



Australian Government

Department of Health

MEDICAL SERVICES ADVISORY COMMITTEE

Application 1428:

**Mechanical thrombectomy
for acute ischaemic stroke**

Protocol

Title of Application

Mechanical thrombectomy for acute ischaemic stroke.

Purpose of application

The purpose of the application is to request Medicare Benefits Schedule (MBS) listing for the therapeutic intervention of mechanical thrombectomy (MT) for the treatment of acute ischaemic stroke (AIS) due to a large vessel occlusion. In this protocol mechanical thrombectomy, describes the use of devices such as stent retrievers and aspiration catheters to remove thrombi/blood clots. These devices are delivered to occluded sites with the aid of microcatheters and guidewires. The aim of this therapy is to restore blood flow to minimise damage to the brain from stroke. It is proposed that this protocol should guide the assessment of the safety, effectiveness and cost-effectiveness of mechanical thrombectomy therapy in the requested populations, to inform MSACs decision-making regarding public funding of this therapeutic procedure.

Stroke is a major cause of prolonged neurologic disability in adults and has significant clinical and cost burdens. Improved management of patients during the acute phase can save patients' lives, and help to reduce both the clinical and cost burden of stroke. For individuals who have an AIS, the key to effective treatment is early reperfusion of ischaemic brain without causing adverse effects. To achieve reperfusion, intravenous thrombolytic therapy (with intravenous tissue plasminogen activator [IV tPA]) is recommended in treatment guidelines¹, however many patients fail to respond to, or are ineligible to receive thrombolytic therapy. MT has become a treatment option for these patients. In addition, for those patients who receive thrombolytic therapy, clinical outcomes can be improved when MT is used as an adjunct to thrombolytic therapy.

In 2014-2015, five mechanical thrombectomy randomized controlled trials (RCTs) - namely, MR CLEAN², ESCAPE³, EXTEND-IA⁴, REVASCAT⁵ and SWIFT PRIME⁶ - were completed and have been published in the *New England Journal of Medicine*. All five RCTs showed a significant clinical benefit and improvement in functional outcomes in carefully selected AIS patients treated with new generation MT technology (stent retrievers – which work by temporarily deploying a stent that captures the thrombus) in comparison to standard therapy alone (IV tPA). As a consequence of the positive results of recent clinical trials, various international management guidelines for AIS were updated in 2015 and late 2014, with new recommendations made on the use of MT⁷ (see Section 3, and Table 2).

In assessing MT, it is important that a broad and inclusive approach is taken. This approach is in accordance with the established Medical Services Advisory Committee (MSAC) mandate to ensure recommendations relating to public funding for generic MBS items are not defined by particular technologies. Hence, it is proposed that the assessment of MT will be generic - i.e. considering evidence for all relevant technologies that can deliver the proposed service. Mechanical thrombectomy interventions for AIS are a new therapeutic option and are not currently listed on the MBS.

Population and medical condition eligible for the proposed medical services

Stroke

According to the World Health Organization (WHO), the definition of stroke is :“*rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin.*”^{8, 9} Strokes can be either ischaemic or haemorrhagic.

Haemorrhagic stroke, also known as spontaneous intracerebral haemorrhage (ICH), occurs when blood spontaneously extravasates outside the blood vessels into the brain parenchyma, that is, it occurs within the brain tissue rather than outside of it (Figure 1). This may involve arterial, venous or capillary vessels^{10,11, 12}. The standard definition of primary ICH excludes haemorrhages related to trauma or secondary haemorrhagic transformation (such as brain bleeds after surgery, or bleeding due to brain tumours etc.). Subarachnoid haemorrhage is a less common type of haemorrhagic stroke. They are mainly due to the rupture of aneurysms at the bifurcations of large arteries at the inferior surface of the brain⁹.

While haemorrhagic strokes happen when there is bleeding into brain tissue that kills brain cells, an ischaemic stroke occurs when an artery supplying the brain becomes occluded, leading to the death of brain tissue and focal neurological deficits¹³ (Figure 1).

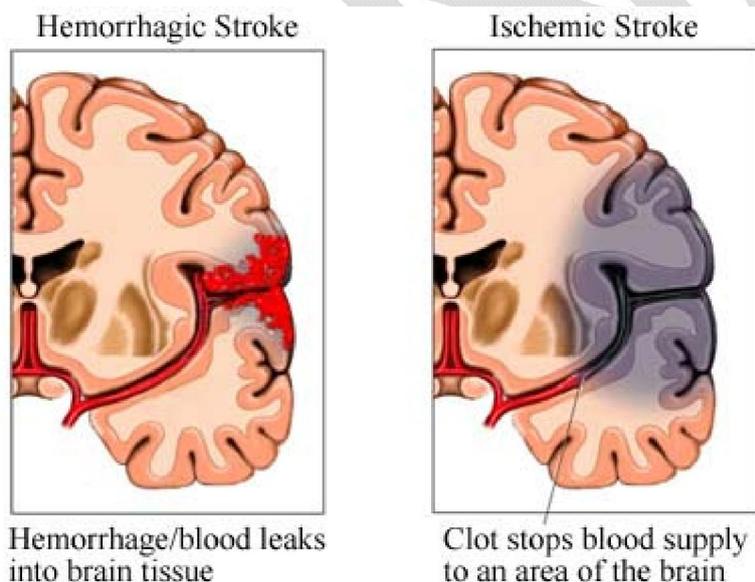


Figure 1 Haemorrhagic vs. Ischaemic stroke types

Source: <http://www.beliefnet.com/healthandhealing/images/si55551195.jpg>

Of all strokes, 88% are ischaemic and 12% are haemorrhagic in nature. Of the haemorrhagic strokes, 9% are due to an intracerebral haemorrhage, and 3% are due to a subarachnoid haemorrhage.^{14,15}

Acute ischaemic stroke

The patient population who would benefit from the proposed service are patients with AIS.

AIS has recently been defined as the occlusion of the brain, retina, or spinal cord supplying artery that results in focal tissue infarction and corresponding sudden neurological deficits.¹⁶ AIS occurs when a sudden occlusion of an intracranial blood vessel (Figure 2) causes an acute onset of symptoms.

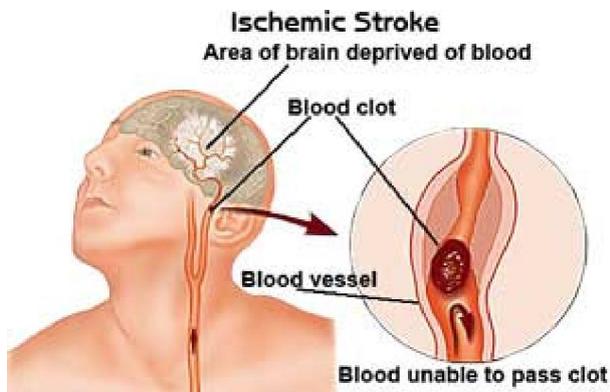


Figure 2 Intracranial blood vessel occlusion

Source: <http://www.medgadget.com/wp-content/uploads/2015/07/Acute-Ischaemic-Stroke.jpg>

AIS – Signs and symptoms

The presenting signs and symptoms of AIS and haemorrhagic stroke are similar, and many studies suggest the two types of strokes cannot be distinguished reliably without brain imaging. Symptoms are of sudden onset and usually maximal in severity at, or within minutes of, onset¹⁷. While the clinical manifestations of stroke vary, depending on the site and size of the brain lesion,^{18, 19} some of the more common symptoms of stroke include:

- Loss of (or abnormal) sensations in an arm, leg or one side of the body
- Weakness or paralysis of an arm or leg or one side of the body
- Partial loss of vision or hearing
- Double vision
- Dizziness
- Slurred speech
- Problems thinking of or saying the right word
- Inability to recognize parts of the body
- Imbalance and falling

While stroke symptoms vary and diagnosis of stroke type relies on imaging, AIS patients will typically present with the sudden onset of weakness, numbness, vision loss, diplopia, dysarthria, gait disorder, vertigo, aphasia, or disturbed level of consciousness. The location of the stroke will determine which particular pattern of symptoms occurs. AIS typically involves an absence of function. For example, an ischaemic stroke patient will often report loss of vision in a single eye or in an entire hemifield²⁰.

The most common historical feature of an ischaemic stroke is awakening with or acute onset of symptoms, whereas the most common physical findings are unilateral weakness and speech disturbance.

AIS – Pathophysiology and risk factors

The underlying pathogenic mechanism for AIS is the occlusion of an artery in the neck or in the brain which results in interruption of blood flow and delivery of essential oxygen and glucose to the brain tissue. The brain does not store glycogen and requires 60-70 mL of perfusion per 100 g of tissue per minute for normal function²¹. A drop in the blood flow to 25 mL/100 g/min leads to neuronal ischaemia, energy failure, and neurologic symptoms, followed by irreversible tissue damage within minutes should ischaemia continue^{22,23}.

Ischaemic strokes can be broadly subdivided into thrombotic and embolic strokes. The occlusion of the artery is most commonly caused by thrombus that has travelled (embolized) to the brain. This thrombus can come from the heart or from an atherosclerotic plaque in a more proximal artery. In an embolic stroke, blood clots or debris from elsewhere in the body, typically the heart valves, travel through the circulatory system and block narrower blood vessels²⁴.

Based on the aetiology of ischaemic stroke, a more accurate sub-classification is generally used (Table 1).

Table 1 Aetiology of acute ischaemic stroke

Sub-classification of Ischaemic stroke	Aetiology
Large artery disease	Atherosclerosis of large vessels, including the internal carotid artery, vertebral artery, basilar artery, and other major branches of the Circle of Willis.
Small vessel disease	Changes due to chronic disease, such as diabetes, hypertension, hyperlipidemia, and smoking, that lead decreased compliance of the arterial walls and/or narrowing and occlusion of the lumen of smaller vessels
Embolic stroke	The most common cause of an embolic stroke is atrial fibrillation.
Stroke of determined aetiology	Such as inherited diseases, metabolic disorders, and coagulopathies.
Stroke of undetermined aetiology	After exclusion of all of the above.

Ischaemic stroke is a heterogeneous disease and occurs due to a multitude of underlying causes. Risk factors for stroke are usually divided into non-modifiable and modifiable²⁵. Although non-modifiable risk factors for stroke, such as age, female gender, Asian ethnicity low birth weight and family history cannot be changed, their presence helps identify those at greatest risk, enabling vigorous treatment of those risk factors that can be modified²⁶. Modifiable risk factors for ischaemic stroke, such as cigarette smoking, hypertension, diabetes and heart disease are well known²⁷.

Key Concept: Core and Penumbra

In understanding the pathophysiological processes that occur during an ischaemic stroke it is important to discuss the key concept of the core and penumbra. In the core area of an AIS, blood flow is so drastically reduced that cells usually cannot recover and subsequently undergo cellular death. The tissue in the region bordering the infarct core, known as the ischaemic penumbra, is less severely affected. This region is rendered functionally silent by reduced blood flow but remains metabolically active. Cells in this area are endangered but not yet irreversibly damaged. They may undergo cell death after several hours or days but if blood flow and oxygen delivery is restored shortly after the onset of stroke, they are potentially recoverable (Figure 3): the ischaemic penumbra is underperfused brain tissue that has the capacity to recover if perfusion is restored.

