with TCD/TCCD bubble testing compared with TTE with bubble contrast? b) What are the indirect harms associated with FP and FN results?

Component	Description
	8. What are the harms associated with definitive, semi-invasive TOE with bubble contrast, and do differences in the TCD/TCCD and TTE diagnostic pathways result in differences in exposure to these harms? 9. What are the harms associated with subsequent treatment (e.g. PFO closure or medical management), and do differences in the TCD/TCCD and TTE diagnostic pathways result in differences in exposure to these harms?

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of transcranial Doppler (TCD) bubble test for patent foramen ovale (PFO) was received from the Australian and New Zealand Stroke Organisation Ltd by the Department of Health, Disability and Ageing.

PICO criteria

Population

The proposed population consists of individuals with a prior cryptogenic ischaemic stroke or embolic stroke of undetermined source (ESUS) who are undergoing evaluation for a potential PFO as an underlying cause.

Ischaemic stroke refers to cerebral infarction resulting from interruption of blood flow to the brain. Embolic stroke is a subtype of ischaemic stroke caused by thrombotic material travelling from elsewhere in the circulation and lodging within a cerebral artery. Investigation for PFO is primarily relevant in patients with a suspected embolic stroke mechanism, as a PFO may permit paradoxical embolism, whereby a venous thrombus passes from the right atrium to the left atrium through the PFO and subsequently enters the arterial circulation, potentially causing cerebral infarction.

Cryptogenic stroke is defined as cerebral ischaemia that cannot be attributed to large artery atherosclerosis, small vessel disease, or a cardioembolic source despite comprehensive investigation. Small vessel disease refers to pathology affecting the small penetrating arteries of the brain and typically results in small, deep infarcts with a lacunar pattern on imaging. Distinguishing small vessel disease from an embolic stroke mechanism is relevant because PFO would not generally be expected to contribute to stroke arising from intrinsic small vessel pathology. However, stroke mechanisms cannot always be determined with certainty, and some infarcts with an apparent lacunar pattern may represent embolic events. While clinical features such as younger age, fewer vascular risk factors, and the absence of an alternative stroke mechanism may increase suspicion of an embolic aetiology, these characteristics are not sufficiently specific to reliably distinguish embolic stroke from small vessel disease in individual patients.

The term embolic stroke of undetermined source (ESUS) is commonly used to describe a subset of cryptogenic stroke characterised by a non-lacunar infarct pattern in which standard investigations have not identified a major cardioembolic source, significant atherosclerotic disease supplying the affected vascular territory, or another specific cause of stroke. ESUS is typically identified following brain imaging, vascular imaging, cardiac assessment, and cardiac rhythm monitoring. Although ESUS provides a more standardised framework for classifying stroke mechanism, uncertainty may remain despite comprehensive investigation. The use of the broader term 'cryptogenic stroke', rather than the more restrictive ESUS definition, reflects clinical practice, where selected patients with lacunar-appearing infarcts may still be considered for investigation of a possible embolic source, including PFO (Chambers et al. 2026).

Cryptogenic stroke is estimated to account for approximately 15–30% of all ischaemic strokes (Elgendy et al. 2020). According to the Australian and New Zealand consensus statement on the diagnosis and management of PFO for stroke prevention (Chambers et al. 2026), PFO is over-represented in this population and is implicated in approximately 25–50% of cases in individuals aged <60 years.

The population most relevant to the proposed test comprises patients aged ≤ 60 years with cryptogenic ischaemic stroke and features suggestive of an embolic mechanism, in whom standard investigations have not identified an alternative cause (Chambers et al. 2026). This age group is of particular interest because the likelihood that a PFO is causally related to stroke is generally higher in younger patients, while competing stroke mechanisms such as atrial fibrillation (AF), atherosclerotic disease, and small vessel disease become increasingly prevalent with advancing age. In addition, the randomised trials demonstrating clinical benefit from PFO closure predominantly enrolled patients aged 18–60 years, and current guideline recommendations are largely based on evidence from this population (Caso et al. 2024; Kleindorfer et al. 2021; Kavinsky et al. 2022). Standard investigations typically include brain imaging (e.g. MRI), vascular imaging to exclude extracranial and intracranial stenosis, cardiac rhythm monitoring to exclude AF, and appropriate laboratory testing. Evidence supports the benefit of PFO closure in reducing recurrent embolic events in selected patients aged 18–60 years with cryptogenic stroke and findings suggestive of a PFO-mediated stroke mechanism, particularly where high-risk PFO characteristics are present (Caso et al. 2024; Chambers et al. 2026).

Selected older patients may also be considered for the proposed test, particularly those in their early 60s, recognising that the 60-year threshold is somewhat arbitrary. A more selective approach to PFO screening has been recommended in this group, focusing on individuals with features consistent with ESUS, such as a non-lacunar infarct pattern on brain imaging and the absence of an identified stroke source despite comprehensive investigation, together with minimal conventional vascular risk factors (e.g. little or no history of hypertension, diabetes mellitus, hyperlipidaemia, smoking, or established atherosclerotic cardiovascular disease) and no AF detected on prolonged monitoring (Chambers et al. 2026). This approach reflects the decreasing likelihood that a PFO is causally related to stroke with advancing age, as well as the increasing prevalence of competing stroke mechanisms, while acknowledging that some older patients may still derive benefit from evaluation.

PASC considered the proposed population to be appropriate. PASC noted that ESUS is a subgroup of cryptogenic stroke characterised by a non-lacunar brain infarct in the absence of proximal arterial stenosis or a major cardioembolic source. PASC also noted that not all cryptogenic strokes are necessarily embolic and that restricting the population to ESUS may exclude some clinically relevant patients. Therefore, PASC supported inclusion of the broader cryptogenic stroke population, rather than limiting the population to ESUS, to avoid excluding patients in whom an embolic mechanism remains possible, as well as younger patients with lacunar infarction that may have been attributed to small vessel disease but for whom the underlying aetiology remains uncertain.

PFO-associated stroke

A PFO is a persistent interatrial communication resulting from incomplete postnatal closure of the foramen ovale, and is present in approximately 25% of the general adult population (Hagen et al. 1984; Meissner et al. 1999). While typically asymptomatic, a PFO may permit right-to-left shunting under conditions where right atrial pressure transiently exceeds left atrial pressure. This can allow a thrombus originating in the venous circulation to bypass the pulmonary circulation and enter the arterial circulation (paradoxical embolism). If an embolus travels to the cerebral circulation, it may result in an ischaemic stroke.

The presence of right-to-left shunting alone does not establish that a PFO is present or that the stroke was caused by the PFO. Right-to-left shunting is a functional finding that may arise from a range of intracardiac and extracardiac causes, including PFO, atrial septal defect, or intrapulmonary shunting. The diagnostic

pathway therefore involves not only confirming the presence of a PFO, but also assessing whether it is likely to be causally related to the index stroke.

The likelihood that an identified PFO is causally related to stroke is increased in the presence of high-risk anatomical and functional features, including large shunt size, spontaneous right-to-left shunting, substantial shunting with provocation (e.g. during a Valsalva manoeuvre), and an atrial septal aneurysm. Younger age and the absence of an alternative stroke mechanism following comprehensive evaluation further increase the likelihood that a stroke is PFO-mediated and are considered in risk assessment tools used to determine PFO-related stroke causality.

The Valsalva manoeuvre is a forced exhalation against a closed airway (e.g. straining with the mouth and nose closed), which transiently increases intrathoracic and right atrial pressure. This may reverse the normal pressure gradient between the atria, in which left atrial pressure is usually higher than right atrial pressure, and provoke temporary right-to-left shunting across a PFO. Provocative manoeuvres are therefore routinely used during bubble studies to improve the detection of clinically relevant shunts.

Relevance to treatment decision-making

In the context of cryptogenic stroke, the key clinical question is whether an identified PFO is causally related to the index event or represents an incidental finding. The European Stroke Organisation (ESO) guidelines on the diagnosis and management of PFO after stroke (Caso et al. 2024) describe two risk tools intended to support this assessment alongside comprehensive clinical evaluation.

The Risk of Paradoxical Embolism (RoPE) Score is based primarily on clinical characteristics and estimates the probability that a PFO identified in a patient with cryptogenic stroke is causally related to the index stroke rather than representing an incidental finding. The RoPE Score ranges from 0 to 10, with lower scores indicating a lower probability that the PFO contributed to the stroke and higher scores indicating an increasing likelihood of a causal relationship (Table 2).

The PFO-Associated Stroke Causal Likelihood (PASCAL) classification extends this approach by integrating the RoPE Score with the presence or absence of high-risk anatomical features on transoesophageal echocardiography (TOE) with bubble contrast – including a large right-to-left shunt and/or an atrial septal aneurysm – to determine the likelihood that the PFO was causally related to the index stroke (Table 3). RoPE-informed assessment and PASCAL classification are applied following confirmation of a PFO and are used to support treatment decision-making.

The Australian and New Zealand consensus statement emphasises that a high RoPE score alone does not predict benefit from PFO closure and should not be used as the sole basis for treatment decisions; instead, integration of both clinical and anatomical factors through the PASCAL classification is recommended (Chambers et al. 2026).

Table 2 Risk of Paradoxical Embolism (RoPE) Score calculator

Characteristic	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or transient ischaemic attack	1
Nonsmoker	1

Characteristic	Points
Cortical infarct on imaging	1
Age, years	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
70+	0
Total RoPE Score (sum of individual points) =	

Note: Based on the RoPE study, scores of 0–3 are associated with an approximately 0% probability that the stroke is attributable to the PFO, scores of 4–5 with a probability of approximately 34–38%, scores of 6–7 with a probability of approximately 62–72%, score 8 with a probability of approximately 84%, and scores of 9–10 with a probability of approximately 88–90%.

Source: Kent et al. (2021), Table 1.

Table 3 PASCAL Classification System

High RoPE Score (≥ 7)	High-risk PFO feature (large shunt and/or ASA)	PFO-related stroke
Absent	Absent	Unlikely
Absent	Present	Possible
Present	Absent	Possible
Present	Present	Probable

ASA = atrial septal aneurysm; PFO = patent foramen ovale; TOE = transoesophageal echocardiography.

Note: The PASCAL algorithm was developed using a mixed methods approach incorporating expert judgement, physiologic and epidemiologic data, and the validated RoPE Score. A higher RoPE Score (≥ 7 points) increases probability of causal association. Large shunt size was defined as >20 bubbles in the left atrium on TOE; ASA was defined as ≥ 10 mm of excursion from midline.

Source: Kent et al. (2021), Table 1.

Following confirmation of a PFO and characterisation of its anatomical features and associated right-to-left shunting on TOE with bubble contrast, the likelihood that the PFO is causally related to the index event is assessed using clinical and anatomical information. This assessment may be undertaken using the PASCAL classification system or an approach that is conceptually consistent with the PASCAL framework, even where the classification is applied implicitly rather than formally.

Patients classified as having a probable PFO-related stroke are generally considered the most appropriate candidates for percutaneous PFO closure in combination with antiplatelet therapy. In contrast, patients classified as having possible or unlikely PFO-related stroke may be managed medically, reflecting greater uncertainty regarding the causal contribution of the PFO. Accordingly, treatment decisions are informed by both the likelihood that the PFO was stroke-related and the overall clinical context, rather than by the presence of a high-risk anatomical feature or a high RoPE Score alone. Surgical PFO closure is not indicated as first-line therapy and is reserved for incidental closure during cardiac surgery or for rare cases where percutaneous management is not feasible.

