MSAC Application 1428

Mechanical thrombectomy

For acute ischaemic stroke due to large vessel occlusion

Submission to the
Medical Services Advisory Committee

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MAIN BODY OF THE SUBMISSION

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EXECUTIVE SUMMARY

Mechanical thrombectomy for acute ischaemic stroke due to large vessel occlusion

This submission-based Application by Medtronic Australasia requests a Medicare Benefits Schedule (MBS) listing for mechanical thrombectomy (MT) to treat acute ischaemic stroke (AIS) due to a large vessel occlusion (LVO). MT offers significantly superior post-stroke functional outcome when compared with usual care in carefully selected patients. Following favourable results from five recent randomised controlled trials (RCTs) and strong positive recommendations in international and local guidelines, stroke care pathways are rapidly being updated to incorporate MT as a treatment option. With strong evidence for superior clinical efficacy and cost benefits, MT has the potential to transform AIS treatment in Australia.

Alignment with agreed PICO confirmation

This Application addresses all of the PICO elements that were pre-specified in the decision analytic protocol (DAP) that was considered by the Protocol Advisory Sub-Committee (PASC). The criteria proposed for the final Protocol are reproduced in the table below.

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

Patients	Intervention	Comparator	Outcomes
Persons with a confirmed diagnosis* of acute ischaemic stroke *Includes definite large vessel occlusion of the anterior circulation identified by imaging. Patients selected for treatment according to acute stroke management guidelines.	**Mechanical thrombectomy** 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.	For indicated patients, **intravenous thrombolytic therapy** is a comparator to the proposed service. For patients contraindicated for intravenous thrombolytic therapy, the alternative comparator to the proposed service is **medical management with anti-thrombotic therapy.**	**Effectiveness** Revascularisation (e.g. TICI score) Function (e.g. Barthel Index) Disability (e.g. mRS) Health-Related QoL Neurological deficit (e.g. NIHSS) Rescue treatment Mortality (all-cause; ischaemic stroke) **Safety** Device or procedure-related adverse events Haemorrhage (e.g. symptomatic intracerebral haemorrhage, any cerebral haemorrhage) New ischaemic stroke **Resource use** e.g. Rehabilitation; hospitalisation; length of stay (general ward, ICU)

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

Section A: CONTEXT

Rationale for Application

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 of stroke treatment 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 is recommended in treatment guidelines – 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.

The inclusion of MT for AIS on the MBS is a key step to improving access to an effective treatment option and to addressing the clinical and cost burdens of stroke. Improvements in reperfusion following MT and subsequent avoidance of neurological complications result 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 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. Improved access to MT has the potential for significant reduction in direct healthcare costs. Broader societal benefits and indirect cost savings from avoided impact on productivity costs and reduced carer burden are also anticipated.

Proposed medical service

MT is a highly specialised and time-critical treatment, with the greatest benefit achieved with early reperfusion of ischaemic brain. It requires a well organised system to identify suitable candidates for therapy, and should only be performed by highly trained neurointerventionists at suitable stroke units.

Delivery of the service involves the use of a specialised endovascular device to remove an obstructing clot from the artery, thereby restoring blood flow to the brain and minimising brain tissue damage. The devices used to perform MT include coil retrievers, aspiration devices and most recently, stent retrievers. All are delivered to occluded sites with the aid of microcatheters and guidewires, but each type of device uses a slightly different mechanical approach to remove the target clot. Although the Applicant manufactures and markets the

Solitaire™ brand of stent retrievers, this submission considers evidence for all types of devices used in MT. MT may be used in addition to the current standard of care for AIS, thrombolysis with recombinant tissue plasminogen activator (IV tPA), or as a standalone in patients who are ineligible or contraindicated to IV tPA.

Proposal for public funding

Current clinical practice guidelines reflect MT's favourable clinical evidence in patients with AIS caused by LVO who are eligible or ineligible for IV tPA. Whilst some evidence suggests that outcomes may be influenced by factors such as time from stroke onset, pattern of stroke damage, and disease severity, subgroup analyses of individual patient data show that the relative benefit of MT is largely consistent regardless of variation in patient selection criteria. On this basis, the item descriptor proposed in this submission takes a relatively non-prescriptive approach to patient selection. The table below presents the proposed MBS item descriptor. 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. Eligibility criteria for MT should retain 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.

Proposed MBS item descriptor

Category 3 - THERAPEUTIC PROCEDURES
MBS [item number] 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 8 hours of stroke onset; including intra-operative imaging, but in association with preoperative diagnostic imaging items[a] - either 56001 or 63064 Fee: $3,500 (Anaes.) (Assist.) Explanatory notes: • Diagnosis confirmed by imaging: ischaemic 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 8 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].

[a]Examples of relevant CT and MRI items included.

Abbreviations: TBD, to be determined; CTA, computed tomography angiography; MRI, magnetic resonance imaging

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.

Comparators

MT is indicated as an additional therapy in patients who are eligible for IV-tPA, and as an alternative therapy in patients for whom IV-tPA is contraindicated. The comparators for these respective groups are:

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

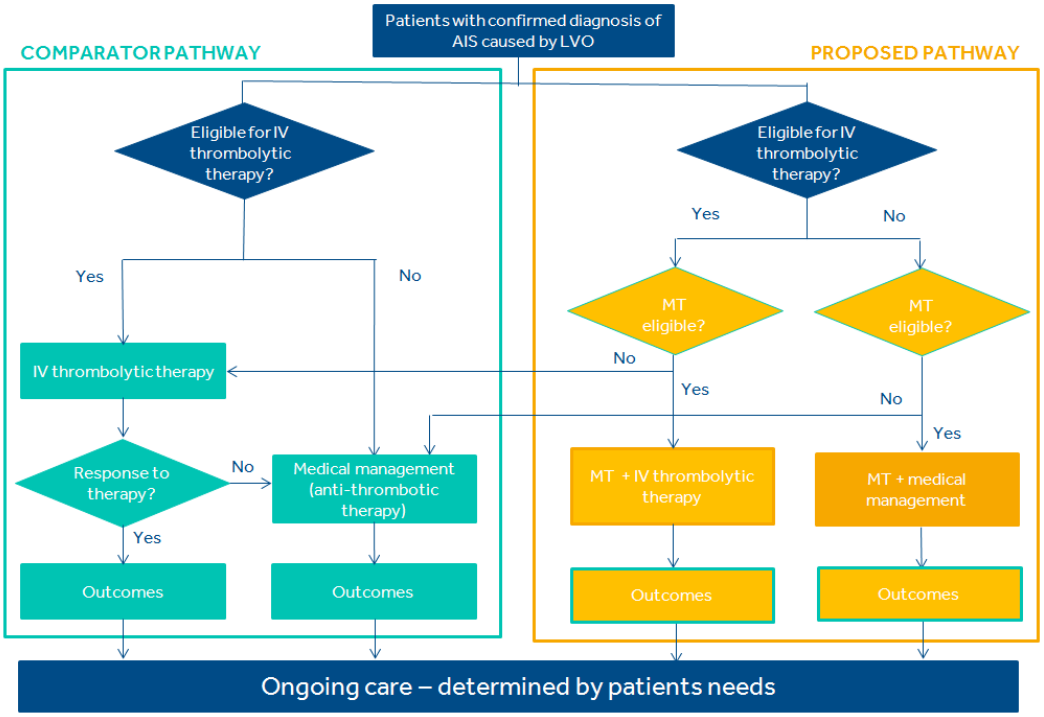
In this submission these comparators are referred to as 'usual care'.

There are strict rules to determine if a patient is eligible for IV-tPA - it is recommended in clinical practice guidelines as first-line therapy approved for LVOs within 4.5 hours of symptom onset. Hence, presentation > 4.5 hours after stroke symptom onset will preclude access to IV-tPA. In addition, patients may be ineligible due to non-time based reasons, examples include: severe, uncontrolled hypertension; previous surgery; widespread ischaemia, patient receiving oral anticoagulants. The only treatment option available to patients who are ineligible for IV-tPA (time and non-time based reasons) is medical management, consisting of anti-thrombotic therapy with antiplatelet agents (aspirin) or anticoagulants.

Proposed clinical management algorithm

The proposed clinical algorithm is consistent with recommendations from clinical practice guidelines (CPGs) and Australian stroke protocols. MT is indicated as an additional therapy in patients who are eligible for treatment with IV-tPA, and as an alternative therapy in patients for whom IV-tPA is contraindicated.

Current and proposed clinical management algorithm



Abbreviations: LVO, large vessel occlusion; MT, mechanical thrombectomy

In line with clinical practice guidelines:

- If eligible for IV-tPA, this should be administered as early as possible, 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 IV-tPA (<6h from symptom onset).

Section B: PRIMARY EVIDENCE

A literature search was conducted to identify all published and unpublished RCTs that could be used to directly compare the efficacy and safety of the use of MT plus usual care versus usual care alone as a treatment for patients with AIS due to a LVO. The search identified five eligible randomised trials of MT plus usual care and usual care alone ESCAPE; EXTEND-IA; MR CLEAN; REVASCAT; SWIFT PRIME which met the PICO-defined inclusion criteria. One of the pivotal studies, EXTEND-IA, was conducted in Australia and New Zealand, led by investigators from the Royal Melbourne Hospital.

The primary outcome presented in this submission was the modified Rankin scale (mRS) at 90 days, which is a measure of functional ability. This primary outcome was assessed as a

"shift analysis" of disability scores (i.e. the odds of improving by one mRS point). Secondary outcomes included functional independence (mRS 0-2 at 90 days) and mortality.

For the primary outcome, the median mRS score at 90 days favoured the intervention treatment arms and was statistically significant in all five trials at 90 days compared to the control group, i.e. the lower the mRS score, the lower the degree of disability and increased functional independence. A post-hoc meta-analysis of these results, based on individual patient data (IPD), shows a pooled cOR of 2.26 (95% CI: 1.67, 3.06; p<0.0001) (Goyal et al, 2016). The corresponding number needed to treat with MT to reduce disability by at least one level on the mRS for one patient was 2·6.

For the secondary outcomes, 46.1% of patients in the intervention treatment arm (i.e. MT) compared to 26.4% of patients in the control arm (i.e. usual care) achieved functional independence at 90 days. This difference was statistically significant with an odds ratio (OR)=2.39 (95% CI: 1.88, 3.04), p<0.0001. For mortality, 15.3% of patients in the intervention treatment arm compared to 18.8% of patients in the control arm had died at 90 days. This difference was not statistically significant with an OR=0.78 (95% CI: 0.54, 1.12), p=0.18. The absence of heterogeneity in the meta-analyses strengthened conclusions about the consistency of effects across major subgroups of age and severity.

For the secondary outcomes, 46.1% of patients in the intervention treatment arm compared to 26.4% of patients in the control arm possessed a mRS score of 0-2 at 90 days. A mRS score of 0-2 indicated functional independence. Overall, 15.3% of patients in the intervention treatment arm compared to 18.8% of patients in the control arm had died at 90 days.