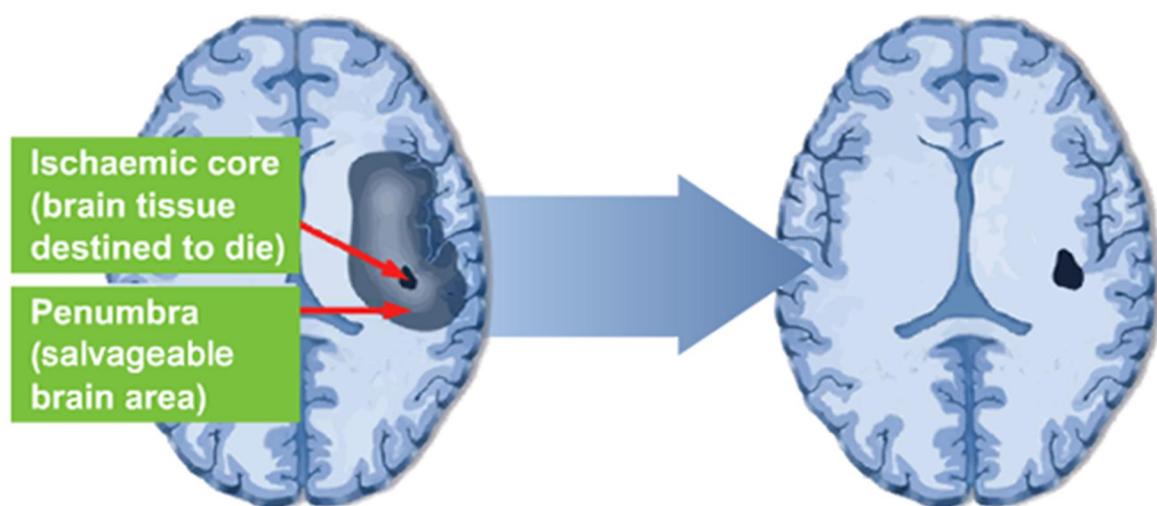


Figure 3 Ischaemic penumbra – Potential to reverse neurologic impairment with post-stroke therapy

Source: <http://www.strokeforum.com/stroke-background/pathophysiology.html>

Evidence for patient population for proposed service

The patient population who would benefit from the proposed service are patients with AIS due to large (or proximal) vessel occlusion (LVO). Large intracranial vessels include the vertebral, basilar, carotid terminus, and middle and anterior cerebral arteries²⁸. LVOs are often associated with a poorer prognosis than stroke unassociated with LVO, and are less likely to respond to IV tPA²⁸.

In their recent systematic review and meta-analysis²⁹, Sardar et al (2015) analysed 8 randomized-controlled trials (RCTs) that randomized 2423 patients - all trials included patients with LVO AIS. The five newer trials (published in 2015) found that, in comparison to standard therapy (IV tPA), MT significantly improved functional outcomes (without compromising safety) in patients with AIS. Of note, analyses from only the recent trials (reported in 2014–15) showed better improvements in functional outcomes, with similar safety results. The use of newer generation MT technology and the more targeted selection of patients likely to benefit are key reasons for these improvements in functional outcomes. Another key reason was a faster time between stroke onset and treatment.

As a consequence of the positive results of recent clinical trials, management guidelines for AIS were updated in 2015 and 2014, with new recommendations made on the use of MT³⁰. Key recommendations from international guidelines/evaluations relevant to the proposed patient populations for MT are presented in Table 2.

The Applicant notes that the updated guidance statements have recommended use of MT in patients who meet particular criteria, (summarised in Table 2). In particular, the American Heart Association and American Stroke Association guidelines recommend use of MT with a stent retriever in patients: with intracranial occlusions of proximal vessels; with smaller ischaemic cores; who commence mechanical MT within six hours of symptom onset; and who received IV tPA within 4.5 hours of symptom onset.

Indeed in practice patient selection for MT considers many factors – including: location of the vessel occlusion; stroke severity; timeframe of intervention; whether the patient received IV tPA; the volume of the ischaemic core, and/or the amount of salvageable tissue on perfusion imaging. As further presented in Table 3, the use of multiple criteria in recent key clinical trials to inform patient selection for MT is important with regards to identifying patients who will benefit from this therapy. With regards to defining the proposed patient populations for this evaluation – patient selection should be aligned with clinical practice guidelines. However, as patient treatment is determined on a case-by-case basis, there should be sufficient flexibility to meet the needs of clinical practice where patient treatment decisions are made on a case-by-case basis in an acute emergency setting. The applicant also notes that the evidence base for MT is still developing, and it is likely that patient selection criteria will further evolve. This will require ongoing and timely revision of clinical practice guidelines and acute-stroke response treatment protocols.

Results of a European evaluation³¹ of MT are also presented in Table 2. In addition, EUnetHTA noted that: *There is currently in-sufficient evidence to determine the applicability of this evidence to the much larger, heterogeneous cohort of patients with ischaemic stroke who are treated in the real-world setting and who may be ineligible for IV tPA, who arrive outside the time window for treatment and/or who are managed in non-specialised institutions or units. ...*

However, EUnetHTA's systematic review was limited to evidence from RCTs – and did not consider evidence from 'real world' settings. To claim there is 'insufficient evidence' is inappropriate when EUnetHTA did not include non-randomised and observational evidence as part of the PICO criteria for their systematic review. It is important to note that there are a number of published observational studies that examine the real world effectiveness of mechanical thrombectomy in acute ischemic stroke patients – including, but not limited to the NASA³² registry data. In the NASA registry clinical outcomes of mechanical thrombectomy with the Solitaire FR device (stent retriever) were comparable with results from the SWIFT³³ and TREVO 2³⁴ RCTs.

'Best practice' HTA should consider evidence from different study designs³⁵. However, it is recognised that EUnetHTA conducted a rapid HTA, which may explain why evidence from non-randomised and observational studies was not considered.

Table 2 Summary of guideline recommendations relevant to proposed populations most suitable for mechanical thrombectomy

Relevant recommendations from guidelines	
US guidelines (AHA/ASA) ⁷	<p>Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatments are being considered (Class I; Level of Evidence A). (Unchanged from the 2013 guideline)</p> <p>Patients <u>should receive</u> MT with a stent retriever if they meet the following criteria: pre-stroke mRS score (0–1), timing of IV tPA treatment from stroke onset (within 4.5 h), causative occlusion of the ICA or proximal MCA (M1), age (≥ 18 years), NIHSS score (≥ 6), ASPECTS (≥ 6), and ability to initiate treatment within 6 hrs of symptom onset.</p> <p>Benefits are uncertain and use may be reasonable in the following patient groups: Occlusion of the M2 or M3, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries (within 6 hrs) mRS >1, ASPECTS <6 or NIHSS <6 and occlusion of the ICA or M1.</p> <p>Observing patients after intravenous r-tPA to assess for clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended. (Class III; Level of Evidence B-R). (New recommendation).</p> <p>In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable (Class IIa; Level of Evidence C). There are inadequate data available at this time to determine the clinical efficacy of endovascular therapy with stent retrievers for those patients whose contraindications are time-based or non time based (eg, prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications). (New recommendation)</p>
European guidance (ESO) ³⁶	<p>Mechanical thrombectomy, in addition to iv tPA within 4.5 hrs when eligible, is recommended to treat acute stroke patients with large artery occlusions in the anterior circulation up to 6 hrs after symptom onset (KSU Grade A)</p> <p>Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis where this is indicated, and intravenous thrombolysis should not delay mechanical thrombectomy (Grade A, Level 1a, KSU Grade A). – changed Mechanical thrombectomy should be performed as soon as possible after its indication (Grade A, Level 1a, KSU Grade A).</p> <p>If intravenous thrombolysis is contraindicated (e.g. Warfarin-treated with therapeutic INR) mechanical thrombectomy is recommended as first-line treatment in large vessel occlusions (Grade A, Level 1a, KSU Grade A) – changed and updated level of evidence.</p>
European assessment (EUnetHTA) ³¹	<p>The evidence suggests that mechanical thrombectomy is of benefit, in terms of morbidity and function and, perhaps, generic quality of life, in selected patients with anterior circulation AIS, treated with 2nd-generation (stent retriever) thrombectomy devices after having first received IV tPA, where appropriate.</p>

AHA = American Heart Association; AIS = acute ischaemic stroke; ASA = American Stroke Association; ASPECTS = Alberta Stroke Program Early Computed Tomography Score; ESO = European Stroke Organisation; EUnetHTA = European Network for Health Technology Assessment; MT = Endovascular thrombectomy; hrs = hours; ICA = internal carotid artery; IV tPA = intravenous tissue plasminogen activator; KSU = Karolinska Stroke Update; M1 = first segment of the MCA; M2 = second segment of the MCA; MCA = middle cerebral artery; mRS = modified Rankin scale; NIHSS = National Institute of Stroke Health Scale; Ref = reference; US = United States of America

Table 3 Summary of the population proposed in the application compared with key trials and international guidance

Requested population	Trial inclusion criteria (5 newer RCTs)	Supported by US ^a /European guidances ^b
Location of vessel occlusion		
Large vessel anterior or posterior occlusions, diagnosed by imaging	Anterior circulation only <ul style="list-style-type: none"> • 2 trials included ICA and M1 only, • 2 trials included ICA, M1 & M2, • 1 trial included ICA, M1, M2, A1, A2. Non-invasive arterial imaging was used (CTA or MRA)	Yes, ICA or M1 (US) Anterior occlusions (European)
Pre-stroke functional ability – mRS score or Barthel Index ^c		
limit to be specified	Pre-stroke mRS thresholds: <ul style="list-style-type: none"> • ≤1 in 2 trials (REVASCAT, SWIFT PRIME); • ≤2 in 1 trial (EXTEND IA); 1 trial required a pre-stroke score on the Barthel Index of ≥90 (ESCAPE).	Yes, pre-stroke mRS score ≤1 (US)
Stroke severity using NIHSS ^d		
limit to be specified	Baseline NIHSS score of: <ul style="list-style-type: none"> • ≥2 in 1 trial (MR CLEAN), • ≥6 in 2 trial (REVASCAT and ESCAPE), • ≥8 in 1 trial (SWIFT PRIME). 	Baseline NIHSS ≥6 (US)
Prior IV tPA		
limit to be specified (includes patients who did and did not receive prior IV tPA)	<ul style="list-style-type: none"> • 2 trials <u>required all patients</u> to have received IV tPA within 4.5 hrs of onset (EXTEND-IA and SWIFT PRIME), • 1 trial required patients to have received IV tPA within 4.5 hrs of onset <u>if they met local guidelines</u> – 73% or pts in the MT arm received IV tPA (ESCAPE), • 1 trial allowed the use of IV tPA - 87% or pts in the MT arm received IV tPA (MR CLEAN) • 1 trial required patients to have either received IV tPA within 4.5hrs of the onset without revascularization after 30 minutes, or were contraindicated to IV tPA (REVASCAT). 	<u>Patients should have had IV tPA within 4.5 hrs (US).</u> <u>-Use in addition to IV tPA within 4.5 hrs when eligible (European)</u>
Time between onset of symptoms and commencement of MT (i.e. time to groin puncture)		
Requirement to be specified	Max time from symptom onset was: <ul style="list-style-type: none"> • 6 hrs in 3 trials(MR CLEAN, SWIFT PRIME, EXTEND-IA), • 8 hrs in 1 trial (REVASCAT, but median time was 4.5 hrs) • 12 hrs in 1 trial (ESCAPE) 	Max of 6 hrs (US & European)
Ischaemic core volume based on ASPECTS score ^e		
Requirement to be specified	ASPECTS score of. <ul style="list-style-type: none"> • ≥ 7 on non-contrast CT, or ≥6 on DWI-MRI (REVASCAT) • ≥6 (ESCAPE) • ≥7 (SWIFT-PRIME). 	ASPECTS ≥6 (US) Pts with radiological signs of large infarcts may be unsuitable (European)
Additional imaging to determine mismatch between core and penumbra; or collateral flow status		
Requirement to be specified	3 trials used complex imaging to identify suitable pts <ul style="list-style-type: none"> • EXTEND-IA & SWIFT-PRIME^f used RAPID software to identify pts with salvageable tissue (i.e. mismatch penumbral profile). • ESCAPE required pts to have moderate-to-good collateral circulation (assessed on multiphase CTA) 	Benefits of CT perfusion, diffusion- and perfusion-weighted imaging unknown (US) Imaging can be used for pt selection.