Percutaneous PFO closure involves deployment of a transcatheter occlusion device (most commonly a double-disc design) across the atrial septum to seal the defect. In Australia, this procedure is funded under

MBS item 38272, and closure devices are listed on the Prescribed List of Medical Devices and Human Tissue Products (e.g. Billing Codes YH002 and SJ479)¹.

Medical management typically consists of long-term antithrombotic therapy, most commonly single antiplatelet therapy (e.g. aspirin). Dual antiplatelet therapy or oral anticoagulants may be appropriate in selected patients, depending on individual risk factors and clinical judgement.

Evidence from randomised controlled trials (RCTs) and meta-analyses indicates that, in appropriately selected patients (particularly those aged <60 years with high-risk PFO features), PFO closure in combination with medical therapy reduces the risk of recurrent stroke compared with medical therapy alone. Pooled analyses of randomised trials have demonstrated a relative reduction in recurrent stroke risk of approximately 50–60% following PFO closure; however, this benefit is accompanied by an increased risk of incident AF (Almuzainy et al. 2025; Hammad et al. 2025; Pristipino et al. 2019). The increased risk of AF is thought to be related primarily to mechanical irritation and remodelling of atrial tissue following device implantation, as well as inflammatory changes occurring in the peri-procedural period. Post-procedural AF is typically transient and self-limiting, although its incidence increases with advancing age (Sposato et al. 2024).

The role of PFO closure in patients aged ≥60 years remains uncertain due to the absence of dedicated RCTs. In this population, competing stroke mechanisms are more prevalent, and there is a higher background risk of subclinical AF and other supraventricular arrhythmias, complicating assessment of whether a PFO is causally related to the index stroke and whether closure is likely to provide net clinical benefit (Sposato et al. 2024).

Accordingly, accurate identification of a pathogenic (stroke-related) PFO is critical to guide treatment selection. Appropriate patient selection enables targeting of closure to those most likely to benefit in terms of reducing stroke recurrence, while avoiding additional invasive procedures, associated risks, and healthcare costs.

Consistent with this, the Australian and New Zealand consensus statement (Chambers et al. 2026) recommends that decisions regarding PFO closure be made by a multidisciplinary heart-brain team, including both a stroke physician and a structural heart cardiologist.

Size of the population

The annual incidence of PFO-associated stroke in Australia is not routinely reported and must therefore be estimated indirectly. The [Stroke Foundation](#) estimated that approximately 45,785 strokes occurred in 2023, the majority of which (37,589) were ischaemic, including 7,679 events in individuals aged <65 years (Kim et al. 2024). Epidemiological evidence suggests that up to 30% of ischaemic strokes remain cryptogenic following standard investigation, indicating that up to 2,300 Australians aged <65 years experienced a cryptogenic ischaemic stroke in 2023. Of these, up to half (approximately 1,150 cases) may be attributable to a PFO.

¹ Figulla Flex II PFO Occluder (Life Systems Medical; ARTG ID [400794](#)) and Amplatzer Talisman PFO Occluder (Abbott Medical; ARTG ID [398663](#)); accessed 08 June 2026.

An alternative estimation approach, based on Sposato et al. (2024), suggests that PFO may be causally implicated in approximately 4% of all ischaemic strokes. Applying this proportion to Australian data yields an estimate of around 1,500 cases annually among individuals aged ≤60 years.

These figures should be interpreted as indicative only, given the uncertainty inherent in indirect estimation methods, variability in diagnostic practices, and differing definitions of PFO causality. More precise estimates will require further validation and detailed consideration in the assessment report.

Notably, utilisation of percutaneous PFO closure has increased in recent years, with 776 MBS services claimed for item 38272 in 2023, rising to 985 services in 2025 (of which 77% were in individuals aged <65 years).²

Intervention

The intervention is the TCD bubble test, also referred to as the TCD bubble study, contrast-enhanced TCD (c-TCD) or TCD with bubble contrast, performed using either conventional transcranial Doppler (TCD) or transcranial colour-coded duplex sonography (TCCD). For the purposes of this document, 'TCD' includes both TCD and TCCD technologies unless otherwise specified. The TCD bubble test has been recommended, where available, as a preferred first-line screening modality for detection of PFO in patients with cryptogenic stroke in the Australian and New Zealand consensus statement on the diagnosis and management of PFO for stroke prevention (strong recommendation, moderate certainty evidence; Chambers et al. 2026).³

The test involves venous injection of saline with microbubbles, which are delivered via the venous circulation to the right side of the heart. In the absence of a PFO, they proceed to the pulmonary circulation where they are removed. The detection of bubbles in a cerebral artery using Doppler ultrasound at the temporal lobe, where the skull is thin, is indicative of a right-to-left shunt. However, the presence of a right-to-left shunt does not, in itself, establish that a PFO is present, as shunting may occur due to other intracardiac or extracardiac causes.

The TCD bubble test is widely used internationally for detection of right-to-left shunts due to its non-invasive nature, favourable safety profile, relative simplicity, and high sensitivity (Pristipino et al. 2019). However, specificity is limited, as the test cannot differentiate intracardiac shunts (e.g. PFO or atrial septal defect) from extracardiac shunts (e.g. intrapulmonary shunting), nor does it provide anatomical characterisation (Mahmoud et al. 2017). Accordingly, it is not suitable as a stand-alone confirmatory test.

A positive TCD bubble test indicates the presence of a functional right-to-left shunt; however, it does not confirm the anatomical cause of the shunt or establish that a PFO is present. Patients with a positive result will therefore undergo TOE with bubble contrast to confirm or exclude the presence of a PFO. If a PFO is confirmed, further assessment incorporating clinical and anatomical factors is required to determine the likelihood that the PFO is pathogenic and whether closure is appropriate. Conversely, a negative test result

² Medicare Statistics, Services Australia, accessed 08 June 2026.

³ The consensus statement was developed by a multidisciplinary expert panel comprising 9 stroke neurologists and 1 interventional cardiologist from major tertiary centres in Christchurch, New South Wales, Queensland, Tasmania, Victoria and Western Australia.

reduces the likelihood of a clinically significant shunt and may obviate the need for further invasive investigation, such as TOE.

Within the diagnostic pathway for suspected PFO-associated stroke, the TCD bubble test functions as a triage tool. It identifies patients who should proceed to more invasive confirmatory anatomical imaging with TOE, while also helping to exclude those unlikely to have a clinically significant shunt.

The application contends that access to TCD bubble testing may reduce reliance on an alternative triage modality – transthoracic echocardiography (TTE) with bubble contrast (the nominated comparator), which is used as a first-line test to detect right-to-left shunting in patients with suspected PFO – and may facilitate more timely diagnosis and treatment of a causally related PFO. However, the extent to which TCD may replace TTE in clinical practice is likely to depend on factors such as service availability, workforce capability, and integration within existing stroke care pathways.

PASC considered that the clinical evaluation should assess the diagnostic performance of TCD bubble testing using conventional TCD systems and TCCD systems separately, given the need to understand whether the 2 modalities provide comparable detection of right-to-left shunts. The applicant advised that, of the 3 centres currently performing bubble testing, the Austin Hospital currently uses TCD, whereas the Royal Adelaide Hospital and John Hunter Hospital use TCCD, with modality selection reflecting the ultrasound equipment available at each institution. The applicant further advised that both modalities have broadly similar diagnostic performance, although TCD may offer some technical advantages related to signal detection, monitoring capability, and operator flexibility that may improve detection of low-grade shunts.

PASC considered the importance of equitable access to the proposed service. PASC noted that, if TCD bubble testing is shown to have superior diagnostic performance compared with TTE with bubble contrast, its use as the preferred triage test may reduce the need for additional diagnostic investigations and allow for earlier PFO closure (i.e. with fewer clinical appointments required). PASC noted that this may reduce associated additional travel for some patients. PASC considered that this could improve access to care and reduce the burden of further diagnostic assessment, particularly for patients who would otherwise need to travel to access specialist services.

Testing procedure

The TCD bubble test combines transcranial ultrasound monitoring with intravenous (IV) administration of agitated saline contrast to detect right-to-left shunting. The procedure is performed without sedation. Patient information from Australian centres indicates that it typically takes 15–30 minutes,⁴ although it may extend up to 45 minutes in more complex cases.

The patient is positioned supine or semi-recumbent, and a peripheral IV cannula is inserted. Ultrasound monitoring is established by positioning one or two probes over the transtemporal acoustic windows to insonate the middle cerebral artery (MCA). Depending on equipment and protocol, unilateral or bilateral monitoring may be used.

Adequate acoustic windows are essential for reliable signal acquisition. However, the literature indicates that suitable temporal bone windows for ultrasound are absent in approximately 5–20% of adults (Yavuz et

⁴ Austin Health [patient information](#), Hole in the Heart Clinic [patient information](#), Heart Brain Private Clinic [patient information](#); accessed 16 June 2026.

al. 2026). In such cases, alternative insonation⁵ approaches (e.g. via the carotid artery in the neck) may be considered, although these are less commonly used and may reduce diagnostic sensitivity (Yavuz et al. 2026). In rare instances where adequate insonation cannot be achieved, patients would typically proceed to TOE.

Agitated saline contrast is prepared immediately prior to injection by mixing saline with a small volume of air, and in some protocols a small quantity of the patient's blood, using two syringes connected via a 3-way stopcock. This produces microbubbles, with the addition of blood improving bubble stability and detection, while also reducing bubble coalescence and the risk of larger air emboli (Mahmoud et al. 2017).

Multiple injections are performed. Initial injections are conducted during normal respiration to assess for spontaneous shunting, followed by injections during a Valsalva manoeuvre to transiently increase right atrial pressure and improve detection of intermittent shunts. Additional injections may be performed if required.

Following each injection, Doppler signals are monitored for approximately 20–30 seconds for high-intensity transient signals (HITS), representing microbubbles entering the cerebral circulation. The number and timing of HITS are recorded and used to determine the presence of a shunt and to grade its severity on a semi-quantitative scale (e.g. 0–5), with higher grades indicating larger shunts.

The threshold used to define a positive TCD bubble test may vary across clinical settings and studies, contributing to heterogeneity in test performance (Yavuz et al. 2026). Some protocols consider the detection of any microbubble (i.e. ≥ 1 HITS) as a positive result in order to maximise sensitivity for screening purposes. In contrast, higher thresholds (e.g. >10 HITS) may be applied to improve specificity and preferentially identify haemodynamically significant shunts, accepting a reduced sensitivity for smaller or clinically insignificant PFOs. The selection of threshold is therefore aligned with the intended clinical role of the test within the diagnostic pathway.

Most protocols include 2–4 bubble contrast injections, with at least one at rest and one during provocation. The patient remains awake throughout the procedure and can typically leave immediately after completion. According to the applicant, adverse events are uncommon and generally limited to minor discomfort associated with venous access. The test does not involve ionising radiation or pharmacological contrast agents.

PASC noted the applicant's clinical experts' comments that, according to the literature, approximately 10% of patients do not have an adequate temporal bone window for successful TCD/TCCD assessment. In these patients, monitoring can instead be performed via the internal carotid arteries (located below the jawline) or the vertebral arteries (located at the back of the head).

PASC queried whether patients who are severely impaired by stroke would have difficulty performing the Valsalva manoeuvre for the TCD/TCCD and TTE tests. The applicant's clinical experts stated that waiting to perform the test until patients have recovered enough function to perform the Valsalva manoeuvre (approximately 2 weeks) is clinically acceptable, and this was similar for both the intervention and comparator arms.