Meta-analysed outcomes in the pivotal trials of MT vs usual care

Outcome	Intervention – MT	Control – Usual care	OR [95% CI]
	n /N (%)	n /N (%)	
Primary outcome			
mRS score reduction (shift analysis)	-	-	2.26 (1.67, 3.06) p<0·0001[a]
Secondary outcomes			
mRS score 0-2 at 90 days	292/633 (46.1%)	170/645 (26.4%)	2.39 [1.88, 3.04], p<0.00001[b]
Mortality at 90 days	97/634 (15.3)	122/649 (18.8)	0.78 [0.54, 1.12], p=0.18[b]

Abbreviations: CI, confidence interval; mRS, modified Rankin scale; MT, mechanical thrombectomy; OR, odds ratio

[a] Common odds ratio indicating the odds of improvement of one point on the mRS. Based on IPD meta-analysis by Goyal (2016).

[b] OR [95% CI] calculated using Review Manager 5.3 for this submission.

In general, the pivotal trials also included a greater proportion of subjects who achieved early neurologic improvement, possessed milder impairment post-stroke and higher Barthel Index

(BI, a measure of daily living capability) score compared to the control arm. Additionally, there was 100% reduction in the perfusion-lesion volume for patients treated with intervention treatment, compared to 37% reduction for those in the control arm.

Overall, the safety data suggest that MT is associated with an increased risk of certain complications compared to usual care alone; in particular, procedural complications and hematoma. However, these risks should be balanced against the poor prognosis of many patients with AIS and the net benefits of treatment with MT in terms of functional outcomes. Furthermore, any adverse effects resulting directly from the procedure would be expected to occur within the 90-day duration of the trial. Therefore, the long-term safety profile of MT relative to usual care is expected to be similar to the 90-day safety profile reported in the clinical trial.

The evidence presented demonstrates that treatment with MT in addition to usual care is superior to usual care alone in terms of effectiveness and non-inferior in terms of safety. A modelled cost-utility analysis is presented to support the cost-effectiveness of MT in addition to usual care.

Section C: SYNTHESIS WITH OTHER EVIDENCE

Applicability of trial population to those for whom listing is sought

The application of MT in clinical practice aims to identify all patients with LVO ischaemic stroke who could potentially benefit from this therapy. Hence, the targeted population is relatively broad, limited only to “patients with confirmed diagnosis of acute ischaemic stroke caused by large vessel occlusion of the anterior circulation”. Despite demonstrating uniformly favourable results for MT relative to usual care, each of the 5 pivotal RCTs had some differences in terms of the populations enrolled and circumstances of use. Thus, a series of subgroup analyses of the primary endpoint were presented to examine possible effect modifications. These analyses, based on IPD, showed no heterogeneity of treatment effect across pre-specified subgroups for reduced disability (Goyal, 2016). Effect sizes favouring MT over usual care were present in several strata of special interest, including in patients aged 80 years or older (cOR 3·68, 95% CI: 1·95–6·92), those randomised more than 300 min after symptom onset (1·76, 1·05–2·97), and those not eligible for intravenous alteplase (cOR 2·43, 95% CI: 1·30–4·55). This supports the use of an intention-to-treat (ITT) approach in the base case of the economic evaluation.

For patients who are eligible for IV-tPA, the baseline characteristics of patients in the Australian EXTEND-IA study appear to be similar to those of the meta-analysed IPD population. A subgroup analysis of the MR CLEAN study shows that patients who are

ineligible for IV-tPA are more likely to be slightly older and suffer vascular comorbidities; however, the clinical efficacy of MT relative to untreated patients remains similar in this subgroup. Furthermore, the reasons for contraindication for IV-tPA observed in the trial are consistent with clinical practice guidelines used in Australia. Therefore, the results of the meta-analysis presented in Section B are also applicable to Australian patients that are ineligible to receive IV-tPA.

Utility values used in the economic model

The Section D model defines its health states according to mRS scores 0 to 5 (plus mRS 6 for death). The source of additional QALYs for MT vs usual care lies in that a greater proportion of patients are in lower mRS health states in the MT arm over time. Utility values were identified via a literature review. The base case values are informed by Sturm et al (2002), reporting utility values from the North East Melbourne Stroke Incidence Study (NEMESIS). Sensitivity analysis explored other values, suggesting this dataset may be conservative (i.e., underestimation of the cost-effectiveness of MT).

Summary of utility inputs for the Section D cost-effectiveness model

Post-stroke disability by mRS	**Utility input (base case)**
0: No symptoms at all	0.63
1: No significant disability despite symptoms	0.63
2: Slight disability	0.40
3: Moderate disability	0.18
4: Moderately severe disability	0.06
5: Severe disability	0.02
6: Death	0

Abbreviation: BI, mRS, modified Rankin Score. Source: Sturm et al (2002)

Selection of costing data

The proposed MBS fee is $3500. The total per-procedural cost is $18,308.49. Cost savings as a result of superior functional outcomes offered by MT are estimated based on the published evidence via a literature review. As would be expected, patients with mRS 5 (i.e., bedridden, incontinent, constant care) incur far more costs for care ($17,943 per annum) than those who are less dependent (e.g., $1,431 per annum for mRS 0-1) even in the long run.

Extrapolation of trial based evidence beyond the duration of the trials

Extrapolation is a necessary and adequate element for a cost-effectiveness assessment of MT. While all procedural costs are absorbed at baseline, much of the functional benefits

offered by MT (and thus their QoL/cost implications) would persist into the future and for many patients be permanent. Indeed, a life-time model can only fully account for mortality benefits offered by MT during the acute phase. The Section D model also captures any improvement (i.e., rehabilitation effects) or deterioration of mRS over time. Also, the base case model accounts for stroke recurrence. These natural history parameters were informed by the locally-relevant published evidence.

Section D: ECONOMIC EVALUATION

A stepped economic evaluation is performed with the base case incremental cost-effectiveness ratio (ICER) being produced from a life-time cost-utility analysis, as shown in the table below. The ICER is $12,880 per QALY gain, demonstrating MT's very favourable cost-effectiveness vs usual care. Expectedly, the model time horizon affects the ICERs; nonetheless, the grossly conservative 5-year model still returns an ICER less than $50,000. A range of sensitivity analysis strongly supported the robustness of these results.

Cost-effectiveness evidence supporting the MBS listing of MT

Analysis	Inc. effectiveness	Inc. costs	ICERs
Trial based			
in terms of additional independent person at 90 days (mRS0-2), MT cost only	0.1950	$18,308	$93,890
12-month analysis			
in terms of additional independent person at 90 days (mRS0-2), 12-month costs	0.1950	$17,837	$91,473
in terms of life years, 12-month costs	0.0492	$17,837	$362,403
in terms of QALYs years, 12-month costs	0.0937	$17,837	$190,361
5-year analysis			
in terms of life years, 5 year costs	0.2912	$15,255	$52,388
in terms of QALYs years, 5 year costs	0.3504	$15,255	$43,542
10-year analysis			
in terms of life years, 10 year costs	0.5074	$13,048	$25,716
in terms of QALYs years, 10 year costs	0.5730	$13,048	$22,773
20-year analysis			
in terms of life years, 20 year costs	0.7247	$11,027	$15,216
in terms of QALYs years, 20 year costs	0.7870	$11,027	$14,012
Life-time analysis (base case)			
in terms of life years, life-time year costs	0.7691	$10,666	$13,868
in terms of QALYs years, life-time year costs	0.8281	$10,666	$12,880

Section E: BUDGET IMPLICATIONS

The available epidemiological data suggests an estimated total of 18,320 AIS cases due to LVO in 2016. The eligibility for MT is estimated to be met by up to 2,700 cases if a full uptake is achieved (i.e., the procedure is given to all potentially eligible patients; private and public combined). However, the infrastructure to provide adequate "hyperacute" care is suboptimal in Australia (National Stroke Foundation 2015). For example, IV-tPA was given in only 7% of all ischaemic stroke cases. The number of MT procedures will be therefore limited by the case load capacity available in Australia; currently there are six private centres offering the service, each performing on average 10 procedures each year. The case load capacity analysis estimates that up to 10 private centres would be offering the service by the fifth year of listing; each centre performing on average 15 procedures each year. This equates to $393,750 in Year 5 for the proposed service. The total MBS costs for that year (including other services such as anaesthetics and imaging tests) would be $578,687.

The availability of MT on the MBS is estimated to provide cost savings to the wider Australian healthcare system: from $884,244 in Year 1, rising to $2,456,232 in Year 5. Broader societal benefits and indirect cost savings from avoided impact on productivity costs and reduced carer burden are also anticipated as result of improved access to MT.

Section F: ADDITIONAL RELEVANT INFORMATION

Lack of definitive funding arrangements for non-implantable medical technology used to deliver MBS services is a barrier to effective adoption of new services implemented following Medical Services Advisory Committee (MSAC) evaluation.

This is a consequence of the 'disconnect' between positive advice for listing from MSAC and new MBS services using non-implanted technology. This arises due to the absence of a definitive funding pathway for non-implanted technology - i.e. do not meet Prostheses List criteria. As a consequence, adoption of new MBS items may be suboptimal, with opportunities to use technology that is more clinically and cost-effective lost.

This is relevant for the current Application – MT devices used to deliver the proposed service do not meet the criteria for inclusion on the Prostheses List (PL) as they are not a permanent surgical implant. Furthermore, due to the emergency nature of MT, case-by-case, pre-intervention, device funding requests cannot be considered by private health insurers.

For the current Application - should positive advice from MSAC lead to the implementation of a MT MBS item – we propose that MSAC and the Department of Health (DOH) consult to determine how stent retrieval devices could be funded under Part C of the existing PL arrangements (e.g. Health Minister consideration for inclusion on Part C of the PL - as was

the step taken for Cardiac Remote Monitoring Systems; Application 1197.1) or through the *selective expansion* of the PL criteria to include non-implantable devices associated with new MBS services.

Conclusions

There is high quality evidence demonstrating that in comparison to usual care, MT significantly improves functional outcomes for patients with AIS. These findings have led to strong positive recommendations in international and local clinical practice guidelines, and are likely to transform the manner in which acute stroke care is delivered in Australia. The economic evaluation presented in this submission assumes that the improved functional outcomes in patients treated with MT translate to improved quality of life and reduced care costs in the long-term. This produces a base case ICER of $12,880 per QALY, a figure which is robust to a range of conservative sensitivity analyses. Medtronic looks forward to working with MSAC in order to facilitate access to this important technology.