^a The summarised text focuses on Class I, Level of evidence A from the American Heart Association/ American Stroke Association guidelines

^b The summarised text focuses on KSU Grade A, Oxford Evidence Grade A, Level 1a from the European Stroke Organisation – Karolinska Stroke Update consensus statement

^c mRS is a measure of disability; uses scores from 0 (no symptoms) to 6 (death). A score ≤2 indicates functional independence. The Barthel index measures the ability to perform the activities of daily living; uses scores from 0 (severe disability) to 100 (no disability).

^d NIHSS quantifies neurological impairment; uses scores from 0 [normal] to 42 [death]

^e ASPECTS is a 10 point quantitative topographic CT scan score (lower scores = larger ischaemic core volume)

^f For SWIFT-PRIME, patient selection using the RAPID software was required for the first 71 patients only

A1 = first segment of the anterior cerebral artery; A2 = second segment of the anterior cerebral artery; ASPECTS = Alberta Stroke Program Early Computed Tomography Score; CT = computed tomography; CTA = computed tomographic angiopathy; DWI-MRI = diffusion-weighted imaging-MRI; MT = endovascular therapy; hr = hours; ICA = internal carotid artery; IV tPA = intravenous tissue plasminogen activator; M1 = first segment of the middle cerebral artery; M2 = second segment of the middle cerebral artery; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; mRS = modified Rankin scale; NIHSS = National Institute of Stroke Health Scale; pts = patients; RCT = randomised controlled trials; US = United States of America.

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The Applicant has noted Protocol Advisory Subcommittee (PASC) advice that: *relevant patient characteristics should be specified in the proposed population including treatment within 8 hours of onset, assessment of stroke severity and pre-stroke functional ability*¹. The Applicant proposes that eligibility guidelines described in the Victorian protocol² for Endovascular Clot Retrieval (ECR – i.e. mechanical thrombectomy) could be used as a basis to better define patients who could benefit from the proposed intervention. These eligibility guidelines are consistent with international guidance described in Table 3. Relevant characteristics for patient selection include:

- Ischaemic Stroke with proven large vessel occlusion on CTA
- Internal carotid artery (ICA)
- Middle Cerebral artery (MCA)
 - M1 segment between the carotid terminus and MCA bifurcation
 - Early M2 segment after bifurcation but proximal within the Sylvian fissure
- Basilar artery

Independent pre-morbid function (modified Rankin score 0–2)

Ability to start procedure within six hours of stroke onset – clinician discretion for basilar artery occlusion and selected anterior circulation patients beyond six hours (e.g. if salvageable brain tissue is identified on imaging)

In further defining the proposed eligible population, the Applicant considers it appropriate that the eligibility criteria retains sufficient flexibility to ensure clinician determination of patient suitability for MT on a case-by-case basis – taking into consideration the complete clinical circumstances in an acute emergency setting. This is consistent with clinician feedback received during public consultation of the draft decision analytic protocol.

As the aim of clinical practice is to identify all patients with LVO ischemic stroke who could benefit from mechanical thrombectomy⁴, the Applicant is concerned that overly prescriptive selection criteria could inadvertently preclude patients who may benefit from MT – noting the lack of heterogeneity observed for treatment effects by age or clinical (stroke) severity³.

Eligible patient population and expected utilisation

Analysis from the Australian Institute of Health and Welfare (AIHW), estimated the rate of all-cause stroke in 2009 at 140 per 100,000 population³⁷. Applying this rate to the current Australian population³⁸ estimates the incidence of all-cause stroke at 33,540 per year. Of these strokes, 88% are ischaemic³⁹ and translates to an estimate of 29,516 AISs per year in Australia. It is estimated that LVO are responsible for 46% of AIS⁴⁰, hence, it is estimated that 13,578 AIS are caused by LVO in Australia every year.

¹ Application 1428: PASC Meeting April 2016, Application Outcome

² Endovascular clot retrieval for acute stroke. Statewide service protocol for Victoria. Department of Health & Human Services. 10th February 2016. This protocol was published after the consultation protocol for this application was finalised.

³ Campbell et al (2015). Endovascular stent thrombectomy: the new standard of care for large vessel ischemic stroke. *Lancet Neurol*: 14:846-54

For these patients intravenous thrombolytic therapy (with IV tPA) is recommended in treatment guidelines⁴¹, however, in Australia the number of patients with stroke receiving appropriate thrombolytic therapy is very low, on average less than 5%⁴². There are several factors which may contribute to this, including: contraindications to IV tPA; delays in seeking care; distance from an acute stroke network and a lack of co-ordinated emergency stroke care that requires 24-hour access to imaging and an emergency interventional neurologist. Access to MT in Australia is expected to have similar challenges, with the projected uptake of MT for AIS amongst eligible patients limited to the capacity of the Australian healthcare system to provide the proposed service. For example, analysis of trends of hospitalised acute stroke care in Germany reported that in 2012 – MT was performed in only 1.63% of all patients with ischaemic stroke⁴³. This is equivalent to an estimated 481 patients treated with MT/year in Australia. Although it is estimated that 13,578 AIS are caused by LVO in Australia every year - in 2013-14 there were only 136 procedures where an embolectomy or thrombectomy of an intracranial artery was performed⁴⁴. It is anticipated that improvements in acute stroke management in Australia will increase the availability of MT to patients with AIS who could benefit from this therapy.

The proposed patient populations for this evaluation include both patients indicated and contraindicated for IV tPA. In both groups MT may not be possible in all patients due to technical reasons or clinical contraindications (e.g. stenosis and/or pre-existing stent proximal to the thrombus site; patients with angiographic evidence of carotid dissection). Hence, of the 5% of patients in Australia who receive IV tPA and the 95% who don't – a proportion of these could receive MT. This is considered in the estimated eligible patient population summarised in Table 4 below.

As illustrated above for the German experience of MT, only a very small group of patients (1.63%) with ischemic stroke have received access to MT. In addition, Australian procedure data described above indicates that there are significant capacity restraints with regards to appropriate expertise to provide the proposed service. Hence, although the estimated potential MT eligible population in Australia is 8148 patients/year – it is anticipated that capacity and infrastructure constraints will severely limit the uptake of MT. However, the estimated annual number of AIS patients with LVO (Table 4) clearly indicates there is a significant clinical need for effective therapies.

Table 4 Estimated potential patient population eligible for mechanical thrombectomy in Australia

	Estimated incidence	Number in Australia	Source	Notes
Population of Australia	-	23,956,654	Australian Bureau of Statistics population clock, 14 December 2015	N/A
All-cause stroke	0.14%	33,540	AIHW "Stroke and its management in Australia: an update", 2013	Assumes all-cause stroke rate is similar in 2016.
% of stroke that is ischaemic	88%	29,516	D'Anna et al, 2015 (observational study, recruited pts in 2007-2009 from 1 hospital in Udine, Italy)	This estimate of incidence requires further confirmation to establish accuracy and whether it is applicable to Australia.
% of ischemic stroke that is LVO	46%	13,578	Wade et al, 2009 (prospective imaging study at 2 academic medical centres in US)	Potential overestimate: 46% appears to be the % of all stroke pts with LVO, so non-ischaemic strokes may be double-counted.
% use of iv tPA in pts with AIS – potential MT candidates (Group A)	5%	679	HealthPACT brief, 2012 (source: Leydon et al 2011 an observational study of pts hospitalised for AIS in 2007-2009 in South Aust)	Possibly an over-estimate as data was mainly from urban hospitals, however the data were from 2007-09 and uptake may have increased since this time. (5% applied to estimate of ischemic stroke that is LVO)
% AIS patients Contraindicated iv tPA (Group B)	95%	12,899	As above	(95% applied to estimate of ischemic stroke that is LVO)
Indicated iv tPA and eligible for MT (Group C)	60%	408	Estimate	60% of Group A

	Estimated incidence	Number in Australia	Source	Notes
Contraindicated iv tPA and eligible for MT (Group D)	60%	7740	Estimate	60% of Group B
Estimated eligible patient population for MT		8148		Group C + Group D

AIHW = Australian Institute of Health and Welfare; AIS = acute ischaemic stroke; Aust= Australia; MT = mechanical thrombectomy; iv = intravenous; LVO = large vessel occlusion; pts = patients;; tPA = tissue plasminogen activator

Burden of disease

In Australia stroke has significant clinical and economic consequences^{45, 46}:

- In 2011 there were 8,800 deaths with stroke recorded as the underlying cause of death, accounting for 6% of all deaths in Australia (1 in 5 cardiovascular disease deaths). ischaemic
- In 2008–09, total health-care expenditure for stroke in Australia was \$606 million, which was 8% of health-care expenditure for all cardiovascular disease and 0.5% of total health-care expenditure. Hospital-admitted patients accounted for the majority of the health expenditure for stroke.
- There were over 420,000 Australians estimated to be living with the effects of stroke in 2012, with two thirds having a disability that impedes their ability to carry out daily living activities unassisted⁴⁷. In 2012 there were about 25% more males living with stroke (233,171) than females (187,099).
- Rehabilitation (inpatient and outpatient) has been previously determined to be the largest component of total cost during the first year after a first-ever stroke, amounting to 28% of overall expenditure for stroke⁴⁸.
- Analysis from 2009 estimated total lifetime average healthcare costs per case for ischaemic stroke at AU\$64 733, with total costs in the first year after the stroke accounting for 38% of lifetime costs⁴⁹.
- Although the rate of stroke events fell by 25% from 1997 to 2009, the total number of Australians experiencing a stroke rose by 6% over the same period - due to the ageing of the population. This is reflected in increased health expenditure for stroke: from \$606 million in 2008-9 to \$818 million in 2012⁵⁰. Hence, as Australia's population continues to age, stroke will continue be a growing public health issue, with significant clinical and economic consequences.
- Health expenditure estimates for 2012 translate to costs of stroke of \$11,847 per person⁴⁷.
- The financial costs of stroke extend far beyond the impact on healthcare budgets⁵¹. In 2012 the total financial costs of stroke in Australia were estimated at \$5 billion. Productivity costs were the largest cost components – estimated at approximately \$3 billion. Carer costs were estimated at \$222 million.