⁵ Insonation refers to the delivery of ultrasound waves into tissues to enable diagnostic imaging or measurement of blood flow.

PASC queried whether injection of the agitated saline contrast into the femoral vein, rather than the antebrachial vein, would increase diagnostic yield. The applicant's clinical experts stated that femoral vein access is not necessary, as TCD demonstrates high sensitivity (approximately 98%) using antebrachial vein access, which is generally more accessible and easier to perform in clinical practice.

Service setting and delivery

TCD bubble testing may be performed in public and private hospital inpatient settings, outpatient clinics, or neurovascular laboratories. In Australia, the applicant stated that availability is currently limited, with services concentrated in a small number of public tertiary centres (e.g. Austin Hospital in Melbourne, Royal Adelaide Hospital, and John Hunter Hospital in Newcastle, New South Wales), and only limited provision in private practice.

The procedure requires an ultrasound system capable of performing transcranial Doppler assessment (either a conventional TCD system or a TCCD system) and trained personnel, including an experienced operator and a clinician or appropriately trained health professional to perform cannulation, administer agitated saline contrast, and supervise the test.

In established centres, testing is often performed during the index admission for cryptogenic stroke or within 1–2 weeks post-discharge. However, testing may be delayed for a month or longer where access to specialised services is constrained, referral pathways are prolonged, additional diagnostic investigations are prioritised, or local resource limitations result in extended waiting times.

In rare cases (approximately 1% according to the applicant),⁶ the test may need to be repeated at a separate visit if the patient is unable to perform an adequate Valsalva manoeuvre or if vascular access cannot be successfully obtained.

Core components of transcranial Doppler systems

TCD and TCCD systems used for bubble studies are designed to detect intracranial microembolic signals following administration of agitated saline contrast. Both modalities use low-frequency (~2 MHz) ultrasound to insonate the MCAs. The choice of modality is generally dependent on local availability, equipment, and expertise, as both can be used to assess the presence of a right-to-left shunt within the diagnostic pathway for PFO.

Conventional TCD systems typically use bilateral probes secured within a headframe to enable continuous and stable monitoring during contrast injection and provocative manoeuvres. TCCD systems incorporate B-mode and colour Doppler imaging, allowing direct visualisation of intracranial vessels and facilitating probe positioning; fixation devices may be used for prolonged monitoring. Available evidence suggests that TCD and TCCD with contrast provide broadly comparative diagnostic performance for right-to-left shunt detection when adequate acoustic windows are obtained and standardised protocols are applied, although direct comparative data remain limited (Yavuz et al. 2026). TCCD offers the additional advantage of anatomical visualisation of intracranial vessels, which may assist with vessel identification and insonation, whereas conventional TCD relies on identification of vessels using Doppler flow characteristics and standard insonation depths. Notably, TCD with bubble contrast has been more extensively validated as a

⁶ Discussed at the Pre-PASC meeting on 15 June 2026.

high-sensitivity method for right-to-left shunt detection, whereas corresponding large-scale diagnostic accuracy data for TCCD in this specific application are more limited.

Both modalities use digital signal processing with high-resolution spectral analysis (often incorporating multigate capability) and automated or semi-automated detection of HITS corresponding to circulating microbubbles. Outputs typically include real-time waveform display and audio feedback to support confirmation and counting of embolic events.

System software generally supports protocol-driven workflows, including timing of contrast injections, coordination of provocative manoeuvres, and semi-quantitative grading of shunt burden. Data storage, reporting, and network connectivity are standard features, and systems are available in both portable and cart-based configurations suitable for inpatient and outpatient use.

Emerging technologies include robot-assisted TCD systems aimed at reducing operator dependence and improving standardisation of testing; however, further evidence is required to establish their clinical utility (Caso et al. 2024; Rubin et al. 2021).

Regulatory status of transcranial Doppler systems

In Australia, TCD systems are regulated as medical devices and must be included on the Australian Register of Therapeutic Goods (ARTG) before they can be supplied. Systems used for applications such as bubble studies are typically classified as active diagnostic ultrasound devices, generally falling within Class IIa or Class IIb depending on their intended use and risk profile. They are largely used for monitoring after cerebral aneurysm, diagnosis of intracranial stenosis and detection of microembolic signals.

ARTG listings encompass both dedicated non-imaging Doppler systems (e.g. ARTG ID [119626](#)) and vascular ultrasound platforms with integrated TCD capability (e.g. ARTG ID [292236](#)). In addition, general-purpose ultrasound systems (e.g. ARTG IDs [387110](#) and [462120](#)), widely used in radiology, cardiology and vascular laboratories, may also be used for transcranial applications when fitted with appropriate probes.

However, these general-purpose systems are not specifically optimised for intracranial Doppler monitoring or emboli detection. While they can perform unilateral TCCD and are capable of detecting embolic signals, their performance and functionality may be more limited compared with dedicated TCD systems designed for continuous monitoring and specialised cerebrovascular assessments.

Current funding of transcranial Doppler systems

The capital cost of establishing a TCD bubble testing service in Australia is primarily driven by the acquisition of a specialised TCD system, with indicative costs ranging from approximately \$40,000 to \$90,000 depending on system configuration, software capabilities, and the number of channels. These systems generally include the required Doppler probes. Ongoing costs include maintenance, servicing contracts, and periodic software upgrades.

Centres with existing neurovascular laboratories and TCD capability would incur minimal incremental costs to introduce bubble testing, largely limited to low-cost consumables (e.g. agitated saline, syringes) and staff training. Consequently, the marginal cost of implementation is substantially lower in such settings compared with centres requiring de novo capital investment.

Headframes are typically reusable and cost approximately \$1,000 to \$3,000, while minor accessories (e.g. probe covers) are generally low-cost and single use.

For centres using TCCD systems, capital costs are higher, typically ranging from approximately \$80,000 to \$180,000 depending on imaging capability and system configuration. These costs generally reflect a full ultrasound platform; however, they may not always include all transducers. Additional phased-array transducers suitable for transcranial imaging may cost in the order of several thousand to tens of thousands of dollars depending on vendor and specifications.

Where TCCD platforms are already in use for broader neurovascular or general ultrasound imaging (e.g. carotid or cardiac applications), the incremental cost of introducing bubble testing is minimal and comparable to conventional TCD. Accordingly, while TCCD systems involve higher upfront costs when purchased specifically for this purpose, their marginal cost for bubble testing remains low when integrated into existing ultrasound services.

Current funding of the service

The application states that TCD bubble testing is currently funded using existing MBS items for diagnostic TCD (Box 1). The application notes that these items do not specifically reflect the additional requirements of bubble testing, including longer procedure duration, use of contrast (agitated saline), and involvement of multiple staff.

Box 1 Existing MBS items for standard diagnostic TCD tests, currently used for transcranial Doppler bubble test

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS Group D1 – Miscellaneous Diagnostic Procedures and Investigations Subgroup 5 – Vascular	
Item 11614	
Transcranial doppler, examination of the intracranial arterial circulation using CW Doppler or pulsed Doppler with hard copy recording of waveforms, examination and report, other than a service associated with a service to which item 55280 of the diagnostic imaging services table applies	
Fee: \$90.55 Benefit: 75% = \$67.95 85% = \$77.00	
Category 5 – DIAGNOSTIC IMAGING SERVICES Group I1 – Ultrasound Subgroup 3 – Vascular	
Item 55280	
Duplex scanning involving B mode ultrasound imaging and integrated Doppler flow measurements by spectral analysis of intra cranial vessels, not being a service associated with a service to which an item in Subgroup 4 applies (R)	
<u>Bulk bill incentive</u>	
Fee: \$199.70 Benefit: 75% = \$149.80 85% = \$169.75	

Source: MBS Online, accessed 14 July 2026.

Workforce and implementation considerations

Implementation of TCD bubble studies has implications for workforce capability, service delivery, and regulatory compliance. As outlined above, current funding relies on existing MBS items that operate within different regulatory frameworks. Where item [11614](#) is used, the service is classified as a diagnostic investigation, whereas item [55280](#) is a diagnostic imaging service subject to the Diagnostic Imaging Accreditation Scheme (DIAS). Consequently, regulatory obligations may vary depending on the MBS item used and local service arrangements. In settings where DIAS requirements apply, providers may need to ensure compliance with relevant accreditation, quality assurance, equipment, record-keeping and clinical

governance requirements. As a result, implementation requirements – and the associated resource implications – may differ across providers and jurisdictions.

The procedure can be delivered through a range of workforce models. TCD bubble tests may be performed by appropriately trained health professionals, including radiologists, neurologists, cardiologists, fellows, registrars, nurse practitioners, sonographers, vascular scientists, and other allied health practitioners, in accordance with local governance arrangements, scope-of-practice requirements, and appropriate clinical oversight.

However, the diagnostic performance of the procedure is operator dependent, and reliable acquisition and interpretation of embolic signals requires demonstrated competency in probe positioning, optimisation of Doppler signals, preparation and administration of agitated saline contrast, and the execution of provocative manoeuvres.

In practice, successful implementation is most likely in appropriately equipped clinical settings with access to suitable ultrasound systems and transducers, trained personnel, and appropriate clinical governance. Accordingly, irrespective of the funding pathway used, providers delivering TCD bubble tests should ensure that practitioners have appropriate training and experience, that equipment complies with relevant regulatory and safety requirements, and that systems are in place to support ongoing competency, supervision, and quality assurance.

Introduction of TCD bubble testing in centres without existing expertise in TCD techniques may therefore require additional investment in workforce training, as well as the establishment of local clinical governance and quality assurance processes to support diagnostic accuracy, consistency and reproducibility.

The Austin Hospital Stroke Unit offers annual 2-day training workshops for centres planning to implement TCD bubble testing. These workshops are tailored for sonographers, stroke clinicians and nurse practitioners, and support the development of practical skills and service capability.

PASC noted the importance of appropriate training and credentialling to support the provision of TCD bubble testing. PASC noted that bubble testing performed using conventional TCD systems requires acquisition of Doppler signals without direct visualisation of the target intracranial artery and therefore may require greater operator experience and expertise than TCCD. PASC further noted the applicant's advice that the centres currently providing TCD bubble testing services meet DIAS requirements, and that all TCD and TCCD bubble testing services should reasonably be expected to comply with DIAS standards and requirements.

Barriers to uptake

Key barriers to uptake include limited access to TCD-capable equipment and trained operators, particularly outside major tertiary centres. As the technique is operator-dependent, variation in practitioner experience and competency may affect the consistency and reproducibility of results and limit scalability in settings without established expertise.

Additional barriers include infrastructure and accreditation requirements where services are delivered under diagnostic imaging frameworks, as well as entrenched reliance on existing echocardiographic pathways (TTE and TOE) and clinician familiarity with these modalities.

As a result, potential benefits of TCD bubble testing, such as reduced time to diagnosis of a causally related PFO and decreased use of invasive investigations, may not be realised in practice where access remains limited or unevenly distributed.

Comparator

The nominated comparator is TTE with bubble contrast, also referred to as contrast-enhanced TTE (c-TTE) or bubble TTE. This is a non-invasive cardiac ultrasound imaging test that uses agitated saline contrast to detect right-to-left shunting and is widely used in clinical practice.