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LIST OF APPENDICES AND ATTACHMENTS

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LIST OF ELECTRONIC FILES

Description	Filename
Cost-Effectiveness Analysis of Solitaire for Acute Ischaemic Strokes due to Large Vessel Occlusions	1. MT MSAC June 2016 Section D
Estimated utilisation and financial implications	2. MT MSAC June 2016 Section E

LIST OF ABBREVIATIONS

ABS	Australian Bureau of Statistics
AHA	American Heart Association
AIHW	Australian Institute of Health and Welfare
AIS	Acute ischaemic stroke
AQoL	Assessment of Quality of Life
ARTG	Australian Register of Therapeutic Goods
ASA	American Stroke Association
BI	Barthel Index
BP	Blood pressure
CPG	Clinical practice guidelines
CT	Computed tomography
CTA	Computed tomography angiography
DAP	Decision analytic protocol
DOH	Department of Health
DSA	Digital subtraction angiography
DVT	Deep vien thrombosis
DWI	Diffusion weighted imaging
EASI	Endovascular Acute Stoke Intervention
ECR	Endovascular clot retrieval
ESO	European Stroke Organisation
EUnetHTA	European Network for Health Technology Assessment
GP	General practitioner
GRIM	General Record of Incidence of Mortality
HERMES	Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HUI	Health utilities index
IA	Intra-Arterial
IAT	Intra-arterial thrombolysis
ICA	Internal carotid artery
ICER	Incremental cost-effectiveness ratio
ICH	Intra-cranial haemorrhage
ICU	Intensive care unit

ABS	Australian Bureau of Statistics
IFU	Instructions for Use
IPD	Individual patient data
IQR	Interquartile range
ITT	Intention-to-treat
IVRS	Interactive voice response system
IWRS	Interactive web response
KOL	Key opinion leader
KSU	Karolinska Stroke Update
LVO	Large vessel occlusion
LY	Life-years
MBS	Medical Benefits Schedule
MC	Multicentre
MCA	Middle cerebral artery
MCID	Minimal clinically important difference
mRS	Modified Rankin Scale
MSAC	Medical Services Advisory Committee
MT	Mechnical thrombectomy
NIH	National Institute of Health
NIHSS	National Institutes of Health Stroke Scale
NNT	Number needed to treat
NSF	National Stroke Foundation
OHTAC	Ontario Health Technology Advisory Committee
OR	Odds ratio
PACS	Picture archiving and communication system
PASC	Protocol Advisory Sub-Committee
PBAC	Pharmaceutical Benefits Advisory Committee
PCSS	Perth Community Stroke Study
PICH	Primary intracerebral hemorrhage
PL	Prostheses List
PTT	Partial thromboplastin time
QALY	Quality-adjusted life-years
QoL	Quality-of-life
RCT	Randomised controlled trials
RD	Risk difference

ABS	Australian Bureau of Statistics
RR	Relative risk
SAH	Subarachnoid haemorrhage
SG	Standard gamble
SOC	Standard of care
S.T.R.O.K.E.	Stroke Time Registry for Outcomes Knowledge and Epidemiology
SICH	Symptomatic intracerebral haemorrhage
STAR	Solitaire Flow Restoration Thrombectomy for Acute Revascularization
TGA	Therapeutics Goods Administration
TIA	Transient Ischaemic Attack
TICI	Thrombolysis in Cerebral Infarction
TTO	Time-trade-off
VST	Victorian Stroke Telemedicine
WHO	World Health Organisation

A. DETAILS OF THE PROPOSED SERVICE AND ITS INTENDED USE ON THE MBS

Summary

- Mechanical thrombectomy (MT) is a highly effective treatment that reduces the occurrence of disability after acute ischaemic stroke (AIS) caused by a large vessel occlusion (LVO).
- Delivery of the service involves the use of a specialised endovascular device to remove an obstructing clot from the artery, thereby restoring blood flow to the brain and minimising brain tissue damage. This improves neurological outcomes, reducing or avoiding prolonged neurologic disability with improved functional independence. Avoiding disability is associated with significant clinical and cost benefits. Broader societal benefits through reduced carer burden and improved workforce participation are also expected.
- MT is a highly specialised procedure. It is a time-critical treatment, with the greatest benefit achieved with early restoration of blood flow. It requires a well organised system to identify suitable candidates for therapy, and should only be performed by highly trained neurointerventionists at suitable stroke units.
- Following favourable results from five recent RCTs and strong positive recommendations in international and local guidelines, stroke care pathways are rapidly being updated to incorporate MT procedures as a treatment option for patients with AIS.
- The fee for the proposed service is $3500. This amount reflects the complexity, duration and skills required to provide the service.
- MT is indicated as an additional therapy in patients who are eligible for treatment with intravenous thrombolytic therapy (IV-tPA), and as an alternative therapy in patients for whom IV-tPA is contraindicated. The comparators for these respective groups are:
    - IV-tPA alone (where indicated), and
    - Medical management (anti-thrombotic therapy) where IV thrombolytic therapy is contraindicated.
- In both groups, AIS is currently associated with very poor long-term outcomes. Compared to the current standard of care, MT devices offer more rapid reperfusion, enhanced efficacy in treating LVO, and a potentially lower risk for haemorrhagic events. These translate to improved long-term functional outcomes.

A.1 Background

A.1.1 Submission history

This Application by Medtronic Australasia requests a Medicare Benefits Schedule (MBS) listing for mechanical thrombectomy (MT) to treat acute ischaemic stroke (AIS) due to a large vessel occlusion (LVO). The proposed service involves the use of a specialised endovascular device to remove an obstructing clot from the artery, thereby restoring blood flow to the brain and minimising brain tissue damage. More specifically, MT aims to salvage the ischaemic penumbra, the area surrounding the core zone of a cerebral infarction. The penumbral region is not irreversibly damaged and successful revascularisation can

improve functional outcomes and quality of life for patients. With strong evidence for a high level of clinical efficacy in comparison to current treatment options, mechanical thrombectomy has the potential to revolutionise the management of acute stroke.

MT can be performed using a range of devices, including coil retrievers, aspiration devices and most recently, stent retrievers (Raychev and Saver, 2012). All are delivered to occluded sites with the aid of microcatheters and guidewires, but each type of device uses a slightly different mechanical approach to remove the target clot. Although the Applicant manufactures and markets the Solitaire™ brand of stent retrievers, this submission considers evidence for all types of devices used in MT. MT may be used in addition to the current standard of care for AIS, thrombolysis with recombinant tissue plasminogen activator (IV tPA), or as a standalone in patients who are ineligible or contraindicated to IV tPA.

Three major initial randomised controlled trials (IMS-III, MR RESCUE and SYNTHESIS) failed to provide definitive evidence for the efficacy of endovascular therapies compared to IV tPA. However, in the past couple of years, five landmark randomised clinical trials have been published, all showing a significant clinical benefit for endovascular therapy with MT in AIS patients presenting with proximal intra-cranial large vessel occlusions (MR CLEAN, EXTEND-IA, SWIFT PRIME, ESCAPE and REVASCAT). One study (EXTEND-IA) was conducted in Australia and New Zealand, led by investigators from Royal Melbourne Hospital (Campbell, 2015). The positive findings of the new cohort of studies is attributable to several improvements in study design. In particular, early studies of MT were limited by the use of first generation thrombectomy devices and intra-arterial thrombolytic agents[1] to achieve recanalisation (Saver et al, 2012; Noguiera et al, 2012), suboptimal patient selection due to the lack of sophisticated imaging techniques employed, and lengthy delays to initiation of treatment.

The results of these studies have now been confirmed through the publication of a number of systematic reviews and meta-analyses (Sardar et al, 2015; Elgendy et al, 2015). A recent meta-analysis provides the most precise estimates of overall treatment effect by using IPD from five pivotal studies of MT (Goyal et al, 2016). This analysis reported an adjusted common odds ratio for reduced disability of 2·49 (95% CI 1·76–3·53; p<0·0001) and

[1] It should be noted that in the context of stroke, the term “endovascular therapy” is used to describe procedures whereby treatment is administered directly to the site of an occluded vessel. In most cases, this refers to mechanical thrombectomy, but it may also include intra-arterial thrombolytic (IV-tPA) administration.

consistent effects across major subgroups of age and severity. The number needed to treat (NNT) with MT to reduce disability by at least one level on the modified Rankin scale (mRS) for one patient was 2·6. The results of this IPD meta-analysis are presented in detail in Section C.2 of this submission.

Major stroke management guidelines were updated in 2015 with a new set of recommendations regarding the use of MT (Powers et al, 2015; ESO, 2014 and EUnetHTA, 2015). On 16th December 2015 EUnetHTA published the results of a rapid health technology assessment of endovascular therapy using MT devices for AIS (EUnetHTA, 2015). Key findings of the report were as follows:

- *"…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 these trials and hence the evidence presented here should not be interpreted as evidence of effect for other types of thrombectomy device".*

EUnetHTA, 2015

Most recently, the Ontario Health Technology Advisory Committee (OHTAC) recommended publically funding stent retrievers and thrombo-aspiration devices for mechanical thrombectomy in patients with AIS, in selected stroke centres. This decision was based on "*high quality evidence (that) showed a significant difference in functional independence in patients who received mechanical thrombectomy relative to intravenous thrombolysis*" and a favourable cost-effectiveness ratio (OHTAC, 2016).

Following overwhelmingly positive clinical trial results and recent recommendations in international guidelines, stroke care pathways are rapidly being updated to incorporate endovascular procedures as a treatment option for patients with AIS. For example, the Victorian State Government has recently published a statewide service protocol for endovascular clot retrieval (Department of Human Health Services, 2016) to ensure that as many Victorians as possible will have access to treatment. The recommendations in this protocol are based on evidence that the treatment is highly effective and associated with an "overwhelming benefit". It is expected that other states will soon develop their own guidance for incorporating MT into stroke management pathways. In addition, the National Stroke Foundation is currently updating its clinical guidelines to incorporate recently published

evidence for MT.

A.1.2 Clinical overview

Acute ischaemic stroke

The World Health Organisation (WHO) defines stroke as "*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".* Strokes are generally classified as either ischaemic or haemorrhagic.

Haemorrhagic stroke, also known as spontaneous intracerebral haemorrhage (ICH), is either a brain aneurism burst or a weakened blood vessel leak. The usual mechanism is thought to be leakage from small intracerebral arteries damaged by chronic hypertension. The seepage of blood creates swelling and pressure, damaging cells and tissue in the brain. A minority of strokes are haemorrhagic, with approximately 80% of all strokes being ischaemic (Donnan et al, 2008).

Ischaemic strokes occur when an artery supplying the brain becomes occluded, leading to the death of brain tissue and focal neurological deficits. The brain does not store glycogen and requires 60-70 mL of perfusion per 100 g of tissue per minute for normal function (Felberg et al, 2003). 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 (Felberg et al, 2000).

There are two types of ischaemic stroke: transient ischaemic stroke (TIA) and acute ischaemic stroke (AIS). Both occur through similar mechanisms; however TIA involves a temporary clot with symptoms that last 24 hours or less (Donnan et al, 2008). TIAs are a risk factor for subsequent AIS, with about 5-10% of TIA patients experiencing further stroke within the following week (Johnston et al, 2000).

The patient population who would benefit from the proposed service are patients with AIS due to large (or proximal) vessel occlusion (LVO). This form of stroke occurs as a result of occlusion of large intra-cranial vessels, including the vertebral, basilar, carotid terminus, and middle and anterior cerebral arteries. LVOs are often associated with a poorer prognosis than stroke not associated with LVO, and are less likely to respond to IV-tPA (Smith et al, 2009).