Intervention – proposed medical service

Description of the proposed medical service

The objective of MT is to restore blood flow to minimize damage to the brain. MT can be performed using a variety of devices. Currently, the most common devices are stent retrievers or those that utilise aspiration or suction techniques. Stent retrievers work by temporarily deploying a stent that captures the thrombus and at the same time aims to instantly restore blood flow to the affected brain territory by displacing the clot peripherally against the artery wall and entangling it within the stent struts. The stent and thrombus are then withdrawn back into the delivery catheter⁵². Aspiration devices work by debulking and aspiration of the occluding thrombus.

MT aims to salvage the ischaemic penumbra – the area surrounding a cerebral infarct that suffers less ischaemia (Figure 3). The penumbral region is not irreversibly damaged and successful revascularisation is intended to result in improved functional outcomes and quality of life for patients, thus reducing the number of patients with stroke requiring intensive rehabilitation.

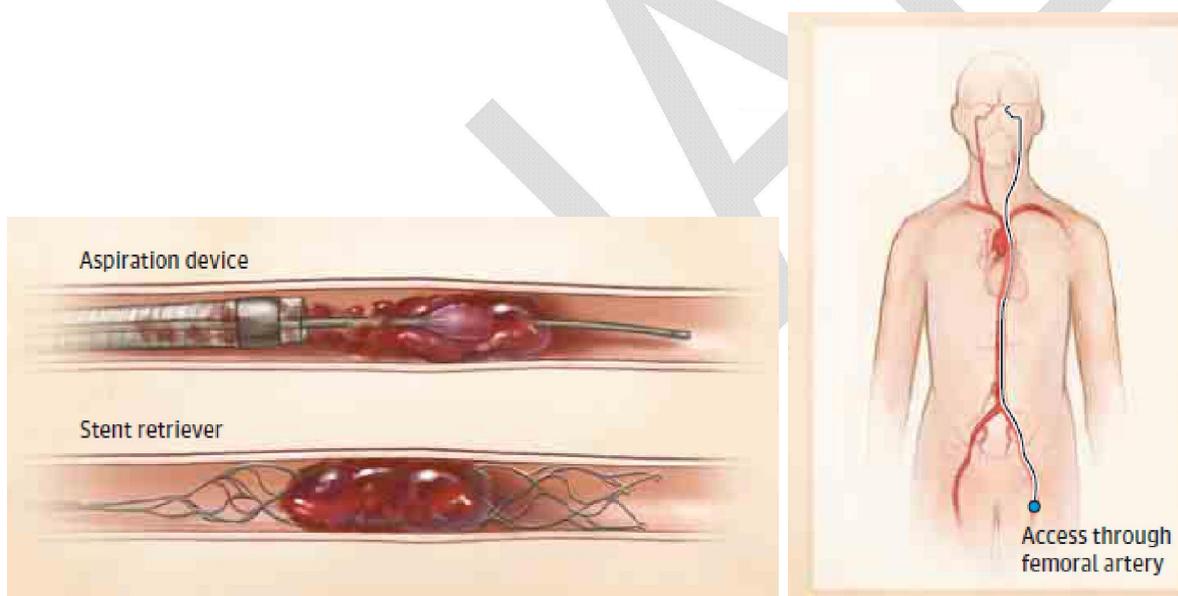


Figure 4 Mechanical thrombectomy devices

Source: Prabhakaran et al (2015)⁵³

MT devices employing stent retrievers are delivered to the thrombus using a micro-catheter percutaneously introduced via the femoral artery. Neuroimaging is used to position the device in the cranial blood vessel. For stent retrievers the micro-catheter is advanced distal to the thrombus position so that when the stent is fully deployed it will extend beyond both ends of the thrombus. The captured thrombus is then removed from the patient through retrieval of the micro-catheter.

Aspiration devices work by advancing a reperfusion catheter over a neurovascular guidewire until it approaches the thrombus – guidance by neuroimaging is also used. A separator device is then introduced into the proximal part of the thrombus through the reperfusion catheter. The thrombus is extracted by aspiration, while the separator is advanced and retracted within the reperfusion catheter to aid with extraction. After aspiration residual thrombus can be removed using a thrombus removal ring to directly extract any remaining blood clot.

The applicant notes that the body of evidence currently appears to be stronger for stent retrievers than for other devices such as aspiration catheters²⁹ and some international guidelines and consensus statements have specifically recommended stent retrievers, rather than mechanical thrombectomy more broadly (Table 2). This is outlined in Table 5. While it appears there is no recent evidence for aspiration catheters published in peer-reviewed journals, there is an on-going trial (the ‘Assess the Penumbra System in the Treatment of Acute Stroke’ (THERAPY) trial, NCT01429350).

Table 5 Summary of mechanical thrombectomy devices used in key trials and international guidance around devices

Requested in application	Trial evidence - 5 newer RCTs & 3 less recent RCTs	US guidelines (ASA/AHA) (Ref 7)	European guidance (ESO) (Ref 36)	European assessment (EUnetHTA) (Ref 31)
Mechanical thrombectomy, employing devices such as stent retrievers and aspiration catheters to remove thrombi/blood clots.	<p>The 3 less recent RCTs used 1st-generation devices, such as the MERCI retriever and the Penumbra clot aspiration system, either exclusively (MR RESCUE) or in the majority of cases (IMS III, SYNTHESIS Expansion).</p> <p>The 5 newer RCTs used newer generation ‘stent retrievers’ in all (EXTEND IA, REVASCAT, SWIFT PRIME) or the majority of cases (MR CLEAN, ESCAPE).</p>	<p>Stent retrievers are preferred to MERCI device (Class I, level of evidence A).</p> <p>Use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances (Class IIb, Level B-NR).</p>	<p>For mechanical thrombectomy, stent retrievers approved by local health authorities should be considered (Grade A, Level 1a, KSU Grade A).</p> <p>Other thrombectomy or aspiration devices approved by local health authorities may be used upon the neurointerventionists discretion if rapid, complete and safe revascularisation of the target vessel can be achieved (Grade C, Level 2a, KSU Grade C).</p>	<p>Evidence supports use of 2nd-generation (stent retriever) thrombectomy devices. Stent retriever technology was used in all, or the majority of the new trials, and hence the evidence should not be interpreted as evidence of effect for other types of thrombectomy device</p>

AHA = American Heart Association; ASA = American Stroke Association; ESO = European Stroke Organisation; EUnetHTA = European Network for Health Technology Assessment; MT = mechanical thrombectomy; KSU = Karolinska Stroke Update; RCT = randomised controlled trial; US = United States

Registered trademark

The application for the proposed item does not limit use to any registered trademark. It is proposed that the assessment of MT will be generic - i.e. considering evidence for all relevant technologies that can deliver the proposed service.

The following MT technologies are available in Australia (see also Section 10 and Table 10):

- The Solitaire 2 and Solitaire FR revascularisation devices – both employ stent retriever technology for clot removal

- The Stryker Trevo Retriever, employing stent retriever technology for clot removal.
- The Penumbra system, utilising aspiration for clot removal.

Proposed clinical setting

The proposed service should be available as an inpatient service in private or public hospitals. Optimal clinical outcomes depend on patients being treated as soon after symptom onset. To achieve this, patients should be transferred to the closest centre that can provide the proposed service: this may be a private or public hospital.

Service delivery

MT is performed in an angiography suite or catheterization lab. Hospitals must have neuroimaging modalities similar to those used for endovascular coiling of intracranial aneurysms. Neuroimaging is required to guide the procedure as well as other general neurointerventional devices such as guidewires, microcatheters, and other access devices.

It is considered that optimization of the proposed service will require its integration within existing protocols for acute stroke management. Hence, the pathway of care for the proposed service will contain elements of current protocols for acute stroke management (see *Proposed service and comparator – the use of protocols and organisation of acute stroke management*, and Table 7). In addition to current protocols for delivering the comparator (summary example in Table 7), ambulance pre-notification of the neurointervention service to initiate preparation of the angiography suite or catheterisation lab is necessary. This should include pre-notification of additional clinical staff necessary to deliver the service (e.g. required for initiation of management of anaesthesia where required).

Mechanical thrombectomy devices should only be used by clinicians trained in interventional neuroradiological treatments and experienced in the treatment of AIS. With regards to this the Applicant notes guidance on the professional experience required to perform the proposed intervention. The European Stroke Organisation consensus statement states that *“mechanical thrombectomy should be performed by a trained and experienced neurointerventionalist who meets national and/or international requirements”*³⁶. Another international guidance document states *“the decision to undertake endovascular stroke therapy should be made jointly by a multidisciplinary team comprising a consultant stroke physician, [neuro]interventionist (with the necessary experience and skills) and an anaesthetist (preferably experienced in neurological care)”*⁵⁴.

In Australia training and accreditation relevant to the proposed service is described in the Conjoint Committee Guidelines for Recognition of Training in Interventional Neuroradiology (INR)⁵⁵.

With regards to the setting for the proposed service, the Applicant notes guidance that MT for AIS states that *“should be confined to neuroscience centres incorporating hyperacute stroke units embedded within a high quality comprehensive stroke service with access to neurosurgical, neurocritical care and specialist in and out-patient stroke services. The findings from the trials are generalisable to only those centres that have access to advanced brain imaging facilities and appropriate [neuro]endovascular expertise with efficient in-hospital hyper-acute pathways”*⁵⁴.

This raises an important question for public consultation:

- How should setting accreditation for delivery of the proposed service be determined?

The procedure can be done under general anaesthesia or conscious sedation. Guidelines are not definitive for either technique. As shown in Table 6, the guidelines generally recommend that the choice should depend on the individual patient based on clinical characteristics (e.g. neurological status and airway control), with a preference for conscious sedation, where appropriate.

Table 6 Summary of the use of general anaesthesia in key trials and international guidance

Requested in application	Trial evidence - 5 newer RCTs	US guidelines (ASA/AHA) (Ref 7)	European guidance (ESO) (Ref 36)	UK Standards of care (Ref 54)
Either general anaesthesia or conscious sedation	4 of the 5 newer RCTs had between 35%-38% of pts given general anaesthesia, and one trial (ESCAPE) had only 9%.	It might be reasonable to favour conscious sedation over general anaesthesia. However, the ultimate selection of anaesthetic technique during MT for should be individualized based on patient risk factors, tolerance of the procedure, and other clinical characteristics. (Class IIb; Level of Evidence C)	The choice of anaesthesia depends on the individual situation; independently of the method chosen, all efforts should be made to avoid thrombectomy delays (Grade C, Level 2b, KSU Grade C)	<ul style="list-style-type: none"> -The choice of anaesthetic should be tailored to the individual patient based on neurological status, airway control and treatment plan in close communication with the interventional neuroradiologist. - Local anaesthesia should be aimed for, if feasible, in patients who are cooperative and can protect their airway. - General anaesthesia is recommended in patients with a reduced level of consciousness, uncooperative or agitated patients, those who cannot protect their airway or those already intubated. - Patients receiving local anaesthesia with sedation should be monitored and provision made to enable rapid conversion to a general anaesthetic if necessary.