TTE with bubble contrast represents an appropriate comparator, as it is commonly used as a first-line, non-invasive investigation for detecting right-to-left shunt in patients with suspected PFO. Similar to the TCD bubble test, it functions as a triage test within the diagnostic pathway, identifying patients who require confirmatory imaging with TOE. The comparison between TCD and TTE therefore reflects alternative triage strategies for selecting patients for further investigation.

In practice, TTE is more commonly used by cardiologists, whereas TCD is typically used by neurologists, reflecting differences in clinical pathways, local expertise, and service availability (Van der Giessen et al. 2020). In the Australian setting, patients with cryptogenic stroke are typically managed by a neurologist with a subspecialisation in stroke where available; in regional and rural settings, care may be provided by general physicians supported by telemedicine stroke consultation services. Patients may be referred for TCD bubble testing where available. Where TCD bubble testing services are not available, patients may be referred to a cardiologist to undergo a TTE with bubble contrast. The proposed test would partially replace TTE with bubble contrast in settings where TCD is available and technically feasible (i.e. where an adequate temporal acoustic window is present).

TTE with bubble contrast involves administration of agitated saline via peripheral IV injection, with imaging performed via a transducer placed on the chest wall to visualise passage of microbubbles through the cardiac chambers. Unlike TCD, which detects microembolic signals in the cerebral circulation, TTE provides direct visualisation of intracardiac flow. However, it has limited sensitivity for detecting small shunts and may have difficulty distinguishing between PFO, atrial septal defect, and extracardiac shunts due to relatively poor visualisation of the interatrial septum (Mahmoud et al. 2017).

TTE with bubble contrast also relies on performance of a Valsalva manoeuvre to provoke right-to-left shunting. In practice, this may be suboptimal, particularly as patients are typically positioned in the left lateral position during examination, which may reduce the effectiveness of the manoeuvre, potentially decreasing test sensitivity and contributing to false-negative results.

TTE is funded under existing MBS echocardiography items [55126](#) and [55129](#) (Box 2). There is no dedicated MBS item for the bubble study component, including IV cannulation, preparation and administration of agitated saline, or additional staff time. These components are generally absorbed within the echocardiography service, and agitated saline is prepared at the point of care without separate reimbursement.

Patient information from Australian centres indicates that the TTE with bubble contrast procedure typically takes 30–45 minutes.⁷

Access to TTE with bubble contrast varies across clinical settings. While it is often readily available in private cardiology practices, wait times may be prolonged in public hospitals (Chambers et al. 2026). In many cases, a standard TTE is initially performed without contrast, necessitating repeat imaging with bubble contrast and potentially delaying the identification of a causally related PFO. Additionally, TTE with bubble contrast may not provide sufficient diagnostic certainty to conclusively exclude a PFO in all patients. As a result, patients frequently proceed to TOE for confirmation and anatomical characterisation irrespective of TTE findings (Chambers et al. 2026).

In the public system, the sequential pathway of TTE with bubble contrast, outpatient review, TOE, and follow-up review may result in substantial delays before treatment is initiated. These delays may have clinical implications, including prolonged uncertainty for patients and risk of recurrent events.

⁷ CardioVascular Clinics (CVC) [patient information](#), SmartCare Diagnostics [patient information](#), Heart HQ [patient information](#), The Heart Centre (THC) [patient information](#); accessed 16 June 2026.

Box 2 MBS items for transthoracic echocardiography (TTE)

Category 5 – DIAGNOSTIC IMAGING SERVICES Group I1 – Ultrasound Subgroup 7 – Transthoracic Echocardiogram and Stress Echocardiogram	
Item 55126 Note: the service only applies if the patient meets the requirements of the descriptor and the requirements of Note: IR.1.2 Initial real time transthoracic echocardiographic examination of the heart with real time colour flow mapping from at least 3 acoustic windows, with recordings on digital media, if the service: (a) is for the investigation of any of the following: (i) symptoms or signs of cardiac failure; (ii) suspected or known ventricular hypertrophy or dysfunction; (iii) pulmonary hypertension; (iv) valvular, aortic, pericardial, thrombotic or embolic disease; (v) heart tumour; (vi) symptoms or signs of congenital heart disease; (vii) other rare indications; and (b) is not associated with a service to which: (i) another item in this Subgroup applies (except items 55137, 55141, 55143, 55145 and 55146); or (ii) an item in Subgroup 2 applies (except items 55118 and 55130); or (iii) an item in Subgroup 3 applies Applicable not more than once in a 24 month period (R) <u>Bulk bill incentive</u>	
Fee: \$271.80 Benefit: 75% = \$203.85 85% = \$231.05	
Item 55129 Note: the service only applies if the patient meets the requirements of the descriptor and the requirements of Note: IR.1.2 Repeat serial real time transthoracic echocardiographic examination of the heart with real time colour flow mapping from at least 3 acoustic windows, with recordings on digital media, if: (a) valvular dysfunction is not the primary issue for the patient (although it may be a secondary issue); and (b) the service is for the investigation of any of the following: (i) symptoms or signs of cardiac failure; (ii) suspected or known ventricular hypertrophy or dysfunction; (iii) pulmonary hypertension; (iv) aortic, thrombotic, embolic disease or pericardial disease (excluding isolated pericardial effusion or pericarditis); (v) heart tumour; (vi) structural heart disease; (vii) other rare indications; and (c) the service is requested by a specialist or consultant physician; and (d) the service is not associated with a service to which: (i) another item in this Subgroup applies (except items 55137, 55141, 55143, 55145 and 55146); or (ii) an item in Subgroup 2 applies (except items 55118 and 55130); or (iii) an item in Subgroup 3 applies (R) <u>Bulk bill incentive</u>	
Fee: \$271.80 Benefit: 75% = \$203.85 85% = \$231.05	

Source: MBS Online, accessed 14 July 2026.

PASC considered the proposed comparator, TTE with bubble contrast and provocation manoeuvre, to be appropriate. PASC noted that TTE with bubble contrast is an imperfect triage test with lower sensitivity for detecting right-to-left shunts than TCD bubble testing. PASC further noted that, in clinical practice, patients with equivocal or negative TTE results may still be referred for confirmatory TOE with bubble contrast where there is a high clinical suspicion of PFO.

Reference standard

The highest-fidelity reference standard for confirming the presence of a PFO is direct anatomical confirmation via right heart catheterisation (RHC), with documentation of guidewire passage across the atrial septum (Mahmoud et al. 2017). While this provides definitive evidence of an interatrial communication, it is invasive and not routinely performed for diagnostic purposes. Furthermore, RHC confirms the anatomical presence of a PFO but does not necessarily assess the presence or magnitude of functional right-to-left shunting under physiological conditions. It is therefore best considered a higher-order anatomical reference standard, applicable primarily in research or selected clinical contexts where such data are available.

Similarly, anatomical confirmation at surgery or autopsy represents a theoretical gold standard for demonstrating the presence of a PFO. However, like RHC, these approaches establish anatomical patency rather than functional shunt characteristics and are neither feasible nor ethical for diagnostic verification in the target population. Their use would also introduce substantial verification bias, as they are restricted to highly selected cases.

In current clinical practice, TOE with bubble contrast (contrast-enhanced TOE or c-TOE) represents the most appropriate pragmatic reference standard for confirmation of anatomical PFO. TOE is widely used within the diagnostic pathway and is the comparator employed in most diagnostic accuracy studies and meta-analyses evaluating TCD bubble testing (e.g. Caso et al. 2024; Katsanos et al. 2016; Mojadidi et al. 2014; Pristipino et al. 2019; Yavuz et al. 2026; Zhang et al. 2024).

Unlike TCD bubble testing, which identifies the presence of a right-to-left shunt without directly visualising its anatomical source, TOE with bubble contrast combines functional assessment of shunting with direct visualisation of the interatrial septum. This enables confirmation of the presence of a PFO, characterisation of shunt severity, and evaluation of anatomical features associated with an increased likelihood of pathogenicity (e.g. atrial septal aneurysm) that may influence clinical decision-making. However, confirmation of a PFO on TOE does not, in itself, establish that the detected PFO is causally related to the index stroke. Determination of causal relevance requires interpretation of PFO findings in the context of the broader stroke work-up and patient clinical characteristics, often supported by risk stratification approaches such as a RoPE-informed assessment and the PASCAL classification framework. TOE therefore remains the current clinical reference standard for confirming the presence of a PFO and assessing the anatomical characteristics relevant to decisions regarding suitability for percutaneous closure.

However, TOE is a semi-invasive procedure that is typically uncomfortable for patients, often requires conscious sedation, and carries a small risk of complications, including bleeding, aspiration or oesophageal perforation (Mahmoud et al. 2017; Pristipino et al. 2019). In addition, access to TOE may be limited, with delays in availability, particularly in public hospital settings (Chambers et al. 2026).

Importantly, TOE with bubble contrast is an imperfect reference standard. Its diagnostic performance may be reduced by factors such as sedation and left lateral positioning, which can impair the patient's ability to perform an effective Valsalva manoeuvre and thereby reduce the likelihood of provoking right-to-left shunting during the examination. More generally, right-to-left shunting through a PFO may be intermittent and dependent on transient haemodynamic conditions, meaning that shunts may not be demonstrated at the time of testing despite the presence of an anatomically patent PFO. Although this limitation applies to TOE with bubble contrast and both triage tests (TTE with bubble contrast and TCD bubble testing), TOE may be particularly vulnerable to under-detection because factors associated with the procedure can impair shunt provocation. Consequently, when TCD is compared against TOE, some apparent false positive TCD bubble testing results may in fact represent true right-to-left shunts that were not detected on TOE with bubble contrast.

Within the clinical pathway, TOE is typically performed as a confirmatory test following initial screening. Patients with a positive TCD bubble test or TTE with bubble contrast are generally referred for TOE to determine whether the identified right-to-left shunt is attributable to a PFO, to assess anatomical features relevant to risk stratification and determination of causal relevance, and to support procedural planning, including device selection where closure is being considered. Conversely, a negative triage test may avoid the need for further PFO-specific investigation, including TOE, enabling more targeted use of this semi-invasive procedure.

TOE is funded under existing MBS echocardiography item [55118](#) (Box 3). As with TTE, there is no dedicated MBS item for the bubble contrast component, including IV cannulation, preparation and administration of agitated saline, or additional staff time, and these are typically absorbed within the overall procedure.

Box 3 MBS item for transoesophageal echocardiography (TOE)

Category 5 – DIAGNOSTIC IMAGING SERVICES	
Group I1 – Ultrasound	
Subgroup 2 – Cardiac	
Item 55118 Heart, two-dimensional or three-dimensional real time transoesophageal examination of, from at least 2 levels, and in more than one plane at each level, if: (a) the service includes: (i) real time colour flow mapping and, if indicated, pulsed wave Doppler examination; and (ii) recordings on digital media; and (b) the service is not: (i) an intra-operative service; or (ii) a service associated with a service to which an item in Subgroup 3 of this Group applies (R) (H) <u>Bulk bill incentive</u> (Anaes.)	
Fee: \$324.50 Benefit: 75% = \$243.40	

Source: MBS Online, accessed 14 July 2026.

PASC considered TOE with bubble contrast and provocation manoeuvre to be the appropriate reference standard. PASC noted that, although TOE is regarded as the gold standard, sedation can limit the ability to

perform provocation manoeuvres and may reduce sensitivity for detecting right-to-left shunts in some patients. Despite this limitation, PASC considered TOE to be an appropriate pragmatic reference standard.