In the "core" zone of a stroke-affected area, blood flow is so drastically reduced that neurons and supporting (glial) cells may undergo necrosis. The "ischaemic penumbra" is the rim of mild to moderately ischaemic tissue lying between tissue that remains perfused with blood

and the area in which the infarction is developing is less severely affected. This region is rendered functionally ineffective by the AIS, but remains metabolically active. The ischaemic penumbra may remain viable for several hours if blood is available through collateral circulation. However, if reperfusion is not established, the cells in the ischaemic penumbra will also die due to lack of oxygen and glucose.

Ischaemic stroke is a heterogeneous disease and occurs due to a multitude of underlying causes. According to the widely used TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system (Table 1), strokes can be caused by: large artery disease, embolism, small-vessel disease, other determined cause, and undetermined cause (Adams et al, 1993). The TOAST investigators noted that stroke prognosis, risk of recurrence, and choices for management were influenced by ischaemic stroke subtype. The subtype definitions were based on risk factor profiles, clinical features, and results of diagnostic tests.

Thrombotic strokes occur when diseased or damaged cerebral arteries become blocked by the formation of a blood clot within the brain. Large vessel thrombosis is the term used when the blockage is in one of the brain's larger blood-supplying arteries such as the carotid or middle cerebral, while small-vessel thrombosis involves one (or more) of the brain's smaller, yet deeper, penetrating arteries. This latter type of stroke is also called a lacuner stroke. An embolic stroke occurs when a thrombus travels from elsewhere in the body (usually the heart) to block narrower blood vessels in the brain.

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.

Symptoms

The presenting signs and symptoms of AIS and other forms of stroke are similar; many studies suggest the two types of strokes cannot be distinguished reliably without brain imaging. Symptoms emerge suddenly and usually peak in severity a few minutes after onset. While the clinical manifestations of stroke vary, depending on the site and size of the brain lesion, 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 recognise parts of the body
- Imbalance and falling

Symptoms associated with AIS include the sudden onset of weakness, numbness, vision loss, diplopia, dysarthria, gait disorder, vertigo, aphasia or a disturbed level of consciousness. The location of the stroke will determine which particular pattern of symptoms occurs. There is usually an absence of function in patients affected by AIS; for example, a patient will often report loss of vision in a single eye or in an entire hemifield.

Management of AIS

The central goal of therapy in AIS is rapid and early reperfusion to preserve tissue in the ischaemic penumbra, where perfusion is decreased but sufficient to stave off infarction. Time to reperfusion has been correlated with worse outcomes, and it is therefore vital that patients are treated as soon as possible after stroke onset (Khatri et al, 2009). Currently, the main approach to restoring blood flow in the affected area is through the administration of intravenous (IV) thrombolytic therapy, the most common of which is recombinant tissue-type plasminogen activator (tPA; alteplase). Blood clots are dissolved when tPA binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin, which in turn degrades the fibrin matrix of the thrombus.

There are strict rules used by doctors in determining if a patient is eligible for tPA. There is strong evidence from RCTs demonstrating that the use of thrombolytic therapy within the first 3 hours of stroke onset improves reperfusion rates; however treatment is associated with an increase in the rate of intracerebral and systemic haemorrhage. Whilst tPA therapy is associated with a net benefit when administered early, this decreases rapidly over time, such that beyond 4.5 hours after stroke onset no net benefit of therapy has been demonstrated (Lees et al, 2010). The Australian National Stroke Foundation (NSF) clinical practice guidelines recommend (Grade A) that IV-tPA should be administered as a first-line therapy in patients with AIS as early as possible, but no later than 4.5 hours after stroke onset (NSF, 2010). With such a narrow window for administration, many patients arrive at hospital too late

to receive thrombolytic therapy.

Mainly due to the high risk of haemorrhage, tPA is also contraindicated in patients that meet any of the following criteria:

- Severe, uncontrolled hypertension
- Previous surgery; widespread ischaemia
- Patient receiving oral anticoagulants with an international normalised ratio >1.3
- Intra-cranial bleeding
- Previous stroke within the past three months.

As a result of these factors, only a small proportion of patients with AIS currently receive thrombolytic therapy with IV tPA. Well organised major stroke units achieve treatment rates of up to 20%; however, across Australia, the use of IV-tPA in patients with AIS is estimated to be less than 5% (NSF, 2010). For patients who are ineligible for thrombolytic therapy because they have missed the 4.5-hour window or have other contraindications, there are few effective treatment options. In general, these patients undergo medical management consisting of anti-thrombotic therapy with antiplatelet agents (aspirin) or anticoagulants.

Finally, 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 lesions (Mehta et al, 2012).

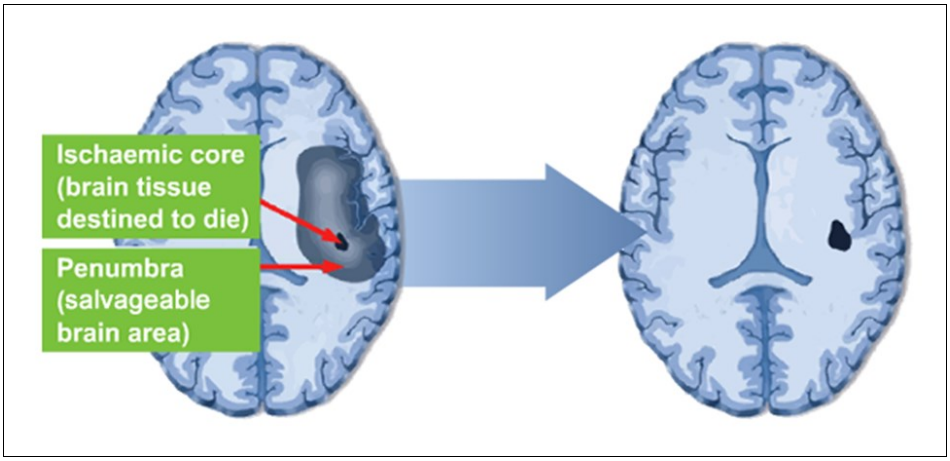
Overall, there is a strong clinical need for safe and effective stroke therapies for use in combination with IV thrombolytic therapy, or as an alternative treatment for patients who are ineligible for IV thrombolytic therapy. Compared to the current standard of care, MT devices offer more rapid achievement of reperfusion; enhanced efficacy in treating large vessel occlusions; and a potentially lower risk for haemorrhagic events. Improved reperfusion and avoidance of neurological complications produces higher rates of functional independence in the target population compared to thrombolysis. These improved clinical outcomes also have the potential to reduce the burden on the healthcare system through shorter hospital stays, less use of rehabilitation services, reduced carer burden, and reduced use of other healthcare resources.

A.1.3 Description of the service

As illustrated in Figure 1, MT aims to salvage the ischaemic penumbra – the area surrounding a cerebral infarct that suffers less ischaemia. 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 1 Ischaemic penumbra – Potential to reverse neurologic impairment with post-stroke therapy



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

The procedure can be performed using a variety of devices, including coil retrievers, aspiration devices and most recently, stent retrievers (Raychev and Saver, 2012). These different types of endovascular devices are described in Table 2. Currently, the devices commonly-used in Australia are either stent retrievers, or those that use aspiration or suction techniques.

Table 2 Description of mechanical thrombectomy devices

Device	Description
Coil retrievers	The coil retrievers are composed of Nitinol shape-memory wire and delivered through a microcatheter across the target clot. As the device is extruded from delivery catheter, it immediately reassumes its native coil form. The neurointerventionalist deploys the loops of the coil through the clot to engage the thrombus, and then pulls both coil and clot back into the catheter, like pulling a cork from a wine bottle.
Aspiration devices	Aspiration devices work by advancing a reperfusion catheter over a neurovascular guide-wire 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, the residual thrombus can be removed using a thrombus removal ring.
Stent retrievers	The stent retrievers are delivered to the thrombus using a microcatheter percutaneously introduced via the femoral artery. Neuroimaging is used to position the device in the cranial blood vessel. The microcatheter is advanced distal to the thrombus position so that when the stent is fully deployed it will extend beyond both ends of the thrombus. Self-expanding stents are deployed in the occluded vessel within the thrombus, pushing it aside and entangling it within the stent struts. The stent and thrombus are then withdrawn back into the delivery catheter.

It should be noted that stent retrievers are supported by a stronger body of clinical evidence

than other devices such as aspiration catheters; the five most recent RCTs used newer-generation stent retrievers in all (EXTEND-IA, REVASCAT, SWIFT PRIME) or the majority of cases (MR CLEAN, ESCAPE). The three older RCTs used first 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). A recent trial of the PENUMBRA aspiration system (the 'Assess the Penumbra System in the Treatment of Acute Stroke' (THERAPY) trial was terminated early due to positive results from other recent MT studies (Tsivgoulis et al, 2016).

On this basis, some CPGs specifically recommend treatment with stent retrievers over MT more broadly (see Table 3).

Table 3 Summary of mechanical thrombectomy devices used in key trials and international guidance around devices

US ASA/AHA guidelines (Powers, 2015)	European guidance (ESO, 2014)	European assessment (EUnetHTA, 2015)
Stent retrievers are preferred to MERCI device (Class I, level of evidence A). Use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances (Class IIb, Level B-NR).	For mechanical thrombectomy, stent retrievers approved by local health authorities should be considered (Grade A, Level 1a, KSU Grade A). 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).	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.

Abbreviations: 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

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 and consider evidence for all relevant technologies that can deliver the proposed service. As discussed further in Section A.2.1, the following MT technologies are currently used in Australia:

- The Solitaire 2 and Solitaire FR revascularisation devices (Covidien)
- The Trevo ProVue retrievers (Stryker)
- The MAX and 5MAX reperfusion catheters (Penumbra)

A.2 Indications and requested restrictions

A.2.1 Regulatory status

Table 4 presents the regulatory status of devices used to deliver the proposed service 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 submission proposes that the clinical evaluation of MT should be generic, including evidence for the different classes of device.

For the Solitaire and Trevo devices, the Public Australian Register of Therapeutic Goods (ARTG) Summaries indicate the devices should be used in “patients who are ineligible for IV-tPA or who fail IV-tPA therapy are candidates for treatment”. It should be noted that the Therapeutics Goods Administration (TGA) indications for MT devices pre-date a number of pivotal clinical trials which were published between 2014 and 2015. The TGA indication is therefore inconsistent with CPGs which now recommend the use of MT in patients who received IV-tPA, regardless of whether the patient “failed” to respond. The American Heart Association/American Stroke Association (United States) guidelines (Powers et al, 2015), the European (ESO, 2014) and EUnetHTA (EUnetHTA, 2015) all recommend MT in addition to IV-tPA in patients with acute stroke and large vessel occlusion state.

The Applicant notes that the current TGA indication for our stent retriever devices is partially aligned with the proposed population (i.e. for patients who fail or are ineligible for IV-tPA). We have contacted the TGA to ensure the indication is revised to allow full alignment with the proposed population, following appraisal of the latest international clinical data. Following submission of an indication variation request to the TGA, we received advice that a revised Instructions for Use (IFU) is required. Once this IFU is ready, we will resubmit for indication variation. We are working to achieve the revised indication by the October 2016 ESC and November 2016 MSAC meetings.