AHA = American Heart Association; ASA = American Stroke Association; MT = endovascular thrombectomy; ESO = European Stroke Organisation; KSU = Karolinska Stroke Update; RCT = randomised controlled trial; UK = United Kingdom; US = United States of America

Stroke is a medical emergency and if outcomes are to be optimised there should be no time delays in accessing treatment⁵⁶. For example - the current Australian and New Zealand clinical practice guidelines⁵⁶ for the management of stroke recommend that intravenous thrombolysis (with IV tPA) is provided up to 4.5 hours after symptom onset. Further, the 2015 American Heart Association/American Stroke Association guidelines⁷ recommend that patients commence MT within six hours of symptom onset. Hence, organisation of pre-hospital and in-hospital pathways and systems for patients with acute stroke is recommended by stroke management guidelines. This is necessary to reduce the time from symptom onset to provision of thrombolytic therapy.

Co-dependent information (if not a co-dependent application go to Section 6)

The proposed medical service is not co-dependent with a service or pharmaceutical medicine that requires coordinated consideration for funding by MSAC or Pharmaceutical Benefits Advisory Committee (PBAC).

Service

There are no co-dependant services requiring evaluation by MSAC

Pharmaceutical

There are no co-dependant pharmaceuticals requiring evaluation by the PBAC

Medical device or prosthesis

MT devices do not meet current criteria for inclusion on the Prostheses List: they are not a permanent surgical implant.

Comparator – clinical claim for the proposed medical service

Comparator

For individuals who have AIS, the key to effective treatment is early reperfusion of ischaemic brain without causing adverse effects. To achieve reperfusion, intravenous thrombolytic therapy is recommended in treatment guidelines⁵⁶.

- For indicated patients, intravenous thrombolytic therapy is a comparator to the proposed service.

Thrombolytic therapy acts by “dissolving” the thrombus or clot, enabling blood to return to the ischaemic part of the brain. Several thrombolytic therapies are available - the most common is the intravenous recombinant tissue plasminogen activator Alteplase⁵⁷ (IV tPA).

Although IV tPA is recommended as first line therapy approved for LVOs within 4.5 hours of symptom onset^{58,59}, data shows that it is highly variable in its effectiveness in achieving recanalization (13-50%) and has a substantial risk for complications^{60,61, 62, 63}, including intracerebral and systemic haemorrhage. One of the major limitations of IV tPA is related to the resistance to enzymatic degradation due to excessive cross-linking within mature embolic clots and emboli composed of cholesterol, calcium, or other debris from atherosclerotic lesions⁶⁴.

Despite the evidence that supports the safe and effective use of IV tPA in the treatment of AIS, and the recommendations endorsed by national and international clinical guidelines, only a small proportion of patients with stroke currently receive thrombolytic therapy⁶⁵. Well organised major stroke units achieve treatment rates of up to 20% of patients with AIS being treated with IV tPA. In contrast, in many centres the use of IV tPA is typically less than 10% of patients with stroke. In Australia the number of patients with stroke receiving appropriate thrombolytic therapy is very low – on average less than 5%⁶⁶. There are several reasons for the low use of thrombolytic pharmacotherapy. Many patients are ineligible, reasons for this include: presentation > 4.5 hours after stroke symptom onset; severe, uncontrolled hypertension; previous surgery; widespread ischaemia, patient receiving oral anticoagulants with an international normalised ratio >1.3, intracranial bleeding, previous stroke within the past three months. For these and other reasons approximately 50% of patients with stroke may be eligible for IV thrombolytic pharmacotherapy⁶⁷. For patients presenting with AIS who are ineligible for IV tPA, where a diagnosis of primary intracerebral haemorrhage has been excluded by brain imaging, antithrombotic therapy with aspirin is recommended in eligible patients⁶⁸. Australian clinical practice guidelines for acute stroke management also recommend the use of aspirin as anti-thrombotic therapy¹.

- Hence for patients contraindicated for IVTPA, the alternative comparator to the proposed service is medical management with anti-thrombotic therapy.

Proposed service and comparator – the use of protocols and organisation of acute stroke management

Optimal organisation of pre-hospital and in-hospital pathways and systems for patients with acute stroke is necessary to ensure patients have timely access to thrombolytic pharmacotherapy. Organisational factors which affect access to thrombolytic pharmacotherapy include: distance from an acute stroke network and a lack of co-ordinated emergency stroke care that requires 24-hour access to imaging and an emergency interventional neurologist. These factors also apply to access to MT, the proposed service.

One finding consistently and strikingly found across multiple trials in acute stroke, regardless of other factors - including therapy, is that faster treatment delivery leads to better long-term clinical outcomes. As a consequence, a good deal of attention has been focused on optimizing efficiency of acute stroke management including evaluation and treatment through protocols that implement time benchmarks for expedient step completion and reduction in unnecessary downtime or delays⁶⁹.

Protocol steps are illustrated in Table 7. This example summarizes a protocol from the Royal Melbourne Hospital, with additions in May 2012 – these were added to improve the time to treatment delivery. Overall this revised approach saved a median of 25 minutes in ‘door-to-needle’ time⁷⁰ – i.e. from arrival at hospital to initiation of thrombolytic therapy.

Of note, this example illustrates the importance of approaching acute stroke management as a parallel process instead of a serialized one – thereby avoiding potential delays from repeated patient transfer between different areas of emergency stroke care. In the example illustrated in Table 7 – changes implemented in May 2012 included request for CT *before* the patient arrives at the hospital.

Table 7 - Summary of Protocol from Royal Melbourne Hospital for Acute Stroke Management

Step	Details
Prenotification	<p>Previous protocol: Ambulance calls hospital ED over open-air radio. Once ED has assessed patient, a "code stroke" page is sent to stroke team.</p> <p>May 2012 additions: ED pages stroke team on receiving ambulance call—stroke team present on patient arrival (5–10 min saved). Stroke team calls ambulance dispatch center for patient details during Transport.</p>
Medical history	<p>Previous protocol: Electronic local lab and PACS since 2007. Paper records. GP sometimes called to obtain detailed history.</p> <p>May 2012 additions When available, history, lab, and imaging evaluated and GP called before patient arrival. (5 min saved)</p>
Registration and CT request	<p>Previous protocol: Noncentralized records with unique identifiers different for each hospital. CT requests only after patient had arrived and was registered in local hospital system.</p> <p>May 2012 additions: Registration done before arrival to retrieve existing record or generate new record based on name and date of birth. CT request form prefilled.</p>
Labs	<p>Previous protocol: Routine blood samples often drawn after tPA initiation. Capillary glucose before tPA. Only wait for INR in known and suspected anticoagulated patients.</p> <p>May 2012 additions: POC-INR available since 11/2012</p>
IV line	<p>Previous protocol: IV access often available on arrival, otherwise inserted in ED.</p> <p>May 2012 additions: IV access often available on arrival, otherwise inserted on CT table.</p>
Straight to CT	<p>Previous protocol: n/a</p> <p>May 2012 additions: Patients go straight to CT on ambulance stretchers (10 min saved)</p>
T PA on CT table	<p>Previous protocol: n/a</p> <p>May 2012 additions: tPA and infusion kit brought to CT room beforehand. Bolus and infusion initiated on CT table (3 min saved)</p>

ED, emergency department; GP, general practice; PACS, picture archiving and communication system; POC-INR, point-of-care; international normalized ratio; tPA, tissue plasminogen activator.

Source: adapted from Meretoja et al (2013)⁶⁵

Australian guidance on acute stroke management recommends patients are treated in a stroke unit with a multidisciplinary team⁵⁶. This is reflected in a protocol for stroke management from South Australia⁷¹, where the use of a 'Code Stroke Team' within the 'Code Stroke Protocol' is described. As described above – faster treatment delivery leads to better outcomes. Hence, this Code Stroke Protocol is designed to expedite workup of stroke patients who may benefit from acute reperfusion therapy including intravenous thrombolytics and MT. In particular, the protocol requires simultaneous notification of members of the 'Code Stroke Team' (minimum requirements: stroke consultant; stroke nurse; and stroke registrar). For the proposed service it is envisioned that the neurointervention team would also be notified. In accordance with current clinical practice guidelines (Table 2), for patients considered suitable for mechanical thrombectomy, this should be provided as soon after IV tPA has been initiated.

Of note, the South Australian protocol recognises that transfer to another hospital may be required to enable treatment of patients who may be potential candidates for mechanical thrombectomy. Where a patient is considered appropriate for mechanical thrombectomy and is accepted for transfer, the Stroke consultant at the accepting hospital should notify their emergency service of transfer and activate their Code Stroke Protocol and provide an estimated time of arrival. The stroke team in the accepting hospital should meet the patient on arrival.

As discussed above, reducing time barriers to therapy is critical. As presented at a recent conference⁴, reduction of in-hospital time barriers to MT is especially critical, and if possible this could include bypass of the emergency department – i.e. patient transferred directly to imaging/neurointerventional service.

In summary, acute stroke management organisation factors relevant to the proposed service and the comparator include:

- Evaluation and treatment protocols to optimize time to therapy delivery
- Parallel process initiation to avoid delays in patient transfer from one area of emergency care/acute response to another
- Co-ordinated activation of an acute stroke response team, and where necessary immediate notification of additional clinical personnel/facilities required to deliver the proposed service (i.e. interventional neuroradiology service, including imaging) or the comparator (e.g. CT imaging service).
- Reduction of in-hospital time barriers – including bypass of emergency department if possible

Proposed service and clinical claims

MT for AIS has emerged as an alternative and additional therapy – intended to address the limitations of thrombolytic pharmacotherapy (IV tPA). Patients can present with contraindications for systemic administration of IV tPA (e.g. outside the time window for effective treatment) and MT devices offer many potential advantages over pharmacologic thrombolysis. These include: more rapid achievement of recanalization; enhanced efficacy in treating large-vessel occlusions; and a potentially lower risk for haemorrhagic events⁷². MT may be used in combination with intravenous thrombolytic therapy or as an alternative treatment for patients who are ineligible for or fail intravenous thrombolytic therapy.

In comparison to intravenous thrombolytic therapy (IV tPA) alone, the adjunct use of MT results in superior rates of revascularization (reperfusion) with low rates of procedural complications. These outcomes are also achieved where MT is used in the absence of thrombolytic therapy for ineligible patients²⁹.

Improvements in reperfusion and subsequent avoidance of neurological complications results in higher rates of functional independence for AIS patients. Achieving higher rates of functional independence and avoiding stroke related disability translates to shorter hospital stays, less use of short- and long-term rehabilitation services, reduced carer burden, and reduced use of other healthcare resources - all of which have the potential to positively impact both clinical outcomes and healthcare costs over the longer term.

⁴ 13th Congress of the World Federation of Interventional and Therapeutic Neuroradiology 2015. Gold Coast, Australia. *Minimising the Time from Acute Ischaemic Stroke Onset to Clot Removal*. Bernard Yan, Melbourne Australia, 9th November, 2015

In their recent systematic review and meta-analysis⁷³, Sardar et al (2015) analysed 8 randomized-controlled trials (RCTs) that randomized 2423 patients. In comparison to standard therapy, endovascular thrombectomy significantly improved functional outcomes (without compromising safety) in patients with acute ischaemic stroke. Of note, analyses from only the recent trials (reported in 2014–15) showed better improvements in functional outcomes, with similar safety results. The use of newer generation MT technology and improvements in patient selection are key reasons for these improvements in functional outcomes. As a consequence of the positive results of recent clinical trials, management guidelines for AIS were updated in 2015, with new recommendations made on the use of MT⁷⁴.