Outcomes

The outcomes relevant to the assessment of the TCD bubble test in the proposed population are summarised in Table 4. The key outcomes relate to the diagnostic performance of TCD bubble testing and its downstream impact on clinical management.

Table 4 Outcomes relevant to the assessment of TCD bubble testing

Outcome type	Outcome
Safety	Harms from the triage test procedure Harms associated with FP or FN results, including complications from potentially avoidable TOE and missed or delayed identification of a causally related PFO Harms associated with TOE with bubble contrast Downstream harms associated with subsequent treatment decisions, including inappropriate, delayed or foregone treatment, and AEs related to PFO closure or medical management
Clinical effectiveness	Test performance Diagnostic accuracy (sensitivity, specificity, PPV, NPV) Concordance of TCD vs TCCD and TCD/TCCD vs TTE Rate of inconclusive or technically inadequate studies Impact on clinical management Proportion of patients referred for confirmatory TOE and other downstream investigations Appropriateness of referral for confirmatory testing Time to diagnosis and definitive classification (i.e. presence or absence of a causally related PFO) Appropriateness of classification and subsequent management Patient health outcomes Stroke recurrence Mortality Health-related quality of life
Healthcare resource use (including patient OOP costs)	Cost of initial triage testing (TCD/TCCD versus TTE) Number and cost of subsequent investigations (e.g. TOE) Procedures avoided or incurred, including: - TOE - repeat or duplicate testing Costs associated with adverse events, including: - complications from triage testing (TCD/TCCD versus TTE) - complications from confirmatory TOE - consequences of FP (additional procedures) and FN (missed treatment) Costs associated with subsequent treatment (PFO closure or medical therapy) Costs associated with stroke recurrence and hospitalisation
Cost-effectiveness	Incremental cost per QALY gained (if feasible)
Health system costs	Total costs to the MBS Total costs to the PBS Hospital and private sector costs (including procedures and admissions) Overall Australian healthcare system costs

AE = adverse event; FN = false negative; FP = false positive; MBS = Medicare Benefits Schedule; NPV = negative predictive value; OOP = out-of-pocket; PBS = Pharmaceutical Benefits Scheme; PFO = patent foramen ovale; PPV = positive predictive value; QALY = quality-adjusted life year; TCD = transcranial Doppler; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

The most important clinical consequences arise from diagnostic accuracy. A patient with a false positive triage test (i.e. TCD bubble testing or TTE with bubble contrast) would generally proceed to confirmatory TOE, at which point the absence of a causally related PFO is likely to be identified. As such, the principal consequence of a false positive result is exposure to unnecessary semi-invasive investigation and associated healthcare resource use, with limited impact on longer-term health outcomes. In contrast, a false negative result may lead to a patient being incorrectly excluded from further PFO-specific investigation, potentially resulting in missed opportunity for confirmatory TOE or a delay in the diagnosis of causally related PFO.

Primary effectiveness outcomes include measures of test performance (sensitivity, specificity, positive and negative predictive values, concordance with reference standards) and rates of inconclusive or technically inadequate studies. Given the acknowledged limitations of TOE with bubble contrast as a reference standard, the assessment should consider concordance between the triage tests and TOE, rather than relying solely on estimates of diagnostic accuracy. Concordance may provide a more informative assessment of relative test performance, particularly where observed discrepancies may reflect limitations of either the triage test or the reference standard. Test performance may be influenced by the operator's technical skills and local expertise, which may affect diagnostic accuracy, reproducibility, and rates of inconclusive studies (Rubin et al. 2021). The application asserts that TCD has higher sensitivity for detecting a right-to-left shunt compared with TTE with bubble contrast (the comparator) and TOE with bubble contrast (the reference standard); however, the extent to which this translates into improved detection and clinical benefit in routine practice is uncertain and may vary according to service availability and access.

The ability of the proposed triage test (i.e. TCD bubble testing) to support appropriate referral, patient classification (i.e. presence or absence of a causally related PFO) and subsequent management decisions represents an important intermediate outcome. Accordingly, the impact of TCD bubble testing on clinical management is a key consideration, including its effects on referral rates for confirmatory TOE and the appropriateness of those referrals. Incorporation of TCD bubble testing may improve triage of patients for confirmatory imaging and has the potential to reduce use of semi-invasive TOE or streamline diagnostic pathways in settings where TCD is readily available. However, these benefits are likely to be context-dependent and may not be realised consistently across all clinical settings.

While earlier or more sensitive detection of right-to-left shunt may influence subsequent management decisions, the extent to which this translates into improved clinical outcomes (e.g. stroke recurrence, mortality, and quality of life) remains uncertain. This is because definitive classification informing treatment decisions is typically determined using TOE with bubble contrast in conjunction with validated risk stratification tools (e.g. PASCAL classification), which are applied alongside comprehensive clinical assessment.

Patient-centred outcomes are also relevant; earlier identification of a PFO-associated mechanism may provide diagnostic clarity and support timely management, although the impact on longer-term quality of life is likely to vary.

From a safety perspective, TCD is non-invasive with minimal direct risk; however, harms may arise indirectly from incorrect results, including complications of additional procedures or missed treatment opportunities.

TCD use may also affect healthcare resource use, particularly the number and type of downstream investigations and procedures. The introduction of TCD may reduce use of more resource-intensive imaging, although the overall resource impact will depend on utilisation patterns, diagnostic accuracy, and access to services.

Evidence for safety and clinical effectiveness

Evidence to inform the safety and clinical effectiveness of TCD bubble testing is expected to be available, although it is likely to be indirect and derived from multiple sources. Clinical effectiveness will primarily be assessed through diagnostic test accuracy studies, in which TCD bubble testing is compared against a reference standard, typically TOE with bubble contrast. These studies, along with systematic reviews and meta-analyses (e.g. Caso et al. 2024; Katsanos et al. 2016; Mojadidi et al. 2014; Pristipino et al. 2019; Yavuz et al. 2026; Zhang et al. 2024), provide evidence on sensitivity, specificity, concordance, and diagnostic yield, including the detection of right-to-left shunts. A small number of diagnostic test accuracy studies directly compare TCD bubble testing versus TTE with bubble contrast, using TOE as the reference standard (e.g. Di Tullio et al. 1993; González-Alujas et al. 2011; Oshima et al. 2026; Tan et al. 2024; Yang et al. 2020). However, the ESO guidelines (Caso et al. 2024) did not identify any such direct comparative studies in their systematic review, highlighting limitations in the consistency and accessibility of the evidence base.⁸ It is possible that relevant studies were not included due to the application of specific eligibility criteria; therefore, a targeted review of primary studies will be required to fully characterise the available comparative evidence.

Substantial heterogeneity is anticipated between studies. Differences in the use and adequacy of provocative manoeuvres (e.g. Valsalva), composition of contrast agent⁹, and thresholds for defining a positive test (e.g. microbubble count and timing of appearance) are likely to influence shunt detection rates. Variation in imaging protocols, patient positioning, and operator expertise – particularly for TCD – may further contribute to variability in reported diagnostic performance, although the extent of these effects will require confirmation through systematic review.

Study populations are also expected to be heterogeneous and may not fully reflect those encountered in contemporary PFO screening pathways. Many studies are likely to include selected patients with known or suspected shunts, potentially overestimating diagnostic performance compared with an unselected stroke population. In addition, TCD is sometimes evaluated as a confirmatory test following TTE with bubble contrast, rather than as a first-line triage tool, which may limit the direct applicability of the evidence to the proposed pathway. These anticipated limitations will require confirmation through a comprehensive review of the available evidence.

Direct evidence linking TCD bubble testing to patient health outcomes (e.g. stroke recurrence) is not expected. Instead, the impact on clinical outcomes will need to be inferred through a linked evidence approach, based on changes in patient management, such as appropriate referral for confirmatory TOE and subsequent decisions regarding PFO closure. Studies such as Tan et al. (2024) provide practical

⁸ Although the ESO guidelines (Caso et al. 2024) identified no direct comparative studies, they included 34 studies evaluating the diagnostic performance of TCD bubble testing against TOE with bubble contrast in patients with cryptogenic stroke, and 19 studies evaluating TTE with bubble contrast against TOE with bubble contrast.

⁹ Agitated saline (mixed with a small volume of air), with or without the addition of a small amount of the patient's blood, is the most commonly used contrast agent for TCD, TTE, and TOE bubble studies, although gelatin-based or commercial contrast agents may be used in specific circumstances.

examples of this pathway, reporting downstream management decisions, including confirmatory TOE and PFO closure, following both TCD and TTE bubble testing.

Safety data for TCD bubble testing are also expected to be limited but sufficient to demonstrate that the procedure is low risk, given its non-invasive nature and use of agitated saline contrast. Evidence is likely to be derived primarily from observational studies and clinical experience, with a focus on minor procedural risks (related to cannulation) and indirect harms arising from incorrect test results (i.e. false positive results leading to semi-invasive TOE, and false negative results leading to missed treatment opportunities).

PASC considered that the clinical evaluation should assess both the performance of the triage tests (i.e. TCD/TCCD or TTE) and their downstream impact on patient health outcomes. PASC noted that TTE with bubble contrast is an imperfect triage test and that, if TCD bubble testing is shown to have superior diagnostic performance compared with TTE, it could increase the identification of patients with a PFO who are at risk of recurrent stroke and should proceed to confirmatory TOE, potentially enabling earlier and more appropriate management, including PFO closure where indicated. This may improve health outcomes by reducing recurrent stroke events and associated morbidity, with consequent benefits for patients' quality of life.

Assessment framework

The proposed use of TCD bubble testing is an alternative triage modality to TTE with bubble contrast within the existing diagnostic pathway for detecting right-to-left shunt and suspected PFO following cryptogenic ischaemic stroke or ESUS. The application claimed that TCD bubble testing has superior sensitivity compared with TTE with bubble contrast for detecting right-to-left shunts and may therefore improve identification and triage of patients for confirmatory TOE with bubble contrast.

The evaluation will adopt a linked evidence approach, incorporating comparative diagnostic accuracy and resulting changes in downstream management that are likely to influence health outcomes.

A graphical representation of each step in the linked evidence analysis is shown in the assessment framework below. Each step represents an evidentiary requirement and corresponds to a specific assessment question.

Figure 1 Assessment framework showing the links from the test population to health outcomes

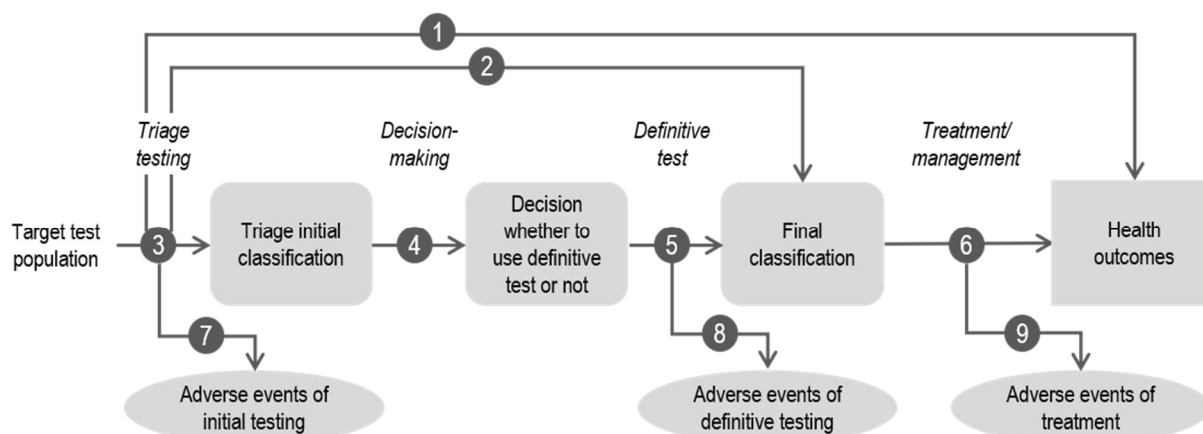


Figure notes: 1: direct evidence from test to health outcomes; 2: impact of triage test on time to final classification (i.e. presence or absence of a causally related PFO) and clinical management decisions; 3: test accuracy; 4: change in referral for definitive testing; 5: influence of the triage test

on definitive test results and final classification; 6: influence of the triage test on treatment selection and subsequent health outcomes; 7: adverse events due to triage testing; 8: adverse events due to definitive testing; 9: adverse events due to subsequent treatment.