MASC should note that our requests for indication variation are commercial-in-confidence information; hence this should not be communicated in any public forum.

Older and less commonly-used devices that are listed on the ARTG for MT in AIS include the Merci Retriever, the Trevo Pro 4, the Penumbra and MAX Penumbra systems, MindFrame 10 and CATCH. All of these devices were TGA-listed prior to 2013, and have since been superseded by newer-generation devices.

Table 4 Details of TGA registration

ARTG no	Product name	Product description	Device class	Sponsor
Products commonly-used in Australia				
230784	SOLITAIRE 2 Revascularisation Device	The SOLITAIRE 2 Revascularisation device is designed to restore blood flow in patients experiencing ischaemic stroke due to large intra-cranial 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	Covidien Pty Ltd
203670	Solitaire FR Revascularisation Device	Solitaire FR Revascularisation Device: For use in the flow restoration of patients with ischaemic stroke due to a large intra-cranial 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 Revascularisation Device should only be used by physicians trained in interventional neuroradiology and treatment of ischaemic stroke.	Medical Device Class III	EV3 Australia Pty Limited
208795	Trevo ProVue	The Trevo Retrievers are 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	Stryker Australia Pty Ltd
230859	Trevo XP ProVue Retriever		Medical Device Class III	Stryker Australia Pty Ltd
216903	5MAX Reperfusion Catheter	The Penumbra System is intended for use in the revascularisation of patients with acute ischaemic stroke secondary to intra-cranial 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	Penumbra Neuro Australia Pty Ltd
Products not commonly-used in Australia				
141107	Merci Retriever	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	Medical Device Class III	Stryker Australia Pty Ltd
193745	Trevo Pro 4	Retrievers are intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischaemic stroke. 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	Stryker Australia Pty Ltd
202744	MAX Reperfusion Catheter	The Penumbra System is intended for use in the revascularisation of patients with acute ischaemic stroke secondary to intra-cranial 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	Penumbra Neuro Australia Pty Ltd

ARTG no	Product name	Product description	Device class	Sponsor
203354	MAX Penumbra Separator	The Penumbra System is intended for use in the revascularisation of patients with acute ischaemic stroke secondary to intra-cranial large vessel occlusive disease (in the internal carotid, middle cerebral ± M1 and M2 segments, basilar, and vertebral arteries) within 8 hours of symptom onset.	Medical Device Class III	Penumbra Neuro Australia Pty Ltd
157312	Penumbra Reperfusion Catheter	The Penumbra Reperfusion catheter, separator and the aspiration tubing should be used to remove thrombus. The reperfusion catheter provides access to the occusion site and then provides a conduit to remove the thrombus. The device is intended for use in the revascularisation of patients with acute ischaemic stroke secondary to intra-cranial large vessel occulusive disease, within 8 hours of onset.	Medical Device Class III	Penumbra Neuro Australia Pty Ltd
157313	Penumbra Separator	The Penumbra Separator is intended to be used with the Penumbra Reperfusion catheter and Penumbra aspiration tubing to remove thrombus. The separator tip is designed to clear the thrombus from the lumen of the Reperfusion catheter during aspiration. The device is intended for use in the revascularisation of patients with acute ischaemic stroke secondary to intra-cranial large vessel occulusive disease, within 8 hours of onset.	Medical Device Class III	Penumbra Neuro Australia Pty Ltd
198621	Separator 3D	Intended for the revascularisation of patients with acute ischaemic stroke secondary to intra-cranial large vessel occlusion disease (within the internal carotid, middle cerebral M1 and M2 segments, basilar, and vertebral arteries) within 8 hours of the symptom onset	Medical Device Class III	Penumbra Neuro Australia Pty Ltd
187249	Separator Flex	The Penumbra Separator is intended to facilitate aspiration and debulking of the thrombus and reduce or eliminate the endovascular clot burden as it is passed through the Penumbra Reperfusion catheter. The Penumbra System consists of the Separator, Reperfusion Catheter, Aspiration pump and pump/canister tubing, all available separately. The Penumbra System is intended for use in the revascularisation of patients with acute ischaemic stroke secondary to intra-cranial 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	Penumbra Neuro Australia Pty Ltd
194903	MindFrame 10 Capture LP	To restore blood flow in the cerebral vasculature of patients suffering from an acute ischaemic stroke. The Mindframe System is positioned across the embolus or blood clot and is used to facilitate the restoration of blood flow and removal of the clot obstruction.	Medical Device Class III	Covidien Pty Ltd
155097	CATCH	The CATCH basket is intended for the removal of clotted blood or other formed elements that cause vascular obstruction. It is used with the VASCO+ microcatheter as a system of removing thrombi and is indicated for the treatment of ischaemic strokes.	Medical Device Class III	N Stenning and Co Pty Ltd

Abbreviations: ARTG, Australian Register of Therapeutic Goods.

A.2.2 Existing reimbursement arrangements

Currently, MT is reported to be available at 19 stroke centres in Australia (NSF, 2015). All stroke centres are based in public hospitals and are therefore currently funded out of State Government health budgets.

A.2.3 Proposed listing of service

Table 5 presents the proposed MBS item descriptor. 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.

Table 5 Proposed MBS item descriptor

Category 3 - THERAPEUTIC PROCEDURES
MBS [item number] 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 8 hours of stroke onset; including intra-operative imaging, but in association with preoperative diagnostic imaging items[a] - either 56001 or 63064 Fee: $3,500 (Anaes.) (Assist.) Explanatory notes: • Diagnosis confirmed by imaging: ischaemic 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 8 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].

[a]Examples of relevant CT and MRI items included.

Abbreviations: TBD, to be determined; CTA, computed tomography angiography; MRI, magnetic resonance imaging

The proposed descriptor is intended 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. The fee for the proposed service is $3,500. This amount reflects the complexity, duration and skills required to provide the service.

From a technical perspective, MT for AIS is considered more challenging than other neurointerventional procedures. A potentially similar service to MT is the endovascular coiling of intra-cranial aneurisms (MBS item 35412; $2,857.55). However, MT is considered technically more challenging than this procedure due to the fact that the average patient for aneurysm is relatively young with more straightforward vascular access. By comparison, typical stroke patients who could benefit from MT are elderly, when vasculature becomes increasingly tortuous and difficult to navigate. 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.

A detailed justification for the proposed fee, including cost estimates for each component of the service, is presented in Section C.5 of this submission.

A.3 Intervention details

A.3.1 Delivery of the intervention

Proposed clinical setting

MT is a highly specialised procedure. It is a time-critical treatment, with the greatest benefit achieved with early restoration of blood flow. Time to reperfusion is well established as a major determinant of outcome in patients with LVO (Goyal et al, 2015; Khatri et al, 2009). To optimise outcomes, patients should be transferred to the closest centre that can provide the proposed service: this may be as an inpatient service in a private or public hospital.

Delivery of the intervention requires a well organised system to identify suitable candidates for therapy and rapidly transport them to an MT-capable centre. With regards to the setting for the proposed service, the Applicant notes guidance for MT states its use "*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 outpatient 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 hyperacute pathways*" (White et al, 2015). Accordingly, the Australian NSF guidelines also recommend that "*all people with stroke should be admitted to hospital and be treated in a stroke unit with a multidisciplinary team*" (NSF, 2010).

Accreditation requirements

MT is a technically challenging procedure, and should only be performed by highly trained radiologists, neurologists or neurosurgeons who have specialist skills in neurointervention.

Close cooperation and integrated care between endovascular clot retrieval (ECR) neurointerventionists and multidisciplinary stroke unit teams is required to maximise the benefit to patients. Increased procedural volume provides opportunities for improved patient outcomes and staff training (Adamczyk et al, 2013).

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*" (ESO, 2014). Similarly, a standards document representing professional bodies from the U.K. states "*the decision to undertake endovascular stroke therapy should be made jointly by a multidisciplinary team compromising a consultant stroke physician, (neuro)interventionist (with the necessary experience and skills) and an anaesthetist (preferably experienced in neurological care)*" (White et al, 2015).

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) (CCINR, 2015). The CCINR are amongst several groups who have developed an international consensus on training for MT The Applicant recognises that appropriate operator training/accreditation and setting capabilities are necessary to achieve optimal patient outcomes with MT that have been observed in clinical trials. Increased procedural volume will also provide opportunities for improved patient outcomes and staff training.

Service delivery

MT is performed in an angiography suite or catheterisation lab. Hospitals must have neuroimaging modalities similar to those used for endovascular coiling of intra-cranial aneurysms. Neuroimaging is required to guide the procedure as well as other general neurointerventional devices such as guidewires, microcatheters, and other access devices. Whilst the exact procedure may vary depending on the type of MT device being used, an example of the procedure with a retrievable stent is explained below:

"*A balloon-guided catheter is placed proximal to the intra-cranial thrombus. A guide-wire is passed through the thrombus and then a microcatheter is passed over the guide-wire through the thrombus. The guide-wire is withdrawn and the stent retriever is passed through the microcatheter to position the distal end a few millimetres distal to the thrombus. The microcatheter is then withdrawn while the retrievable stent device is held in place and the stent opens within the thrombus, allowing the tines of the stent to capture the thrombus. At this point, contrast can be injected through the balloon guide catheter to assess for distal perfusion. After a short period (5 minutes), the balloon is inflated proximally to achieve flow*

arrest and the microcatheter and stent is retracted gradually into the guiding catheter while aspirating the guide catheter. The balloon is then deflated and a control angiogram confirms if the clot has been removed. If not, this process can be repeated several times" (OHTAC, 2016).

Additionally, the Instructions for Use for the SOLITAIRE 2 Revascularisation Device (Medtronic) are provided in Appendix A to this submission.

To minimise delays in access to thrombolytic therapy, stroke management guidelines recommend coordinating pre-hospital and in-hospital pathways and systems for patients with acute stroke (NSF, 2010; Department of Human Health Services, 2016). Similarly, stroke centres often aim to optimise efficiency of acute stroke management through the implementation of protocols that precisely guide patient evaluation and treatment, providing benchmarks for the time that should be required to complete each step. It is expected that optimised delivery of MT will require its integration within these existing protocols. Hence, the pathway of care for the proposed service will contain elements of current protocols, including ambulance pre-notification of the neurointervention service to initiate preparation of the angiography suite or catheterisation lab. A recently published Victorian state protocol details the management protocol for patients identified as potential candidates for endovascular clot retrieval and outlines the process for transferring patients to a statewide clot retrieval centre. The patient journey is described, including the duties and responsibilities of the principal care providers, including metropolitan and regional hospitals; Ambulance Victoria; the Victorian Stroke Telemedicine (VST) program; and the specialist stroke centres (Department of Human Health Services, 2016). The use of protocols to guide patient assessment and treatment is discussed further in Section A.5.