On 16th December 2015 EUnetHTA published the results of their Rapid health technology assessment of endovascular therapy using mechanical thrombectomy devices for AIS⁷⁵. Key findings include:

- Evidence indicates that mechanical thrombectomy is of benefit, in terms of morbidity and function and, perhaps, generic quality of life, in selected patients with anterior circulation AIS, treated with second-generation (stent retriever) thrombectomy devices after having first received IV tPA, where appropriate.
- Stent retriever technology was used in all, or the majority of cases, in the 5 most recent trials and hence the evidence considered here should not be interpreted as evidence of effect for other types of thrombectomy device.

Economic evaluation

On the basis of the clinical claims described above it is proposed that a cost-effectiveness/cost-utility analysis is provided.

Expected health outcomes relating to the medical service

Patient-relevant health outcomes and healthcare resources expected to be affected by the introduction of the proposed service are presented below.

Primary effectiveness outcomes

- Revascularisation (e.g. TICl score⁵ or modified TICl score at 24 hours, with some of the trials defining successful revascularisation as a score of 2b or 3 on the post procedure angiogram)
- Function (e.g. Barthel Index⁶, assessed as the proportion of patients achieving a score of 95 or more [as a proxy for no disability that interferes with daily living, on the 100 point scale] at 90 days)
- Disability (e.g. mRS⁷ score at 90 days, assessed as: the common odds ratio of an improvement of one point; median score; or the percent of patients achieving a score of 0-2 [as a proxy for functional independence] at 90 days adjusted for baseline risk)
- Health Related Quality of Life using EuroQol 5-dimension instrument (EQ-5D)
- Neurological deficit (e.g. NIHSS⁸)
- Mortality (all-cause mortality at 90 days)

Secondary effectiveness outcomes

- Rescue treatment
- Rehabilitation
- Hospitalisation
- Length-of-stay (general ward, ICU)

Primary safety outcomes (including potential risks to patients)

- Device or procedure related adverse events (e.g. bleeding at puncture sight; air embolism; vascular spasms; vascular dissection⁹)
- Haemorrhage (e.g. symptomatic intracerebral haemorrhage, any cerebral haemorrhage)
- New ischaemic stroke within 90 days

Evidence for outcomes affected by the proposed service

A non-exhaustive search found five randomised controlled trials that were published in 2015, and that assessed the effectiveness and safety of MT. Characteristics of the trials are presented in Table 8.

⁵ TICl, Thrombolysis in Cerebral Infarction perfusion scale grade: The scale ranges from grade 0 (no perfusion) to grade 3 (complete perfusion)

⁶ The Barthel Index assesses daily activities such as feeding, dressing, bathing, with activities graded from depended on patients capabilities (e.g. bathing is one of the ten variables, a score of 0 = unable; 5 = independent). The index ranges from 0 to 100 with a higher score indicating good performance of the activities of daily living.

⁷ mRS, modified Rankin Scale: a common measure of disability and dependence following stroke. The scale ranges from 0 to 6 with 0 representing no symptoms and 6 representing death.

⁸ NIHSS, National Institutes of Health Stroke Scale/Score : used to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4 – where 0 represents normal function and higher scores represent different levels of impairment.

⁹ Additional safety outcome added in response to PASC feedback.

Table 8 Characteristics of the “newer” clinical trials of MT, all published in 2015

Trial	MR CLEAN ²	ESCAPE ³	EXTEND-IA ⁴	SWIFT PRIME ⁶	REVASCAT ⁵
Country	Netherlands (16 centres)	Canada (11 centres), US (6), Ireland (1), UK (1), South Korea (3)	Australia and New Zealand (14 centres)	US and Europe (39 centres)	Spain (4 centres)
N	502	316	70	196	206
Design	MC, randomised, open-label tx, blinded end-point evaluation	MC, randomised, open-label tx, blinded end-point evaluation	MC, randomised, open-label tx, blinded end-point evaluation	MC, randomised, open-label treatment, blinded endpoint	MC, randomised, open-label treatment, blinded endpoint
Comparison	Intra-arterial tx (intra-arterial thrombolysis, mechanical tx or both) plus usual care (which could include IV tPA) vs usual care alone.	MT (retrievable stents were recommended) plus guideline-based care (which could include IV tPA) vs guideline-based care alone.	MT with a stent retriever plus IV tPA vs IV tPA alone	MT with a stent retriever plus IV tPA vs IV tPA alone	MT with a stent retriever vs medical therapy alone in eligible patients who had received IV tPA without revascularization after 30 minutes or who had a contraindication to IV tPA
Device used	Any approved (82% stent retriever)	Any approved (79% stent retriever, 61% Solitaire)	Solitaire FR device	Solitaire FR or Solitaire 2 devices	Solitaire FR device
Primary outcome	Score on modified Rankin scale at 90 days	Score on modified Rankin scale at 90 days	Co-primary outcomes: - reperfusion (% reduction in the perfusion-lesion volume at 24 hrs); & - neurologic improvement at 3 days (a reduction of ≥8 points on the NIHSS or reaching a score of 0 or 1 at 3 days).	Score on modified Rankin scale at 90 days ^a	Score on the modified Rankin scale at 90 days. (severe disability and death, scores of 5 and 6, were combined into the worst category)
Safety/ AEs	- haemorrhagic complications - progression of ischaemic stroke - new ischaemic stroke - death	- ICH - angiographic complications - neurological disability at 90 days - death	-symptomatic ICH, including any subarachnoid haemorrhage - parenchymal haematoma	- all serious AEs - symptomatic ICH at 27 hrs including subarachnoid haemorrhage - parenchymal haematoma	- all-cause death at 90 days - clinically significant ICH at 24 hrs - procedural related complications: arterial perforation, arterial dissection, & embolization in a previously uninvolved vascular territory
Premature termination	No	Yes, release of data from MR CLEAN led to interim analyses being performed. The pre-specified boundary was crossed and the trial was stopped for efficacy.	Yes, release of data from MR CLEAN led to interim analyses being performed. A pre-specified stopping boundary was applied to the co—primary outcome, and the trial was stopped for efficacy.	Yes, release of data from MR CLEAN & ESCAPE led to interim analyses being performed. A pre-specified stopping-criteria (based on modified Rankin scale) was met.	Yes, because of claimed loss of equipoise due to release of data from MR CLEAN, EXTEND IA & ESCAPE. Interim results did not reach the pre-specified stopping boundaries.

AE = adverse events; MT = endovascular treatment; FR = flow restoration; hrs = hours; ICH = intracranial haemorrhage; iv = intravenous; MC = multi-centre; NIHSS = National Institute of Stroke Health Scale; tPA = tissue plasminogen activator; tx = treatment; UK = United Kingdom; US = United States; vs = versus

Four of the five trials compared mechanical MT plus standard care (which either had to include IV tPA or included IV tPA where appropriate) versus standard care. The other trial (MR CLEAN) studied a broader intervention – any intra-arterial treatment which could include mechanical MT and/or intra-arterial thrombolysis. However, the majority of patients in the active treatment arm of this trial were treated with mechanical MT (84% of patients), and almost all these patients were treated with stent retrievers (82% of patients in the active treatment arm). One trial only enrolled patients who either were contraindicated to IV tPA, or who received IV tPA but were not revascularised after 30 minutes (REVASCAT).

All trials followed up patients for a minimum of 90 days. In four of the five trials, the primary outcome was score on the modified Rankin scale at 90 days, which is a measure of functional independence. This was a secondary outcome in the remaining trial. All trials reported all-cause mortality at 90 days.

Four of the five trials were terminated early due to external evidence and/or efficacy. In three trials (ESCAPE, EXTEND-IA and SWIFT PRIME), unplanned interim analyses were conducted following the release of results from MR CLEAN. In these three trials, the pre-specified stopping boundaries were met, and the trials were terminated early due to efficacy. The stopping boundaries were based measures of disability (score on the modified Rankin scale), reperfusion or neurological function (i.e. not mortality outcomes). REVASCAT was terminated due to a stated loss of equipoise (the emerging results from other trials were stated to raise ethical concerns about further assignment of patients to the control group), despite the trial's interim results not meeting the pre-specified stopping boundaries.

Fee for the proposed medical service

Type of funding proposed for this service

The following MBS item descriptor is proposed:

Table 9 Proposed MBS Item descriptor

Category 3 - THERAPEUTIC PROCEDURES
<p>MBS [item number]</p> <p>Mechanical thrombectomy of patients with a confirmed diagnosis of acute ischaemic stroke caused by large vessel occlusion of the anterior circulation; procedure to be started within eight hours of stroke onset; including intra-operative imaging, but in association with the following pre-operative diagnostic imaging items^a: - either 57350 or 63101</p> <p>Fee: \$TBD</p> <p>(Anaes.) (Assist.)</p> <p>Explanatory notes:</p> <ul style="list-style-type: none">• Diagnosis confirmed by imaging: ischemic stroke with large vessel occlusion on CTA or MRI• Patients selected for treatment according to acute stroke management guidelines.• Clinician discretion for procedure use in selected patients beyond eight hours of stroke onset, where clinical assessment indicates patient is likely to benefit from treatment (salvageable brain tissue identified on imaging)• Service to be provided by suitably trained and accredited operators in suitably accredited hospitals [requirements TBD]. This should include contribution to systematic registry data for audit purposes [requirements TBD].

^aExamples of relevant CT angiography and MRI angiography items included

The Applicant notes that the evidence base for MT has evolved rapidly and will continue to evolve. Similar to any new therapy, patient selection criteria and procedure delivery will continue to be refined and this should be reflected in evolving clinical practice guidelines. Hence, the MBS descriptor for the proposed service should retain sufficient flexibility to accommodate changes in clinical practice, while aligning with clinical guidelines. This need for flexibility is consistent with clinician feedback received during public consultation of the draft decision analytic protocol – and is necessary to ensure clinician determination of patient suitability for MT on a case-by-case basis – taking into consideration the complete clinical circumstances in an acute emergency setting.

The Applicant has revised the proposed descriptor (highlighted text) in response to feedback from PASC. These revisions have been made to ensure that provision of MT on the MBS achieves optimal patient outcomes, consistent with those observed in clinical trials. Further consultation with relevant clinical societies is required to determine accreditation and registry participation requirements. Considered together, selection of patients in accordance with clinical practice guidelines and provision of the proposed service by suitably accredited operators and hospitals should ensure that MT is only provided to patients that will benefit from this therapy.

Direct costs associated with the proposed service

The following staff/resources are required to deliver the proposed service. Direct costs will be identified during the assessment phase of this application:

- Mechanical thrombectomy devices and associated neuro-interventional devices such as guidewires, microcatheters, and other access devices
- Neuroimaging: e.g. fluoroscopy
- Monitoring equipment: blood pressure, heart rate and oxygenation
- Neurologist
- Interventional neuroradiologist
- Angiography suite or catheterization laboratory
- General consumables: e.g. dressings
- Anaesthetist (the proposed service can be done under general anaesthesia or conscious sedation)
- Follow-up imaging
- Nursing staff for post-intervention care
- Overnight stay in hospital

Proposed fee

The fee for the proposed service should reflect the complexity, duration and skills required to provide the service. From a technical perspective, MT for AIS is considered more challenging than other neuro-interventional procedures (expert clinician advice) –hence, the fee for this service should reflect this. . By way of reference, a potentially similar service is MBS Item 35412 Endovascular coiling of intracranial aneurisms. However, MT is considered technically more challenging: typical stroke patients who could benefit from MT are elderly, when vasculature becomes increasingly tortuous and difficult to navigate. Whereas the patient demographic for aneurysm is younger, where vascular access is more straightforward. Furthermore, traversing occluded vessels in AIS is more technically challenging – wire/microcatheter navigation requires precision in circumstances where there is no definitive path through an occlusion.