While TOE with bubble contrast is commonly used as the reference standard for PFO assessment, it is not perfectly sensitive for detecting right-to-left shunt. However, under the PASCAL classification framework, which incorporates shunt size and clinical features to determine the likelihood that a PFO is causally related to the index stroke, additional small right-to-left shunts detected by TCD but not confirmed on TOE may not change the overall classification of PFO-related stroke causality. Consequently, improvements in the analytical sensitivity of shunt detection may not necessarily translate into changes in the final clinical classification of a causally related PFO, nor into differences in downstream management or patient outcomes for all patients. The assessment should therefore examine whether any incremental diagnostic yield associated with TCD bubble testing compared with TTE with bubble contrast results in meaningful changes in PFO classification, clinical management and patient outcomes.

Direct evidence

Step 1: Test to health outcomes

- In patients with prior cryptogenic ischaemic stroke or ESUS undergoing evaluation for a causally related PFO, does the use of TCD bubble testing followed by TOE with bubble contrast, compared with TTE with bubble contrast followed by TOE with bubble contrast, result in comparable or superior health outcomes?

Direct evidence linking TCD bubble testing to health outcomes (e.g. stroke recurrence, mortality) is not anticipated.

Indirect evidence

Step 2: Impact on time to final classification (i.e. presence or absence of a causally related PFO)

- Does the use of TCD bubble testing, compared with TTE with bubble contrast, reduce the time to final classification of the presence or absence of a causally related PFO, and to subsequent clinical decision-making?

Step 3: Test accuracy

- What is the comparative diagnostic accuracy and concordance of bubble testing using a TCD system compared with a TCCD system?
- What is the comparative diagnostic accuracy of TCD bubble testing compared with TTE with bubble contrast against the reference standard (TOE with bubble contrast)? What is the concordance of TCD bubble testing compared to TTE with bubble contrast?
- What are the clinical consequences of a false-negative triage test (i.e. TCD bubble testing or TTE with bubble contrast) result?

If the comparative diagnostic accuracy of TCD and TCCD systems is not found to differ materially, the two technologies may be considered together for the remainder of the assessment. If meaningful differences in diagnostic accuracy are identified, TCD and TCCD should be assessed separately.

Step 4: Change in initial classification and referral for definitive testing

- Does the use of TCD bubble testing, compared with TTE with bubble contrast, alter the proportion of patients referred for TOE?

Populations considered at this step include:

- triage test-positive patients (referred for TOE with bubble contrast)
- triage test-negative patients (no further PFO investigation, unless clinical suspicion persists after TTE with bubble contrast)
- triage test-equivocal patients (considered for repeat triage testing or referral for TOE with bubble contrast).

Step 5: Impact on final classification

- Does the use of TCD bubble testing (followed by TOE with bubble contrast) result in the same classification (i.e. presence or absence of a causally related PFO) compared with TTE with bubble contrast (followed by TOE with bubble contrast)?

Step 6: Impact on treatment selection and subsequent health outcomes

- Do differences in the diagnostic performance of TCD bubble testing and TTE with bubble contrast translate into differences in treatment selection (e.g. PFO closure or medical management) and subsequent health outcomes?

Step 7: Adverse events due to triage testing

- What are the direct harms associated with TCD bubble testing compared with TTE with bubble contrast?
- What are the indirect harms associated with false positive and false negative results?

Step 8: Adverse events due to definitive testing

- What are the harms associated with definitive, semi-invasive TOE with bubble contrast, and do differences in the TCD and TTE diagnostic pathways result in differences in exposure to these harms?

Step 9: Adverse events due to subsequent treatment

- What are the harms associated with subsequent treatment (e.g. PFO closure or medical management), and do differences in the TCD and TTE diagnostic pathways result in differences in exposure to these harms?

PASC considered that a full assessment framework, without truncation, is appropriate given the claim of superior diagnostic performance for TCD bubble testing compared with TTE with bubble contrast. PASC noted that the choice of triage test may alter the spectrum of patients referred for confirmatory TOE, affecting both the likelihood of confirming a PFO and the performance of the overall diagnostic pathway. PASC further noted that there is relatively robust downstream evidence comparing PFO closure with medical management in patients with a confirmed PFO. As improved identification of patients with a PFO who are at risk of recurrent stroke may increase access to appropriate treatment and improve health outcomes, PASC considered that assessment of downstream clinical consequences is required.

Clinical management algorithms

Current clinical management

In current practice (Figure 2), patients presenting with suspected cryptogenic ischaemic stroke undergo a structured diagnostic work-up, typically coordinated by a neurologist or stroke physician, to exclude common causes of stroke. This includes brain imaging, vascular imaging, cardiac rhythm monitoring (e.g. to exclude AF), and laboratory investigations. Where no alternative cause is identified, patients proceed to evaluation for a PFO, usually in collaboration with cardiology services.

Initial evaluation for PFO is commonly undertaken using TTE, increasingly with bubble contrast, which functions as a triage test for the detection of a right-to-left shunt. TTE with bubble contrast provides a non-invasive means of identifying or excluding a potential shunt and may also provide information on other structural cardiac abnormalities. However, detection of a right-to-left shunt does not confirm that a PFO is present, and TTE does not generally provide sufficient detail to fully characterise PFO anatomy or associated high-risk features relevant to treatment decision-making.

Based on the results of the triage test (i.e. TTE with bubble contrast), patients may be classified as having a right-to-left shunt detected, not detected, or equivocal findings. Patients with positive or equivocal findings are typically referred for TOE with bubble contrast, which serves as the confirmatory test for a PFO. Patients with negative TTE results may also be referred for TOE with bubble contrast where there is persistent clinical suspicion of a PFO-mediated stroke, such as in younger patients with an embolic-pattern stroke, no alternative stroke aetiology identified following standard investigations, a high RoPE score, or a history of venous thromboembolism. Referral to TOE may be particularly warranted where the TTE examination was technically limited or where there are concerns regarding its sensitivity to exclude a clinically significant PFO. Where equivocal findings are considered to reflect technical limitations (e.g. inadequate Valsalva manoeuvre, incomplete examination, or uncertainty regarding study quality), repeat TTE with bubble contrast may be considered before proceeding to TOE.

Other triage modalities, such as TCD bubble testing, may be used in some centres; however, their use in Australia is currently limited and variable, and they are not routinely incorporated into standard diagnostic pathways.

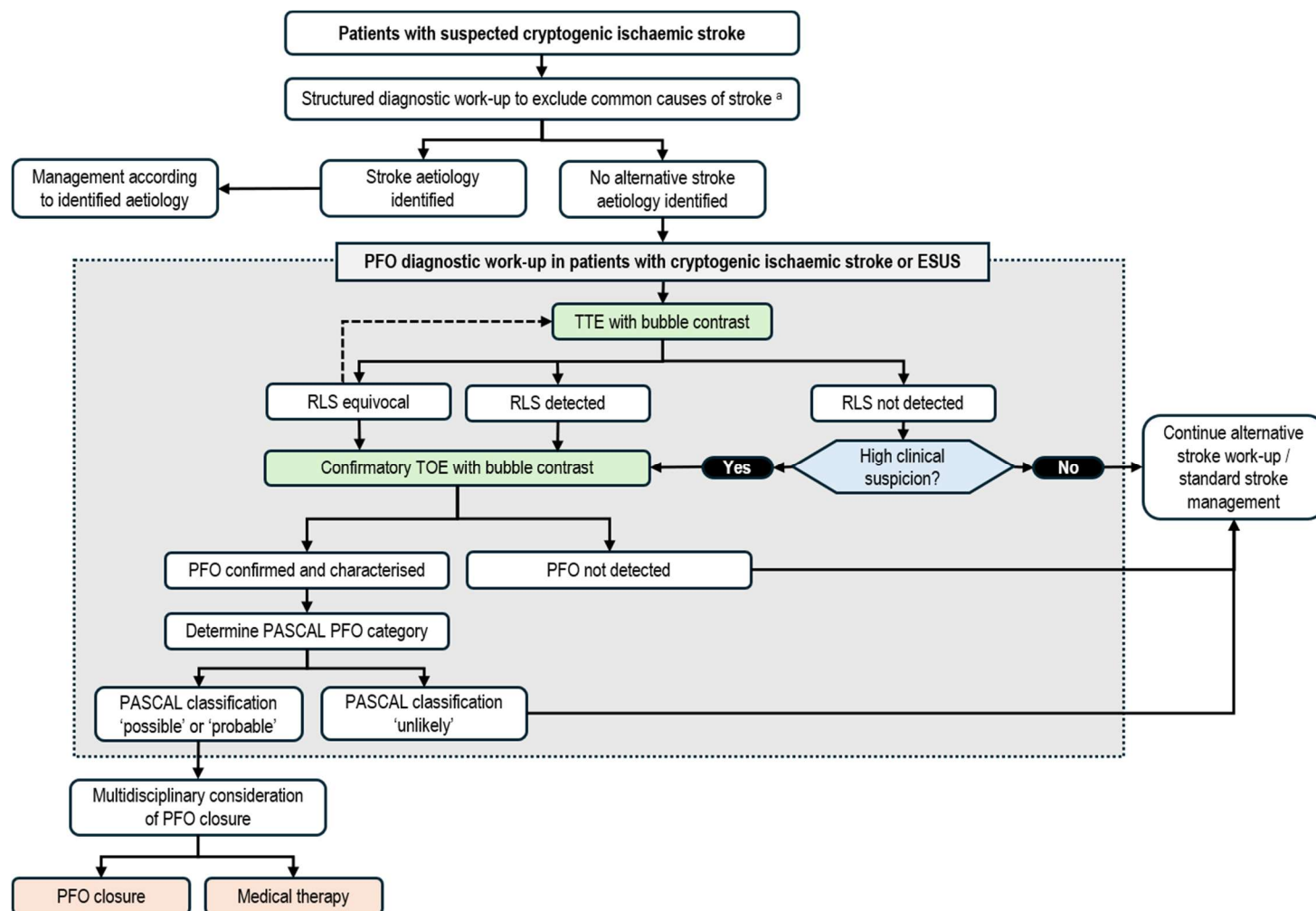
Where a PFO is confirmed by TOE with bubble contrast, clinical assessment focuses on determining the likelihood that the PFO is causally related to the index stroke. This involves integration of clinical factors (e.g. age, vascular risk factors), often captured in the RoPE Score, and anatomical features identified on TOE (e.g. shunt size, presence of an atrial septal aneurysm). In practice, this combined assessment is frequently undertaken in a manner conceptually consistent with frameworks such as the PASCAL classification, although application is not standardised and may be implicit rather than formally defined.