MT can be done under general anaesthesia or conscious sedation. Guidelines are not definitive in recommending one technique over the other. As shown in Table 6, the guidelines generally recommend that the choice should depend on individual patient characteristics (e.g. neurological status and airway control), with a preference for conscious sedation, where appropriate. However, it should be noted that an increasing body of retrospective data demonstrate that patient outcomes are worse for patients treated under general anaesthesia compared to monitored anaesthesia care or conscious sedation. Patients under conscious sedation have been shown to have a lower final infarct burden, lower incidence of pneumonia and shorter stay in the ICU (Jumaa et al, 2010; Abou-Chebl et al, 2010). More recent data from MR CLEAN demonstrated a similar effect in prospective fashion (Berkhemer, 2015). Conscious sedation accelerates times from suite arrival to groin access

by eliminating anaesthesia induction and intubation times. Further, it permits intra- and post-procedural neurological examination and rapid post procedure recovery (Telles Cougo-Pinto et al, 2015).

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

Trial evidence	US guidelines (Powers et al., 2015)	European guidance (ESO, 2014)	UK Standards of care (White et al, 2015)
Four out of five recent RCTsa had between 35%-38% of patients given general anaesthesia; one study (ESCAPE) had only 9% general anaesthesia.	It might be reasonable to favour conscious sedation over general anaesthesia. However, the ultimate selection of anaesthetic technique during MT for should be individualised 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)	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.

Abbreviations: AHA, American Heart Association; ASA, American Stroke Association; MT, endovascular thrombectomy; ESO, European Stroke Organisation; KSU, Karolinska Stroke Update; RCT, randomised controlled trial
[a] MR CLEAN, EXTEND-IA, REVASCAT and SWIFT PRIME

A.3.2 Other healthcare resources

In the short-term, the majority of healthcare resources required to identify AIS patients who could benefit from reperfusion (proposed service or comparator) are considered to be the same, whether the patients are managed with tPA alone, or with tPA plus MT. However, MT is associated with some additional resources required for neuroimaging (e.g. fluoroscopy) monitoring equipment, and follow-up imaging. For patients who are contraindicated for IV-tPA, these same resources are additional to medical management with anti-thrombotic agents.

Overall, the availability of MT is anticipated to result in improved rates of reperfusion, and subsequent avoidance of neurological complications with higher rates of functional independence compared to current clinical practice. This translates to reduced healthcare resource use over the longer-term (Campbell et al, 2015).

A.4 Main comparator

For individuals who have AIS, the key to effective treatment is early reperfusion of ischaemic

brain without causing adverse effects. To achieve reperfusion, IV thrombolytic therapy is recommended in treatment guidelines (NSF, 2010). Several IV thrombolytic therapies are available, the most common being the intravenous recombinant tissue plasminogen activator alteplase (IV-tPA). Therefore, for patients considered eligible for treatment with IV thrombolytic therapy, the main comparator for MT plus IV thrombolytic therapy is IV thrombolytic therapy alone.

There are strict rules used by doctors in determining if a patient is eligible for tPA. Therefore, in practice the group of patients who receive treatment with IV thrombolytic therapy represents a relatively small proportion (~7%) of all patients presenting with AIS (NSF, 2015). The majority of remaining patients are considered ineligible because they have missed the 4.5 hour window for administration, or have other contraindications such as treatment with oral anticoagulants. The only treatment option available to these patients is medical management, consisting of anti-thrombotic therapy with antiplatelet agents (aspirin) or anticoagulants. On this basis, for patients who are contraindicated for IV thrombolytic therapy, the alternative comparator to the proposed service is medical management with anti-thrombotic therapy.

A.5 Current and proposed clinical management algorithms

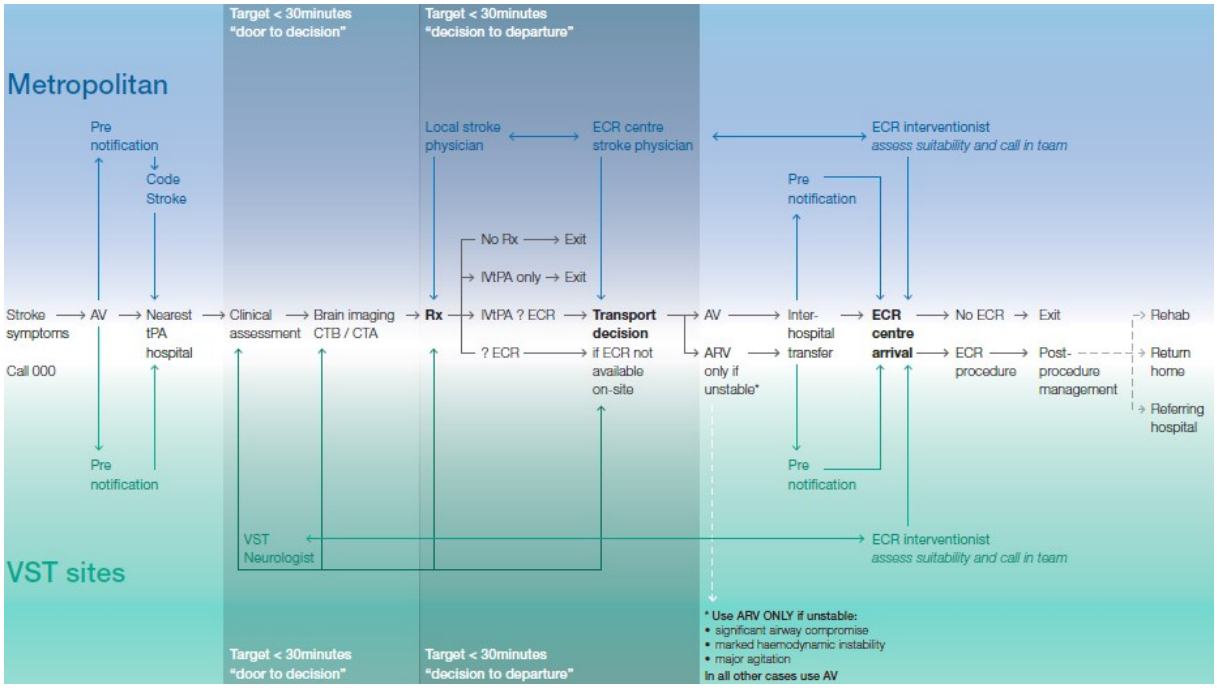
A.5.1 Summary of clinical practice guidelines and Australian protocols

One consistent finding across multiple trials in acute stroke is that faster treatment delivery leads to better clinical outcomes (Emberson et al, 2014). Stroke centres currently optimise efficiency of acute stroke management through the implementation of protocols that precisely guide patient evaluation and treatment, providing benchmarks for the time that should be required to complete each step (Meretoja et al, 2013). Protocols also emphasise the importance of managing acute stroke as a parallel process instead of a serialised one, thereby avoiding potential delays from repeated patient transfer between different areas of emergency stroke care.

With some variations in sequencing and timing, it is expected that most Australian stroke centres will treat AIS in a manner that broadly reflects the Victorian state protocol for endovascular clot retrieval, presented in Figure 2. As discussed previously, this protocol was written in response to positive results from clinical trials of MT with the explicit purpose of integrating the procedure into current stroke management pathways (Department of Human Health Services, 2016).

Based on advice from clinical practice guidelines and the Victorian state protocol for endovascular clot retrieval, key elements of the treatment algorithm for MT are presented under the headings below. These include pre-hospital pathways, initial assessment, administration of IV tPA, administration of MT, and post procedure care.

Figure 2 Victorian statewide flow diagram of endovascular clot retrieval pathway



Pre-hospital pathways

The Victorian guidance recommends patients whose stroke symptoms started within 4.5 hours are candidates for IV tPA. A patient with a stroke due to a large vessel occlusion is a candidate for both IV tPA and endovascular clot retrieval, if the patient can get to the clot retrieval centre within six hours of symptom onset. The approach taken by the Victorian Government is concentrating the expertise for delivering the therapy to two centres capable of providing a 24-hour, seven-day service for potential MT patients from across the state.

Initial assessment

Patients admitted for stroke are rapidly assessed on arrival in the emergency department or imaging/neurointerventional service using a validated stroke screening tool such as National Institutes of Health Stroke Scale (NIHSS) or Scandinavian Stroke Scale (SSS) (NSF, 2010). Following this, patients eligible for IV tPA and/or MT are selected primarily on the basis of the time from stroke onset and the results of advanced imaging. Imaging is an important element of patient selection as it can be used to identify the location of the occlusion and size of the penumbra, the extent of the infarct, the presence of collateral circulation and the extent of

tissue at risk for irreversible ischaemia. The use of up-to-date non-invasive arterial imaging is one of the factors attributed to the success of recent studies of MT when compared to earlier thrombectomy trials (Vo et al, 2015).

According to the Victorian statewide service protocol, routine brain imaging for AIS would generally include a non-contrast CT brain and CTA from the aortic arch to the vertex (see Table 7). Evidence from the five pivotal RCTs of MT shows this approach to selecting patients results in a substantial clinical benefit (Goyal et al, 2016). Overall, angiography using CTA or MRA was the most widely used approach to vascular imaging and detection of LVO; in most cases for the detection of the occlusion and determining the core size. Whilst it is possible use either CT or MR-based imaging for most parameters, CTA is known to be effective (as shown in the ESCAPE trial) and more rapid than MRA.

The contribution of other imaging approaches to further refine study populations (such as perfusion or diffusion imaging) remains unclear. Accordingly, the US ASA/AHA guidelines (Powers, 2015) make the following recommendation regarding imaging:

"the benefits of additional imaging beyond CT and CTA or MR and MRA, such as CT perfusion or diffusion- and perfusion-weighted imaging, for selecting patients for endovascular therapy are unknown (Class IIb; Level of Evidence C). Further randomised, controlled trials may be helpful to determine whether advanced imaging paradigms employing CT perfusion, CTA, and MRI perfusion and diffusion imaging, including measures of infarct core, collateral flow status, and penumbra, are beneficial for selecting patients for acute reperfusion therapy who are within 6 hours of symptom onset and have an ASPECTS <6. Further randomised, controlled trials should be done to determine whether advanced imaging paradigms using CT perfusion and MRI perfusion, CTA, and diffusion imaging, including measures of infarct core, collateral flow status, and penumbra, are beneficial for selecting patients for acute reperfusion therapy who are beyond 6 hours from symptom onset".

CT perfusion, although it is listed as an imaging option in Table 7, has many limitations, including lack of standardisation, effect of motion and the potential to introduce delays in the decision-making process (Zerna et al, 2015). On this basis, this form of advanced imaging is recommended primarily in patients who are treated 6-8 hours after stroke onset and who are at high risk of "futile" MT.