The fee for the proposed service will be determined during the assessment phase of this application.

Clinical Management Algorithm - clinical place for the proposed intervention

Current (comparator) and proposed clinical management



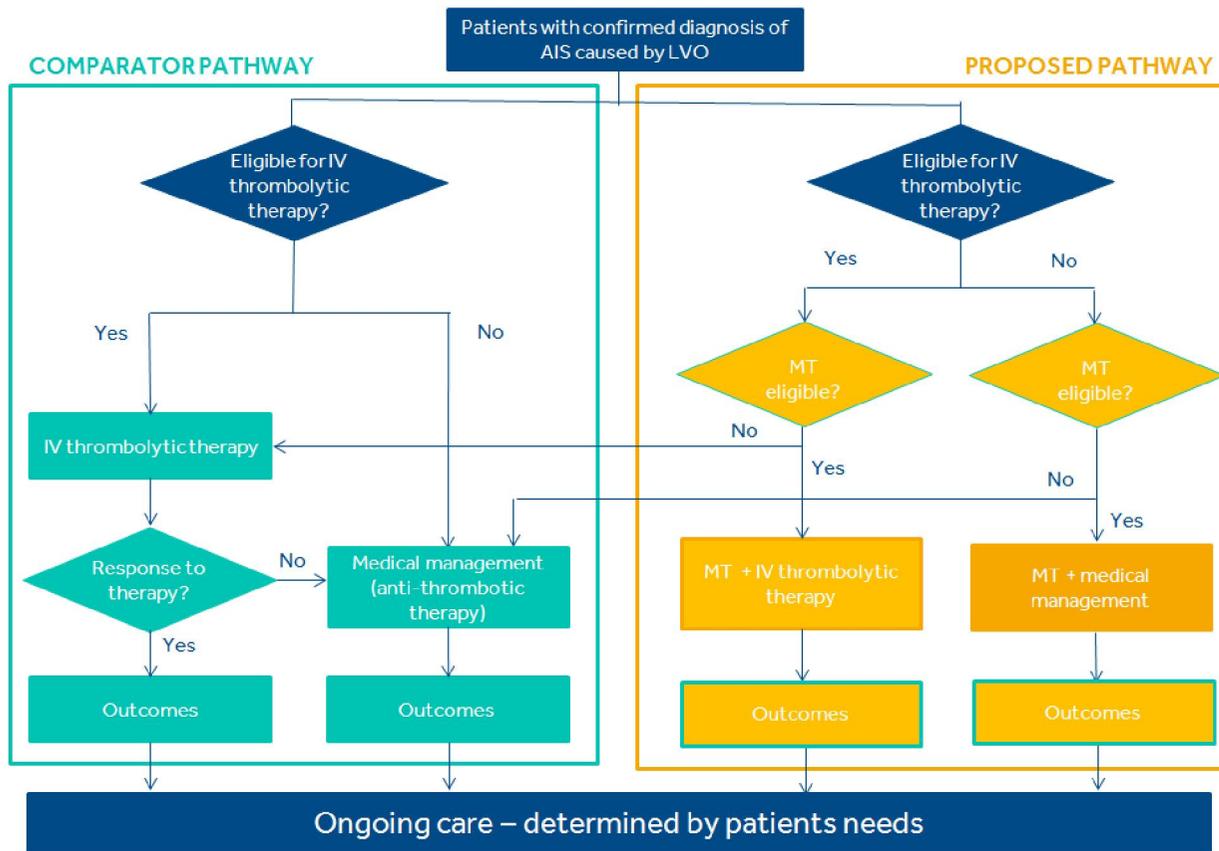


Figure 5 – Comparator and proposed service clinical pathways

Relevant outcomes are described in Section 7. Response to therapy is considered as successful reperfusion: see TIC1 scores described in Section 7.

As presented in Figure 5 the comparators for the proposed service are:

- IV thrombolytic therapy (IV tPA) where indicated, and:
- Medical management (anti-thrombotic therapy) where IV thrombolytic therapy is contraindicated.

The timing of provision of IV thrombolytic therapy (IV tPA) and mechanical thrombectomy should be aligned with current clinical practice guidelines (Table 2), which is a maximum of six hours from onset of symptoms to groin puncture (e.g. AHA/ASA 2015⁷⁶), reflecting the most up-to-date evidence for this therapy. This includes a recommendation to provide mechanical thrombectomy as soon after IV tPA has been initiated: *Observing patients after intravenous r-tPA to assess for clinical response before pursuing endovascular therapy* (i.e. mechanical thrombectomy) *is not required to achieve beneficial outcomes and is not recommended* (Table 2). Hence, in line with guidance: IV tPA should be initiated prior to mechanical thrombectomy, without waiting for a response before starting mechanical thrombectomy.

For the proposed pathway in Figure 5, for further clarification, the following advice from PASC was provided:

If eligible for tPA, this should be administered ASAP, before or during assessment of patient suitability for MT (<4.5h from symptom onset).

If suitable for MT, this should be performed without awaiting a clinical response to tPA (<6h from symptom onset)

With regards to the latter point, the Applicant notes eligibility guidelines described in the Victorian protocol for ECR, which recognise that some patients outside the 6 hours time window could benefit from MT (salvageable brain tissue identified on imaging).

The Applicant notes that in Australian clinical practice guidelines⁵⁴, *"Intra-arterial thrombolysis within six hours can be used in carefully selected patients"*. Intra-arterial thrombolysis (IAT) describes therapy where thrombolytic drugs are directly applied to the blocked artery using endovascular surgical techniques. Due to this similarity with mechanical thrombectomy – IAT is also an endovascular therapy, the clinical management pathway described here assumes that IAT would not be a treatment option: i.e. if endovascular access to the cerebral occlusion is possible, then mechanical thrombectomy would be used. However, there may be circumstances where MT is not possible, but IAT may be – it is proposed that the use of IAT is clarified during consultation of this protocol.

Following consultation feedback, the Applicant notes the following advice from PASC:

It was agreed that intra-arterial tPA (i.e. IAT) was not a valid comparator in the Australian context¹⁰.

1. Regulatory Information

The regulatory status of devices that can be used to deliver the proposed service is described in Table 10. Devices listed in this table represent those commonly used in Australia: The Solitaire 2 and Solitaire FR revascularisation devices and the Trevo devices are stent retrievers, while the Penumbra System is an aspiration/suction device. This protocol proposes that the assessment of MT will be generic - i.e. considering evidence for all relevant technologies listed on the ARTG that can deliver the proposed service.

¹⁰ Application 1428: PASC Meeting April 2016, Application Outcome

Table 10 - Australian regulatory status of mechanical thrombectomy devices for treatment of AIS

ARTG no.	Sponsor	Intended purpose from ARTG (Device/item description)	Product category	Date registered ^a
230784	Covidien Pty Ltd	The Solitaire 2 Revascularisation device is designed to restore blood flow in patients experiencing ischaemic stroke due to large intracranial vessel occlusion. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment. The device is designed for use in the neurovasculature such as the internal carotid artery, M1 and M2 segments of the middle cerebral artery, basilar and the vertebral arteries.	Medical Device Class III	18/11/14
203670	EV3 Australia Pty Limited	Solitaire FR Revascularization Device: For use in the flow restoration of patients with ischaemic stroke due to a large intracranial vessel occlusion. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment. The Solitaire FR Revascularization Device should only be used by physicians trained in interventional neuroradiology and treatment of ischaemic stroke.	Medical Device Class III	5/12/12
208795 (Trepo ProVue), 230859 (Trepo XP ProVue Retriever)	Stryker Australia Pty Ltd	The Trepo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischaemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment.	Medical Device Class III	Trepo XP ProVue Retriever: 20/11/14 Trepo ProVue: 27/04/13
216903 , (5MAX Reperfusion Catheter) 202744 (MAX Reperfusion Catheter)	Penumbra Neuro Australia Pty Ltd	The Penumbra System is intended for use in the revascularization of patients with acute ischaemic stroke secondary to intracranial large vessel occlusive disease (within the internal carotid, middle cerebral ± M1 and M2 segments, basilar, and vertebral arteries) within 8 hours of symptom onset.	Medical Device Class III	5MAX Reperfusion Catheter: 4/11/13 MAX Reperfusion Catheter: 6/11/12

Abbreviations: ARTG, Australian Register of Therapeutic Goods.

^a ARTG start date

For the Solitaire and Trevo devices the Australian Register of Therapeutic Goods (ARTG) public summaries state that “*Patients who are ineligible for IV tPA or who fail IV tPA therapy are candidates for treatment*”. International guidelines, based on trial results released after the registration of these items, recommend use in patients who received IV tPA, regardless of whether the patient “*failed*” to respond. The American Heart Association/American Stroke Association (United States) guidelines state: *Observing patients after intravenous tPA to assess for clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended* (Table 2).

- Older devices, (which are presumably not commonly used in Australia) that are listed on the ARTG for MT in AIS include:
 - The MERCI retriever, an older generation coil retriever, is listed on the ARTG (number 141107) as *“a single use device consisting of a flexible tapered core wire with helical loops at the distal end to remove thrombus or the retrieval of foreign bodies from the neurovasculature”*. This was registered in June 2007.
 - the Trevo Pro 4. This is listed on the ARTG (number 193745), registered in January 2012.
 - MAX Penumbra Separator (ARTG number 203354), MAX Reperfusion Catheter (202744), Penumbra Reperfusion Catheter (157312), Penumbra Separator (157313), Separator 3D (198621), and Separator Flex (187249). All were registered between November 2008 and November 2012.
 - MindFrame 10 Capture LP (ARTG number 194903), registered in February 2012.
 - CATCH (155097), registered in September 2008.

Decision analytic

Table 11 summarises the population, intervention, comparator and outcomes to define the research questions for the evaluation of MT for AIS.

Table 11 - Summary of PICO criteria to define research questions that assessment will investigate

Patients	Intervention	Comparator	Outcomes
<p>Persons with a confirmed diagnosis* of acute ischaemic stroke</p> <p>*Includes definite large vessel occlusion of the anterior circulation identified by imaging. Patients selected for treatment according to acute stroke management guidelines.</p>	<p>Mechanical thrombectomy</p> <p>Mechanical thrombectomy may be used in combination with intravenous thrombolytic drug therapy or without thrombolytic drug therapy for patients who are ineligible or fail thrombolytic therapy.</p>	<p>For indicated patients, intravenous thrombolytic therapy is a comparator to the proposed service.</p> <p>For patients contraindicated for intravenous thrombolytic therapy, the alternative comparator to the proposed service is medical management with anti-thrombotic therapy.</p>	<p>Effectiveness</p> <p>Revascularisation (e.g. TICI score)</p> <p>Function (e.g. Barthel Index)</p> <p>Disability (e.g. mRS)</p> <p>Health Related QoL</p> <p>Neurological deficit (e.g. NIHSS)</p> <p>Rescue treatment</p> <p>Mortality (all-cause; ischaemic stroke)</p> <p>Safety</p> <p>Device or procedure related adverse events</p> <p>Haemorrhage (e.g. symptomatic intracerebral haemorrhage, any cerebral haemorrhage)</p> <p>New ischaemic stroke</p> <p>Resource use</p> <p>e.g. Rehabilitation; hospitalisation; length-of-stay (general ward, ICU)</p>

Abbreviations: ICU, intensive care unit; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale/Score; QoL, quality of life; TICI, Thrombolysis in Cerebral Infarction perfusion scale grade.