Management decisions are then based on this integrated clinical judgement. Patients considered to have a higher likelihood of PFO-related stroke may be referred for percutaneous closure following multidisciplinary discussion (typically involving neurology and cardiology), while others are managed with medical therapy alone.

While this approach is broadly consistent with contemporary clinical practice guidelines (Stroke Foundation; Caso et al. 2024; Kavinsky et al. 2022; Kleindorfer et al. 2021; Pristipino et al. 2019), there is

substantial variation in test sequencing, escalation to TOE, and the consistency with which structured risk stratification approaches (e.g. RoPE and PASCAL-type assessments) are applied, reflecting differences in clinician preference, local expertise, and access to imaging.

Figure 2 Current clinical management algorithm



AF = atrial fibrillation; CT = computed tomography; ESUS = embolic stroke of undetermined source; MRI = magnetic resonance imaging; PFO = patent foramen ovale; RLS = right-to-left shunt; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

^a Standard work-up includes: **brain imaging** (e.g. MRI, CT); **vascular imaging** (e.g. CT or MR angiography) to exclude extracranial and intracranial arterial stenosis; **cardiac evaluation** (including TTE to assess for structural cardiac sources of embolism and prolonged rhythm monitoring to exclude AF); **targeted laboratory investigations** (e.g. vasculitis or thrombophilia in selected patients); **additional investigations as indicated**.

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Proposed clinical management

Under the proposed clinical management algorithm (Figure 3), patients presenting with suspected cryptogenic ischaemic stroke or ESUS undergo the same structured initial diagnostic work-up as in current practice to exclude alternative causes of stroke. Patients in whom no alternative cause is identified proceed to targeted evaluation for a PFO.

Initial evaluation is undertaken using either TTE with bubble contrast or TCD bubble testing, both of which function as triage tests for the detection of a right-to-left shunt. The choice of triage modality may be based on local availability, clinician expertise, and access to imaging services.

Following triage testing, patients are categorised as having a right-to-left shunt detected, not detected, or equivocal findings. Patients with positive results typically proceed directly to TOE with bubble contrast, which serves as the confirmatory test for PFO.

Where triage testing is negative (i.e. no right-to-left shunt is detected), a PFO is generally considered unlikely to be the cause of the index event, particularly when TCD bubble testing has been used as the initial triage modality, given its high sensitivity. In such cases, further investigation should focus on identifying alternative stroke mechanisms. A negative TCD result may not completely preclude further cardiac assessment where clinical suspicion of a PFO remains high, although this was expected to occur infrequently.

In cases of equivocal findings, further assessment may be considered depending on the initial test performed and the level of clinical suspicion. Patients with equivocal TTE with bubble contrast findings may be referred for TCD bubble testing, if available, particularly where substantial delays to confirmatory TOE are anticipated. TTE is not routinely performed following TCD bubble testing specifically for PFO assessment, as it is generally undertaken as part of the standard post-stroke cardiac evaluation. Nevertheless, TTE may provide complementary information on structural cardiac abnormalities, such as impaired ventricular function, valvular heart disease, or cardiomyopathy, which may inform subsequent investigation and management in selected patients.

From the point of confirmatory TOE onwards, clinical management is consistent with that described in the current clinical management pathway. Specifically, where a PFO is confirmed, assessment of causal relevance integrates clinical and anatomical factors (often including RoPE-informed assessment and PASCAL classification), and management decisions regarding PFO closure versus medical therapy are made accordingly.

Compared with current practice, the proposed algorithm primarily differs in the flexible selection of the initial triage modality based on local availability.

The proposed clinical management algorithm is broadly consistent with contemporary Australian and international clinical practice guidelines and position papers (Caso et al, 2024; Chambers et al. 2026; Kleindorfer et al. 2021; Messe et al. 2020; Pristipino et al. 2019). However, guideline recommendations vary in the positioning of diagnostic modalities within the pathway. In particular, while the proposed algorithm allows either TTE with bubble contrast or TCD bubble testing to be used as initial triage tests, the ESO guidelines (Caso et al. 2024) position TCD as an additional investigation following a negative or inconclusive TTE result in patients with ongoing clinical suspicion.

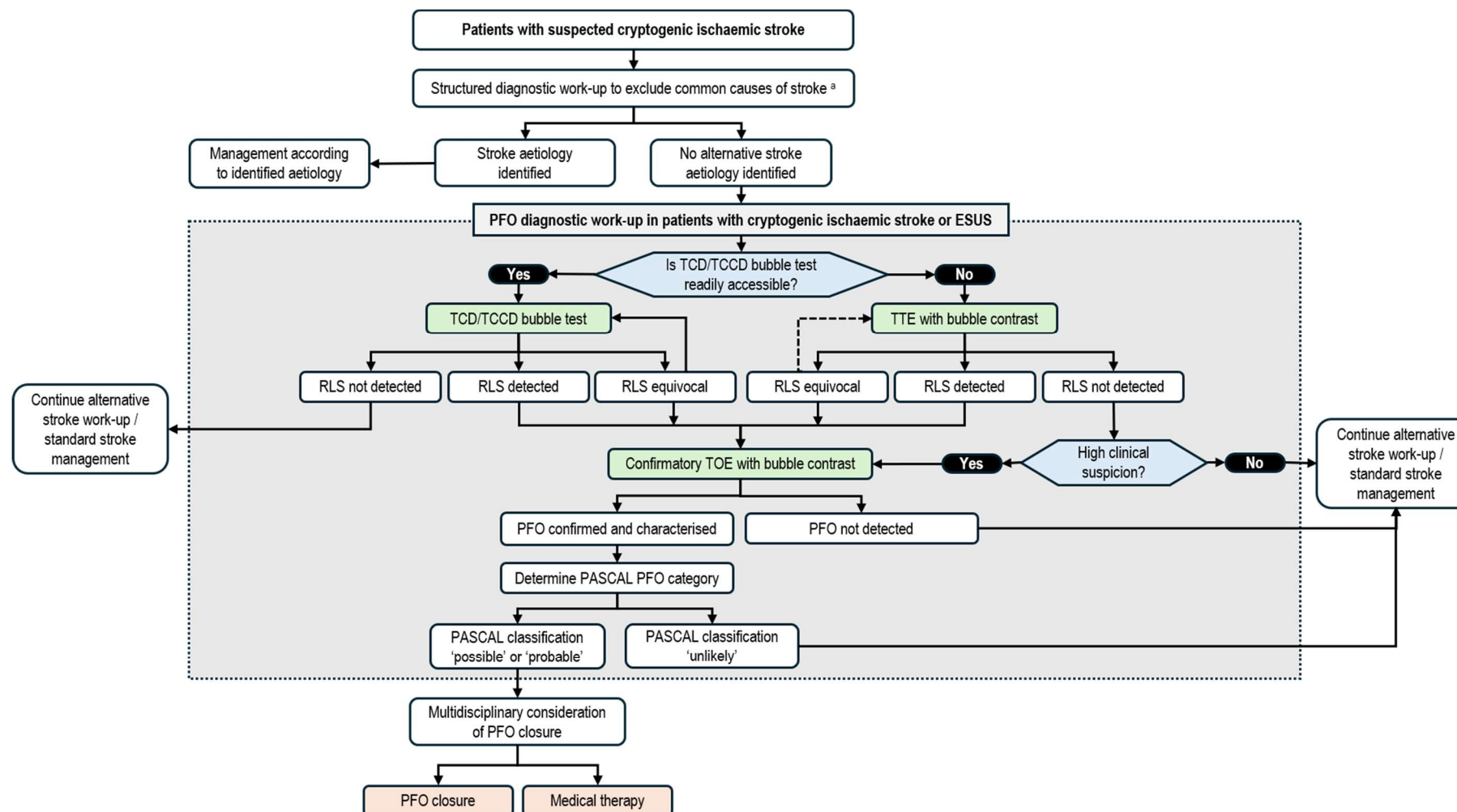
The Australian and New Zealand consensus statement, in contrast, recommends that, where available, TCD bubble testing be considered the preferred first-line screening modality for detection of PFO in patients with cryptogenic stroke, reflecting its higher sensitivity for detecting right-to-left shunt (Chambers et al. 2026).

In practice, selection of the initial modality may also be influenced by technical and logistical considerations, including the availability of services and patient-specific factors (e.g. adequacy of the acoustic window for TCD).

PASC considered that, where available, TCD bubble testing should be preferred over TTE with bubble contrast (that is, TTE should be used only where TCD bubble testing is not available, or otherwise not possible) in the clinical pathway due to its claimed superior performance in detecting right-to-left shunts. PASC noted that the use of TCD bubble testing as the preferred triage test may improve the identification of patients who should proceed to confirmatory TOE.

PASC further noted that the high sensitivity of TCD bubble testing may provide greater confidence in excluding a clinically significant right-to-left shunt when no shunt is detected (i.e. TCD result is negative), thereby reducing the need for confirmatory TOE in these patients and supporting investigation of alternative causes of stroke. The applicant confirmed that referral for TOE following a negative TCD bubble test would be uncommon and would generally be limited to cases where TOE is required to investigate alternative cardiac sources of stroke or other clinically relevant cardiac pathology. PASC considered that TTE with bubble contrast would remain an appropriate alternative triage test where TCD bubble testing is not readily accessible.

Figure 3 Proposed clinical management algorithm



AF = atrial fibrillation; CT = computed tomography; ESUS = embolic stroke of undetermined source; MRI = magnetic resonance imaging; PFO = patent foramen ovale; RLS = right-to-left shunt; TCD = transcranial Doppler; TCCD = transcranial colour-coded duplex sonography; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

^a Standard work-up includes: **brain imaging** (e.g. MRI, CT); **vascular imaging** (e.g. CT or MR angiography) to exclude extracranial and intracranial arterial stenosis; **cardiac evaluation** (including TTE to assess for structural cardiac sources of embolism and prolonged rhythm monitoring to exclude AF); **targeted laboratory investigations** (e.g. vasculitis or thrombophilia in selected patients); **additional investigations as indicated**.

Proposed economic evaluation

The application claimed that TCD bubble testing is superior to TTE with bubble contrast in sensitivity for detecting right-to-left shunt, while being noninferior in terms of safety. On this basis, where TCD is available, it is expected to improve identification of a causally related PFO and support more appropriate and timely downstream management, including referral for confirmatory testing and consideration of PFO closure. The application also suggests that a shorter time to diagnosis and treatment of a causally related PFO may reduce the risk of recurrent stroke in the intervening period.

In accordance with the classification matrix (Table 5), a claim of superior effectiveness and noninferior safety would typically support a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA).

Table 5 Classification of comparative effectiveness and safety of the proposed investigative medical service, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Noninferior ^b	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior ^b	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis.

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis.

a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations.

b An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence.

The economic evaluation should adopt a linked evidence approach, whereby differences in test performance between TCD and TTE are modelled in terms of their impact on downstream clinical management (such as referral for confirmatory TOE, PFO closure, or medical management), which in turn influence health outcomes, including stroke recurrence and quality of life.