Table 7 Recommended brain imaging for suspected stroke in the Victorian statewide service protocol

Brain imaging for suspected stroke	
Non-contrast CT brain	Diagnoses intracerebral haemorrhage, established ischaemic stroke, mimics (such as a tumour), subtle early ischaemic changes and hyperdense thrombus in the arteries Note: In addition to standard axial views, 1 mm thin slice reconstructions improve detection of hyperdense thrombus and should be a standard series
CT angiogram (aortic arch to brain vertex)	Confirms diagnosis in non-lacunar ischaemic stroke
	Provides immediate knowledge of carotid stenosis and proximal vasculature
	Provides critical information if considering transfer for ECR
	For intracerebral haemorrhage CTA can demonstrate underlying vascular malformation requiring intervention and risk of on-going haematoma enlargement – 'spot sign' on-going contrast extravasation.
	When to perform CT angiography: • time of onset within six hours, with a longer window for suspected basilar occlusion • potentially treatable clinical deficit • there is no requirement to wait for creatinine results unless there is known kidney disease with eGFR < 30 mL/min (CTA is OK if the patient is already on dialysis; consider risk-benefit if eGFR < 30 mL/min) • consider risk-benefit and premedication if history of contrast allergy
CT perfusion	Improves diagnostic sensitivity for ischaemic stroke
	Indicates brain tissue viability (extent of irreversible injury and tissue at risk)
	Recommended whenever possible to reduce the incidence of futile ECR

*Updated American, Canadian and European guidelines have been released; updated Australian guidelines are in development

Thrombolytic therapy

The AHA/ASA CPG update on endovascular treatment of patients with AIS recommends rapid administration of IV tPA to appropriate patients remains the mainstay of early treatment of acute ischaemic stroke. Timely restoration of blood flow in ischaemic stroke patients is effective in reducing long-term morbidity. For patients who meet national and international eligibility guidelines, IV-tPA administration improves functional outcomes at 3 to 6 months when given within 4.5 hours of ischaemic stroke onset and should be administered. If patients who are eligible for IV-tPA do not have intra-cranial vascular imaging as part of their initial evaluation, they should begin receiving thrombolytic therapy before being transported for additional imaging and before being transferred for endovascular treatment. This approach helps to minimise onset-to-treatment times, which are a key driver of efficacy for tPA (Powers et al, 2015).

This advice is reiterated in other relevant CPGs for stroke management, including the Australian NSF guidelines, which state: "intravenous rtPA should be given as early as possible in carefully selected patients with acute ischaemic stroke as the effect size of thrombolysis is time-dependent. Where possible, therapy should commence in the first few hours but may be used up to 4.5 hours after stroke onset" (NHF, 2010).

Consistent with this guidance, the Victorian statewide service protocol for endovascular clot retrieval integrates advice regarding the use of MT and IV tPA, as eligible patients should be assessed and considered for both interventions. In relation to thrombolytic therapy, the protocol states that IV tPA should be administered to all eligible patients within 4.5 hours, in parallel with imaging and MT decision-making to avoid delays.

Administration of MT

Table 103 presents a summary of recommendations from CPGs relevant to the administration of MT. The majority of these guidelines were updated in 2014 and 2015 following the publication of favourable results in pivotal clinical trials of the proposed service. The advice is consistent in its recommendation that in patients that are eligible for IV thrombolysis, MT should be administered in addition to IV tPA. Furthermore, guidelines also recommend IV-tPA should be initiated prior to mechanical thrombectomy, without waiting for a response before starting mechanical thrombectomy: "*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"* (Powers et al, 2015). All three of the included guidelines also recommend the use of MT as a first-line therapy in patients who are contraindicated to IV-tPA (e.g. treated with warfarin) (Powers et al, 2015; ESO, 2014; EUnetHTA, 2015).

The AHA/ASA guidelines further recommend criteria that could be applied to select patients most likely to benefit from this therapy, including: pre-stroke mRS score (0–1), timing of IV tPA treatment from stroke onset (within 4.5 h), causative occlusion of the internal carotid artery (ICA) or proximal middle cerebral artery (MCA) (M1), age (≥18 years), NIHSS score (≥6), ASPECTS (≥6), and ability to initiate treatment within 6 hrs of symptom onset.

This guidance reflects the fact that a patient's suitability for MT is based on 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 the amount of salvageable tissue. Whilst these factors should be considered by clinicians in the selection of patients, there should be sufficient flexibility to allow treatment decisions to be 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 on-going and timely revision of clinical practice guidelines and acute stroke response treatment protocols.

Two guidelines specifically recommend that MT should be delivered with a stent retriever, rather than an aspiration device (Powers et al, 2015; EUnetHTA, 2015). The current

submission notes the weight of evidence for retriever devices is greater than for aspiration devices, but nonetheless requests an MBS listing for all MT devices to accommodate future technical developments in this therapeutic area.

Table 8: Summary of guideline recommendations relevant to proposed populations most suitable for mechanical thrombectomy

Relevant recommendations from guidelines	
US guidelines (Powers, 2015)	Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatments are being considered (Class I; Level of Evidence A). Patients should receive 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. 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. 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). 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, haemorrhagic coagulopathy, or receiving anticoagulant medications).
European guidance (ESO, 2014)	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) Mechanical thrombectomy should be performed as soon as possible after its indication (Grade A, Level 1a, KSU Grade A). 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).
European assessment (EUnetHTA, 2015)	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.

Abbreviations: 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

Overall, the clinical guidance reflects a strong body of evidence to support the use of MT in patients with AIS caused by LVO in patients that are eligible and ineligible for IV tPA. It should be noted that since the publication of these guidelines in 2015, meta-analyses based on IPD have provided additional data to support the use of MT in patients as a standalone treatment in patients that are ineligible for IV tPA. Whilst outcomes may also be influenced by

factors such as time from stroke onset, pattern of stroke damage, and disease severity, their interaction with treatment efficacy is sufficiently complex to justify a relatively non-prescriptive approach to patient selection. This approach is reflected in the Victorian protocol for endovascular clot retrieval. These eligibility guidelines, presented in Table 9, could be used as a model to better define patients who could benefit from the proposed intervention.

Table 9 Recommended selection of patients for MT in the Victorian statewide service protocol

Guidelines for endovascular clot retrieval (ECR) eligibility
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 premorbid function (modified Rankin score 0–2)
Ability to start procedure within six hours of stroke onset – discretion for basilar artery occlusion and selected anterior circulation patients beyond six hours (CT perfusion is strongly recommended for these cases) as per current national/international guidelines*
Intravenous thrombolysis commenced if eligible
Accessible to clot retrieval – assessment by neurointerventionist (requires remote picture archiving and communication system (PACS) access at all referral sites)

*Updated American, Canadian and European guidelines have been released; updated Australian guidelines are in development

Finally, it should be noted that the Australian NSF guidelines state that "intra-arterial thrombolysis within six hours can be used in carefully selected patients" (NSF, 2010). This procedure involves the direct administration of thrombolytic drugs to the blocked artery using endovascular surgical techniques; as such, this treatment is also referred to as an endovascular therapy. The clinical management pathway presented in this submission assumes that intra-arterial thrombolysis is not a potential comparator due to a lack of evidence and poor uptake. If endovascular access to the cerebral occlusion is possible, clinical practice guidelines recommend the use of MT over the use of intra-arterial thrombolysis. Comments received during the Public Consultation phase of this Application had general consensus amongst respondents: intra-arterial thrombolysis (IAT) has a minor role in Australian clinical practice and would therefore not represent an alternative comparator to MT.

Post procedure care

The Victorian statewide protocol states that following MT, the patient would generally remain at the centre for 24 hours for post procedure monitoring and repeat brain imaging. Recommended post procedure observations are similar to post-thrombolysis observations,

with the addition of arterial access site and limb vascular observations:

- quarter-hourly for two hours
- half-hourly for four hours
- one-hourly for four hours
- two-hourly for 12 hours
- four-hourly until reviewed

Medical management

As discussed above, there are strict rules used by doctors in determining if a patient is eligible for tPA. In addition to restrictions around the timing of administration (i.e. less than 4.5 hours after stroke onset), tPA is also contraindicated in patients that meet any of the following criteria:

- Severe, uncontrolled hypertension
- Previous surgery; widespread ischaemia
- Patient receiving oral anticoagulants with an international normalised ratio >1.3
- Intra-cranial bleeding
- Previous stroke within the past three months.

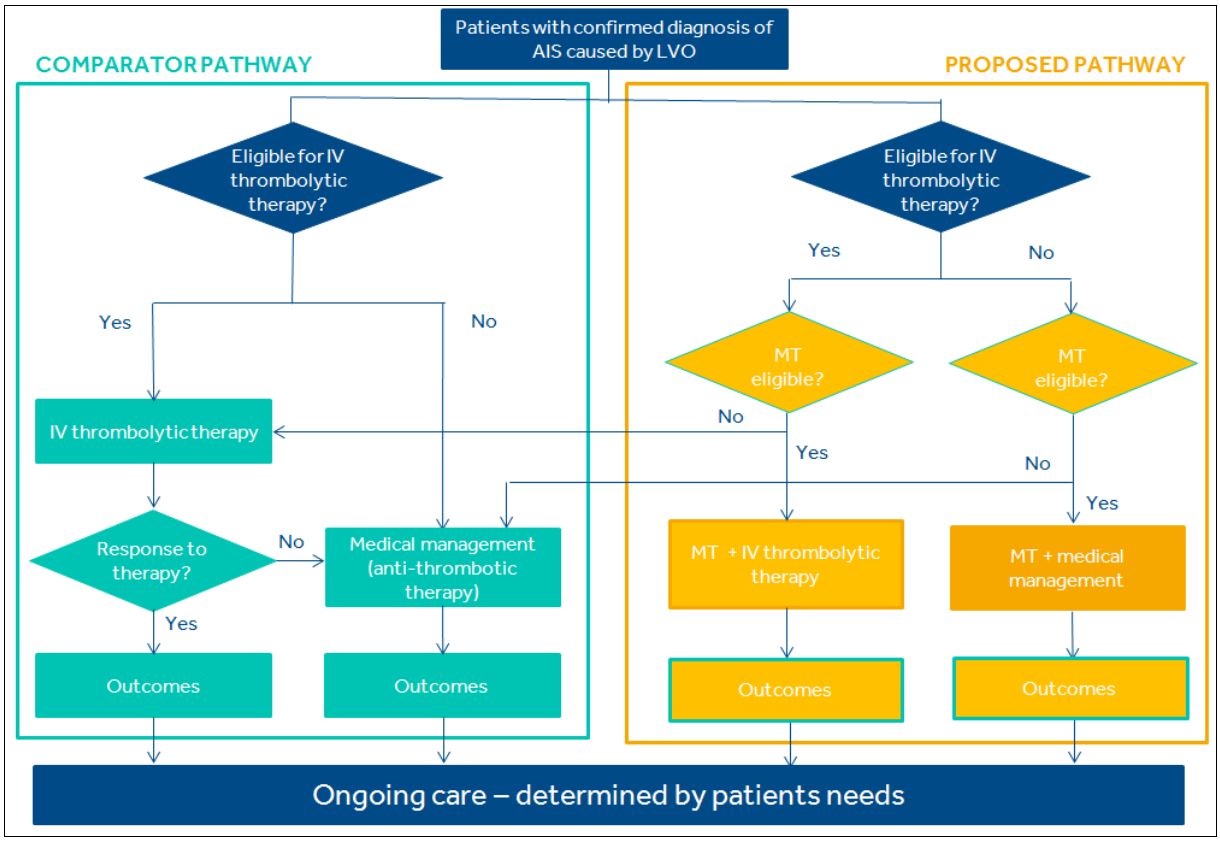
In these patients, the NSF guidelines recommend medical management in the form of anti-thrombotic therapy. This includes the administration of aspirin orally or via a nasogastric tube or suppository as soon as possible after the onset of stroke symptoms. The routine use of early anticoagulation (standard unfractionated heparin, low molecular weight heapains, heparinoids, oral anticoagulants or thrombin inhibitors) in unselected patients following ischaemic stroke is not recommended (NSF, 2010).