Similar to EUnetHTA, and recent clinical practice guidelines, MSAC should consider whether the evidence for mechanical thrombectomy should differentiate old vs. newer studies, especially where there are clear differences in mechanical thrombectomy technologies used and methods for patient selection in more recent studies which result in improved outcomes (see *Proposed service and clinical claims*).

Healthcare resources

Healthcare resources to be considered in the evaluation of the proposed service are presented in Table 12. Further details of resource use will be identified during the assessment phase of this application. For example, it will be necessary to determine which resources to identify and treat patients (for current management and the proposed service) are encompassed within existing funding arrangements pertaining to stroke and cerebrovascular disease. Relevant Australian Refined Diagnosis Related Groups (AR-DRG) are listed in Table 12 – these may already encompass relevant resource use (e.g. hospital stay, theatre time, nursing staff, consumables etc.). Hence, if this is correct, then ‘double-counting’ of resource use should be avoided.

Healthcare resources required to identify patients with AIS caused by LVO who require reperfusion are considered to be the same whether the patients are managed by the comparator pathway or by the proposed service¹¹. This assumes that CT perfusion is not standard practice. It also considers that the availability of MT has changed the imaging used to assess all stroke patients – i.e. has changed because alternative options (e.g. MT or thrombolytic drug therapy) are now available. The Applicant recognises resources to identify eligible patients may vary according to imaging used - hence, sensitivity analysis will explore the impact of additional resources used to provide the proposed service.

The aim of both current clinical practice (comparator) and MT (proposed service) is to restore blood flow to minimize damage to the brain. Reperfusion is intended to avoid or limit neurological complications, the extent of which will determine the degree of success in achieving functional independence and avoiding stroke related disability. Resources required to manage patients (e.g. hospital stays, short- and long-term rehabilitation services, allied healthcare and carer services) will therefore vary depending on patient degree of independence and disability that is achieved following the acute intervention phase of treatment. Hence, as requested in Table 12, following treatment patients cannot be readily categorised as ‘successfully’ or ‘unsuccessfully’ treated.

In comparison to current practice, the availability of the proposed service is anticipated to result in improved rates of reperfusion, and subsequent avoidance of neurological complications with higher rates of functional independence. This is anticipated to translate to reduced healthcare resource use over the short and long-term.

Questions for public funding

Public consultation included the following questions:

- Which health / medical professionals provide the service?
 - What are the appropriate training/qualification/accreditation requirements?

¹¹ This is consistent with imaging for suspected stroke (non-contrast CT and CT angiography) described in the Victorian protocol for endovascular clot retrieval

- What is the appropriate setting for the service? What capabilities should this setting have?
 - How should setting accreditation for delivery of the proposed service be determined?
- What are the key inclusion and exclusion criteria for the medical service?
 - How can patient selection be appropriately defined to best identify patients where MT is beneficial, but also retain sufficient flexibility to meet the needs of clinical practice where patient treatment decisions are made on a case-by-case basis in an acute emergency setting?
- Are there any cost-savings from using the proposed medical service?
- What are the economic benefits of using the proposed medical service?
- Have all resources relevant to the economic analysis been identified?
- Is intra-arterial thrombolysis (IAT) part of current practice in Australia?
 - Would IAT be an alternative to MT in any circumstances?

Table 12 List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS (MBS item, fee)	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
Brain imaging (e.g. CT, MRI)	Private or Public Hospital	Radiology clinic/department	100%		CT: 56001 \$195.05 MRI: 63064 \$403.20					
Brain and carotid imaging (e.g. CTA, MRA)	Private or Public Hospital	Radiology clinic/department	100%		CTA: 57350 \$510.00 MRA: 63101 \$492.80					
Routine investigations: e.g. full blood count, ECG, renal function	Private or Public Hospital	ED/stroke service	100%		FBC: 65070 \$16.95 ECG: 11700 \$31.25					
ED/stroke service clinician and nursing staff	Private or Public Hospital	ED/stroke service	100%							
Resources provided to deliver proposed intervention										
Mechanical thrombectomy devices and associated neurointerventional devices such as guidewires, microcatheters, and other access devices	Private or Public Hospital	Angiography suite or catheterization laboratory	Variable (depends on clinical/technical contraindications)							
Mechanical thrombectomy procedure provision	Practitioner	Angiography suite or catheterization laboratory	Variable (as above)							
Neuroimaging: e.g. fluoroscopy	Private or Public Hospital	Angiography suite or catheterization laboratory	Variable (as above)		eg. Item 60009 ^c \$1,376.30					

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost						
					MBS (MBS item, fee)	Safety nets*	Other government budget	Private health insurer	Patient	Total cost	
Anaesthesia: Examples of the types of relevant MBS items include: -Initiation of management of anaesthesia -Intra-arterial cannulation with anaesthesia ^b	Anaesthetist	Surgical	Variable and whether service done under general anaesthesia or conscious sedation		Examples: MBS 20210 \$297.00 MBS 22025 \$79.20						
General consumables: e.g. dressings	Private or Public Hospital	Angiography suite or catheterization laboratory	100%								
Monitoring equipment: blood pressure, heart rate & oxygenation	Private or Public Hospital	Angiography suite or catheterization laboratory	100%		BP ^b : 22012 \$59.40						
Hospitalisation for procedure (overnight stay)	Private or Public Hospital	Private or Public Hospital	100%								
Resources provided in association with proposed intervention											
Pre-intervention: Routine investigations: e.g. full blood count, ECG, renal function	Private or Public Hospital	ED/stroke service	100%		FBC: 65070 \$16.95 ECG: 11700 \$31.25						
Follow-up brain imaging	Private or Public Hospital	Angiography suite or catheterization laboratory	100%		as an example: 60009 \$1,376.30						
Resources provided to deliver current clinical practice – that are also required for the intervention											
Drug therapy: IV tPA in eligible patients; anti-thrombotic	Private or Public Hospital	ED/stroke service	Variable (determined by	Variable			IV tPA: Alteplase:				TBA

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS (MBS item, fee)	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
therapy for IV tPA ineligible patients			time or non time based contraindication to. IV tPA)	(dose dependent on patient)			Anti-thrombotic: aspirin			
Monitoring equipment: blood pressure, heart rate & oxygenation	Private or Public Hospital	Angiography suite or catheterization laboratory	100%		BP ^b : 22012 \$59.40					
Resources provided in association with current clinical practice										
Pre-intervention: Routine investigations: e.g. full blood count, ECG, renal function.	Private or Public Hospital	ED/stroke service	100%		FBC: 65070 \$16.95 ECG: 11700 \$31.25					
Follow-up: brain imaging	Private or Public Hospital	Angiography suite or catheterization laboratory	100%							
Resources used to manage patients successfully treated with the proposed intervention. Resources required to manage patients (e.g. hospital stays, short- and long-term rehabilitation services, allied healthcare and carer services) will vary depending on patient degree of independence and disability that is achieved following the acute intervention phase of treatment.										
Diagnostic and pathology services.			Depends on individual patient needs							
Management of AEs	Private or Public Hospital	Private or Public Hospital	Varies							
Hospital stay - AR-DRG for stroke and other cerebrovascular diseases ^d B70A: +CCC B70B: +SCC B70C: -CSCC	Private or Public Hospital	Private or Public Hospital	Depends on individual patient needs				\$17,443 \$9,766 \$6,794			

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS (MBS item, fee)	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
B70D: DIE/TRN<5D							\$3,599			
Rehabilitation services			Depends on individual patient needs							
Community based services (residential care; allied health; home nursing; carers; ambulance etc.)			Depends on individual patient needs							
Resources used to manage patients who are unsuccessfully treated with the proposed intervention										
Resources required to manage patients (e.g. hospital stays, short- and long-term rehabilitation services, allied healthcare and carer services) will vary depending on patient degree of independence and disability that is achieved following the acute intervention phase of treatment.										
Diagnostic and pathology services			Depends on individual patient needs							
Management of AEs	Private or Public Hospital	Private or Public Hospital	Varies							
Hospital stay– AR-DRG B70A to B70D ^d	Private or Public Hospital	Private or Public Hospital	Depends on individual patient needs				\$17,443 to \$3,599			
Rehabilitation services			Depends on individual patient needs							
Community based services (residential care; allied health; home nursing; carers; ambulance etc.)			Depends on individual patient needs							
Resources used to manage patients successfully treated with current clinical practice										
Resources required to manage patients (e.g. hospital stays, short- and long-term rehabilitation services, allied healthcare and carer services) will vary depending on patient degree of independence and disability that is achieved following the acute intervention phase of treatment.										
Diagnostic and pathology			Depends on							

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS (MBS item, fee)	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
services			individual patient needs							
Hospital stay AR-DRG B70A to B70D ^d	Private or Public Hospital	Private or Public Hospital	Depends on individual patient needs				\$17,443 to \$3,599			
Rehabilitation services			Depends on individual patient needs							
Community based services (residential care; allied health; home nursing; carers; ambulance etc.)			Depends on individual patient needs							
Resources used to manage patients who are unsuccessfully treated with current clinical practice										
Resources required to manage patients (e.g. hospital stays, short- and long-term rehabilitation services, allied healthcare and carer services) will vary depending on patient degree of independence and disability that is achieved following the acute intervention phase of treatment.										
Diagnostic and pathology services			Depends on individual patient needs							
Hospital stay AR-DRG B70A to B70D ^d	Private or Public Hospital	Private or Public Hospital	Depends on individual patient needs				\$17,443 to \$3,599			
Rehabilitation services			Depends on individual patient needs							
Community based services (residential care; allied health; home nursing; carers; ambulance etc.)			Depends on individual patient needs							

* Include costs relating to both the standard and extended safety net.

Abbreviations: AEs, adverse events; AR-DRG, Australian Refined Diagnosis Related Groups; BP, blood pressure; C(S)CC, catastrophic (or severe) complication or comorbidity; CT, computed tomography; CTA, computed tomography angiogram; ECG, electro cardiogram; ED, emergency department; FBC, full blood count; IV tPA, intravenous tissue plasminogen activator; MRI, magnetic resonance imaging; MRA, magnetic resonance angiogram; SCC, severe complication or comorbidity; TBA, to be advised

^a Patients receive either general or conscious sedation

^b When performed with administration of anaesthesia

^c MBS Item 60009 is for Digital Subtraction Angiography, examination of head and neck with or without arch aortography

^d National Hospital Cost Data Collection Cost Weights for AR-DRG Version 6.0x, Round 17 (2012-13)

EMVA

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