Key considerations expected to influence the economic evaluation include:

- differences in diagnostic accuracy, particularly the consequences of false negatives (missed PFOs) and false positives (potentially avoidable TOE procedures)
- the cost of TCD bubble testing, including capital equipment, workforce requirements and training
- the potential for stroke recurrence associated with delays in diagnosis and treatment of a causally related PFO
- downstream treatment effects, including eligibility for and uptake of PFO closure versus medical management
- adverse events, including procedure-related complications (e.g. TOE, PFO closure)

- the effect of test availability and service configuration on diagnostic pathways and time to treatment.

PASC considered that a CUA was appropriate given the claim that TCD bubble testing has superior diagnostic performance compared with TTE with bubble contrast and the potential for this to translate into improved patient health outcomes. PASC noted that improved identification of patients with a PFO at risk of recurrent stroke may influence downstream management, including access to PFO closure where indicated, with consequent impacts on health outcomes, quality of life and healthcare resource use.

Proposal for public funding

The application proposed the creation of a new MBS item to support the use of TCD bubble testing as a first-line triage investigation in patients with prior ischaemic stroke (Box 4).

Box 4 New MBS item proposed in the application

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
MBS item XXXXX Bubble study for detection of patent foramen ovale in patient with previous ischaemic stroke. Must be performed by an accredited sonographer, in an accredited practice, using a registered TCD or TCCD device, with an attending medical practitioner or accredited health professional.
Fee: \$250.00 Benefit: 75% = \$187.50 85% = \$212.50

Proposed fee

The applicant has proposed a schedule fee of \$250 for the new item. This fee is intended to bundle the TCD monitoring components (including acquisition, interpretation, and reporting) with the additional procedural elements required for the bubble study, such as IV cannulation, preparation and administration of agitated saline contrast, Valsalva manoeuvre coaching, and repeat injections where necessary.

At present, there is no MBS item specifically covering the bubble study component when performed with TCD, TTE or TOE for the detection and grading of a PFO. For TTE and TOE, the bubble study component is incorporated within existing echocardiography service items.

The proposed fee is higher than current MBS items used in practice to deliver TCD bubble testing (item 11614: \$90.55; item 55280: \$199.70) but is broadly comparable to TTE services (items 55126 and 55129), which are used with or without bubble contrast and have a schedule fee of \$271.80. While the resource requirements for the bubble study component of TCD and TTE are similar, the overall duration of TTE with bubble contrast (typically 30–45 minutes) may be somewhat longer than for TCD bubble testing (approximately 20–30 minutes).

The department suggested that a schedule fee of \$202.05 may be appropriate, benchmarked against MBS item 11724 (\$202.05) for up-right tilt table testing for the investigation of syncope of suspected cardiothoracic origin. Both services involve intravenous administration of a substance; however, while item 11724 generally requires a longer duration (approximately twice that of TCD bubble testing), the TCD procedure necessitates specialised sonographic acquisition and interpretation. This is typically more

technically complex than the blood pressure and electrocardiographic (ECG) monitoring and interpretation required for MBS item 11724 and may justify a relatively higher weighting of procedural complexity despite the shorter duration.

Proposed descriptor

The proposed descriptor specifies that the service be performed by an accredited sonographer, within an accredited practice, using a registered TCD or TCCD system, with the presence of an attending medical practitioner or appropriately trained health professional. This specification is consistent with governance and quality standards applied to diagnostic imaging services.

However, the proposed descriptor wording – “bubble study for detection of patent foramen ovale in a patient with previous ischaemic stroke” – is relatively broad and may allow use beyond the intended role of the test in initial diagnostic evaluation. In particular, it could permit use in the assessment of residual shunt following PFO closure, which is not the intended purpose of the application.

Further, the descriptor does not explicitly limit use to patients with cryptogenic stroke who are undergoing evaluation for suspected PFO. Closer alignment of the descriptor with this target population may improve clarity, ensure consistency with the relevant clinical evidence, and reduce the risk of use outside the intended clinical context.

An alternative version of the item descriptor and fee, incorporating advice from the department, is shown in Box 5. Notably, the proposed wording is intentionally non-restrictive, allowing use at any appropriate point within the diagnostic pathway.

Box 5 Alternative descriptor and fee for the new MBS item, proposed by the department and supported by PASC

Category 2 – DIAGNOSTIC PROCEDURES AND INVESTIGATIONS
MBS item XXXXX Transcranial Doppler or transcranial colour-coded duplex study of the intracranial circulation, including agitated saline contrast and provocative manoeuvres, for detection of right-to-left shunt consistent with patent foramen ovale in a patient with prior cryptogenic ischaemic stroke or embolic stroke of undetermined source, performed by, or on behalf of, a medical practitioner.
Fee: \$202.05 Benefit: 75% = \$151.55 85% = \$171.75

Proposed fee is benchmarked against MBS item 11724 (fee at 01 July 2026) for up-right tilt table testing for the investigation of syncope of suspected cardiothoracic origin. Both services involve intravenous administration of a substance.

From a utilisation perspective, the test is expected to be performed once per diagnostic episode. Consideration could be given to restricting frequency of use (e.g. once per patient, with allowances for repeat testing where clinically indicated), recognising that most patients require only a single test to establish the presence or absence of a right-to-left shunt, while maintaining flexibility for inconclusive studies or selected follow-up scenarios.

PASC considered whether separate MBS items would be needed for bubble testing performed using TCD or TCCD systems. PASC noted that the existing MBS items are not indication-specific and do not incorporate the bubble testing component of the service. PASC further noted that MBS item 11614, used for TCD systems, is classified as a diagnostic procedure and investigation under Category 2, whereas MBS item 55280, used for TCCD systems, is classified as a diagnostic imaging service and is subject to accreditation,

workforce and service delivery requirements, including compliance with DIAS, and attracts a higher schedule fee.

PASC noted the applicant's advice that TCD and TCCD bubble testing have similar diagnostic performance for the detection of right-to-left shunts, and that use of either modality would be expected to reflect local resource availability and service configurations rather than differences in clinical effectiveness. PASC further noted that TCD bubble testing is currently being provided in DIAS-accredited centres and considered that a single MBS item may be appropriate, provided that the service specification clearly outlines the required governance, accreditation and workforce requirements, including that the test be performed by a suitably trained and credentialled ultrasonographer or equivalent practitioner.

After the PASC meeting, the department advised that inclusion of both conventional TCD and TCCD within a single Category 5 item may present implementation challenges and would require further consideration of diagnostic imaging accreditation, equipment and credentialling requirements. Given that conventional TCD is a non-imaging modality currently funded under Category 2 and the proposed service model extends beyond the traditional diagnostic imaging workforce, the department noted that inclusion of both TCD and TCCD within a single Category 2 or Category 5 item would require further consideration of accreditation, equipment and workforce requirements. If the item was placed in Category 5, overarching changes would be required to the diagnostic imaging services table to accommodate TCD and non-diagnostic radiology providers. Alternatively, if the item was placed in Category 2, clauses would be required in the regulation to ensure at a minimum, that those providers undertaking the ultrasonography component of the service were appropriately credentialled. .

Summary of public consultation input

PASC noted and welcomed consultation input from 4 organisations and no individual input was received. The 4 organisations that submitted input were:

- South Australian (SA) Stroke Clinical Network
- Stroke Foundation
- The Royal Australian and New Zealand College of Radiologists (RANZCR)
- Australia & New Zealand Association of Neurologists (ANZAN).

Consultation input was mostly supportive of public funding for TCD bubble testing for PFO. RANZCR raised concerns in relation to the service providers for TCD and the proposal that TCD may replace TTE and TOE rather than be an adjunct test.

Consumer Experience

The Stroke Foundation stated that people who have a cryptogenic ischaemic stroke often experience significant stress and uncertainty, as without knowing the cause, it can be difficult to determine the best treatment to prevent another stroke. Many patients experience difficulties with movement, strength, coordination, speech, swallowing and completing everyday activities. Patients may also experience less visible challenges such as fatigue, memory problems, difficulty concentrating, and changes in thinking and planning, which can affect independence, employment and quality of life.

Consultation input from the Stroke Foundation also included that carers play an important role in supporting people recovering from stroke, including helping with medical appointments and providing care

at home. However, caring responsibilities can have a substantial impact on carers' own lives. Many carers reduce their work commitments, participate less in leisure activities, and experience changes in their relationships and social connections. These pressures can lead to poorer physical and mental health and a reduced quality of life for carers.

Benefits and Disadvantages

The main benefits of public funding reported in the consultation input included earlier and more accurate diagnosis of PFO-associated stroke, reduced delays to accessing treatment, reduced risk of recurrent stroke, and improved use of health system resources through reduced reliance on other diagnostic procedures. Consultation input also highlighted the potential to reduce hospital length of stay and improve patient outcomes. The Stroke Foundation stated that in comparable high-income countries, TCD bubble test is the standard of care as it has a higher sensitivity for PFO compared to TTE bubble testing.

The main disadvantages of public funding reported in the consultation input related to implementation challenges, including workforce training requirements, limited availability of specialised equipment and expertise, and the potential for some patients to be unsuitable for testing due to anatomical limitations or challenges in executing the required Valsalva manoeuvre. RANZCR stated that whilst TCD could confirm a shunt malfunction had occurred, it could not identify the actual location and is less specific for distinguishing intracardiac from extracardiac shunts.

Population, Comparator (current management) and Delivery

The consultation input was largely supportive of the proposed population. The SA Stroke Clinical Network, Stroke Foundation and ANZAN considered the proposed population appropriate and consistent with current clinical practice.

The consultation input was generally supportive of the proposed comparator, noting that TTE with bubble test reflects current Australian clinical practice for investigating suspected PFO-associated stroke. RANZCR stated that TCD bubble testing should be considered as part of the broader diagnostic pathway and not as a complete replacement for other cardiac investigations where clinically required.

Other services identified as being needed after the intervention included TTE and/or TOE, to confirm PFO and assess anatomical features. The Stroke Foundation stated that TOE is the gold standard for identifying high-risk PFO anatomical features which are associated with recurrent stroke.

MBS Item Descriptor and Fee

The consultation input was generally supportive of the proposed service descriptor. RANZCR consultation input stated that radiologists and interventional neuroradiologists are not included in the application as service providers despite being the principal providers of this service.

The consultation input did not comment on the proposed service fee.

Additional Comments

RANZCR consultation input noted that the application does not acknowledge the broader use of TCD for PFO diagnosis across Australia and underrepresents the number and diversity of providers routinely using

this diagnostic approach. They also stated that waiting times for TTE/TOE vary across regions, and long waiting times should not be used as a general rationale for replacing these modalities with TCD.

PASC noted stakeholder support for the application from the Australian Stroke Foundation, the SA Stroke Clinical Network, and ANZAN. Stakeholders highlighted the potential for TCD bubble testing to facilitate earlier diagnosis of PFO-associated stroke and access to treatment. However, feedback also noted that current expertise is concentrated in a limited number of specialist centres and that training may be required to support wider implementation.

PASC also noted feedback from RANZCR that TCD bubble testing detects the presence of a right-to-left shunt rather than directly diagnosing a PFO, reinforcing the ongoing role of confirmatory TOE. PASC further noted RANZCR's comments that access to, and waiting times for, TTE and TOE vary across Australia, and that radiologists and interventional neuroradiologists also provide TCD services. PASC noted the applicant's advice that radiologists and interventional neuroradiologists do not currently routinely provide TCD bubble testing services in Australian stroke centres, with existing services primarily delivered through neurology-led stroke and neurovascular centres.

Next steps

PASC advised the application could proceed to the assessment stage.

Applicant Comments on Ratified PICO

The applicant had no comment.

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