A.5.2 Proposed clinical algorithm

As shown in Figure 3, the proposed clinical algorithm presented in this submission is consistent with recommendations from CPGs and Australian stroke protocols. MT is indicated as an additional therapy in patients who are eligible for treatment with IV-tPA, and as an alternative therapy in patients for whom IV-tPA is contraindicated. The comparators for these respective groups are:

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

Figure 3 Current and proposed clinical management algorithm



Abbreviations: LVO, large vessel occlusion; MT, mechanical thrombectomy

For the proposed pathway in Figure 3, for further clarification, the following pieces of advice from PASC were 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 endovascular clot retrieval, which recognise that some patients outside the 6 hour time window could benefit from MT (salvageable brain tissue identified on imaging).

A.6 Differences between the proposed intervention and the main comparator(s)

The main differences between MT and IV-tPA are presented in Table 10. Since alteplase is available under a variety of marketed names, and there are various types of MT devices available in Australia, this comparison is based on the Product Information for Actilyse® (Boehringer-Ingelheim) and the Instructions for Use brochure for the SOLITAIRE 2 Revascularisation device (Medtronic; Appendix A).

Table 10 Differences between alteplase and MT using Solitaire stent retriever

Characteristic	Alteplase	Solitaire 2
Indications	Myocardial infarction Pulmonary embolism Acute ischaemic stroke	Patients with AIS due to LVO. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment. The SOLITAIRE 2 Revascularisation Device should only be used by physicians trainined in interventional neuroradiology and treatment of ischaemic stroke
Contraindications	Significant bleeding disorder at present or within the past 6 months, known haemorrhagic diathesis History or evidence of or suspected intra-cranial haemorrhage, including subarachnoid haemorrhage History of central nervous system damage (e.g. neoplasm, aneurysm, intra-cranial or spinal surgery) Severe uncontrolled hypertension Recent (within 10 days) prolonged or traumatic cardiopulmonary resuscitation (> 2 minutes), obstetrical delivery, organ biopsy, puncture of noncompressible blood vessel (e.g. subclavian or jugular vein puncture) Major surgery (e.g. coronary artery bypass graft) or significant trauma (including any trauma associated with acute myocardial infarction) within the past 3 months, recent trauma to the head or cranium Documented ulcerative gastrointestinal disease during the last 3 months Arterial aneurysms, arterial/venous malformations Neoplasm with increased bleeding risk Bacterial endocarditis, pericarditis Acute pancreatitis Haemostatic defects including those secondary to severe hepatic or renal disease; special attention should be paid to coagulation parameters in patients with significant liver dysfunction Severe hepatic disease/dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis	Patients with known hypersensitivity to nickel-titanium. Patients with stenosis and/or pre-existing stent proximal to the thrombus site that may preclude safe recovery of the SOLITAIRE™ 2 Revascularisation Device. Patients with angiographic evidence of carotid dissection

Characteristic	Alteplase	Solitaire 2
	Patients receiving other intravenous thrombolytic agents Patients currently receiving effective oral anticoagulant treatment, e.g. warfarin sodium (INR> 1.3) <u>In patients with acute ischaemic stroke:</u> Symptoms of ischaemic attack began more than 4.5 hours prior to infusion start or when time of symptom onset is unknown Minor neurological deficit or symptoms rapidly improving before start of infusion Severe stroke as assessed clinically (e.g. NIHSS > 25) and/or by appropriate imaging techniques Seizure at onset of stroke Evidence of intra-cranial haemorrhage (ICH) on the CT scan Symptoms suggestive of subarachnoid haemorrhage, even if CT scan is normal Administration of heparin within 48 hours preceding the onset of stroke and with an elevated activated partial thromboplastin time (aPTT) at presentation History of prior stroke and concomitant diabetes History of previous stroke or serious head trauma within the last 3 months Platelet count of below 100,000/mm3 Systolic blood pressure (BP) > 185 mm Hg or diastolic BP > 110 mm Hg, or aggressive management (IV medication) necessary to reduce BP to these limits Blood glucose < 50 mg/dL (< 2.8 mmol/L) or > 400 mg/dL (> 22.2 mmol/L) Patients < 18 years.	
Precautions	Bleeding Additional Warnings in Acute Myocardial Infarction / Pulmonary Embolism Arrhthmias Cholesterol embolisation Use of anticoagulants	Possible complications include, but are not limited, to the following: Hematoma and haemorrhage at puncture site Vascular occlusion Perforation or dissection of the vessel Pseudo aneurysm formation Vascular spasm Post procedure bleeding Change in mental status Distal embolisation including to a previously uninvolved territory Neurologic deterioration including stroke and death Adverse reaction to antiplatelet/ anticoagulation agents or contrast media Ischaemia Device(s) deformation, collapse, fracture or

Characteristic	Alteplase	Solitaire 2
		malfunction Infection Thrombosis (acute and subacute) Air Embolism Arteriovenous Fistula Intra-cranial Haemorrhage

B. CLINICAL EVALUATION FOR THE MAIN INDICATION

Summary

- A literature search was conducted to identify all published and unpublished randomised controlled trials (RCTs) that could be used to directly compare the efficacy and safety of the use mechanical thrombectomy (MT) plus usual care versus usual care alone as a treatment for patients with AIS due to a LVO.
- The search identified five eligible randomised trials of MT plus usual care and usual care alone ESCAPE; EXTEND-IA; MR CLEAN; REVASCAT; SWIFT PRIME which met the PICO-defined inclusion criteria. One of the pivotal studies, EXTEND-IA, was conducted in Australia and New Zealand, led by investigators from the Royal Melbourne Hospital.
- The primary outcome presented in this submission was the modified Rankin scale (mRS) at 90 days, which is a measure of functional ability. This primary outcome was assessed as a "shift analysis" of disability scores (i.e. the odds of improving by one mRS point). Secondary outcomes included functional independence (mRS 0-2 at 90 days) and mortality.
- As shown in the table below, for the primary outcome, a meta-analysis based on IPD shows a pooled cOR of 2.26 (95% CI: 1.67, 3.06; p<0.0001). The number needed to treat with MT to reduce disability by at least one level on the mRS for one patient was 2·6. The absence of heterogeneity strengthened conclusions about the consistency of effects across major subgroups of age and severity.
- For the secondary outcomes, 46.1% of patients in the intervention treatment arm compared to 26.4% of patients in the control arm achieved functional independence at 90 days. For mortality, 15.3% of patients in the intervention treatment arm compared to 18.8% of patients in the control arm had died at 90 days.

Outcome	Intervention	Control	OR [95% CI]
	n /N (%)	n /N (%)	
mRS score reduction (shift analysis)	-	-	2.26 (1.67, 3.06) p<0·0001[a]
mRS score 0-2 at 90 days	292/633 (46.1%)	170/645 (26.4%)	2.39 [1.88, 3.04], p<0.00001[b]
Mortality at 90 days	97/634 (15.3)	122/649 (18.8)	0.78 [0.54, 1.12], p=0.18[b]

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio

a) Common odds ratio indicating the odds of improvement of one point on the mRS;

b) OR [95% CI] calculated using Review Manager 5.3 for this submission.

- The adverse events within and across trials presented were low and the long-term safety profile of MT is expected to be similar.
- The evidence presented in Section B clearly demonstrates that treatment with MT in addition to usual care is superior to usual care alone in terms of effectiveness and non-inferior in terms of safety. A modelled cost-utility analysis is presented to support the cost-effectiveness of MT in addition to usual care.

B.1 Description of search strategies

The objective of the literature search was to identify all published and unpublished randomised controlled trials (RCTs) that could be used to directly compare the efficacy and safety of the use MT plus usual care versus usual care alone as a treatment for patients with AIS due to a LVO. The intervention and its comparator are defined in Section A.3 and A.4. of this submission.

To ensure that all relevant studies were identified, the following approaches were applied:

- A search of the MEDLINE and EMBASE databases
- A search of the Cochrane Library
- A search of the National Institute of Health clinical trials registry
- Manual search of reference lists of other relevant articles

The databases and sources used during the search are summarised in Table 11.

Table 11 Summary of search strategies for RCTs

Database
Search of the published literature
MEDLINE + EMBASE[1]
Cochrane Library[2]; comprising of the following databases
Cochrane Database of Systematic Reviews (CSDR)
Database of Abstracts of Reviews of Effects (DARE)
Cochrane Central Register of Controlled Trials (CENTRAL)
Cochrane Methodology Register (CMR)
Health Technology Assessment Database (HTA)
NHS Economic Evaluation Database (NHSEED)
Search of clinical trial registers
National Institutes of Health – ClinicalTrials.gov
Manual search of reference lists of other relevant articles

Methods: For complete search strategies, see Attachment 1. All searches were conducted on 3 March 2016 and 18 April 2016.

1. The EMBASE.com platform enables simultaneous searching of EMBASE and MEDLINE.
2. http://www.cochranelibrary.com
3. ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the US and around the world (https://clinicaltrials.gov/)

Citations were evaluated using predefined inclusion/exclusion criteria.

Inclusion criteria

Randomised controlled trials (RCTs) conducted with the following PICO, were included:

Population: Adults (> 18yrs) with a confirmed diagnosis of AIS due to LVO
Intervention: MT devices +/- standard/usual care
Comparator: Standard/usual care
Outcomes: Measured at least one or more effectiveness outcome:

- Revascularisation (e.g. TICI score)
- Function (e.g. Barthel Index)
- Disability (e.g. mRS)
- Health-Related QoL
- Neurological deficit (e.g. NIHSS)
- Mortality (all-cause; ischaemic stroke)

Systematic reviews and meta-analyses of RCTs meeting the inclusion criteria above were included for review.

Exclusion criteria

Citations with the following characteristics were excluded from review:

- Non-randomised clinical trials, including observational studies, case series, single-arm studies, case studies
- Studies conducted in patients without a confirmed diagnosis of AIS due to LVO
- Intra-arterial treatment without the use of MT (i.e. intra-arterial thrombolysis)
- Studies that failed to measure effectiveness of MT treatment

Full citation details and abstracts were downloaded and scrutinised for all records identified in the search. If a publication could not be included or excluded on the basis of the information in the title or abstract, the full paper or record was retrieved and reviewed. A detailed description of the search strategies and the results of the search are provided in Attachment 1. A full list of the identified citations and inclusion/exclusion status is provided in Attachment 1. All searches were completed on 3 March 2016 and 18 April 2016.

B.2 Listing of all direct randomised trials

B.2.1 Identification of included studies

Published literature

Table 12 summarises the results of the published literature search for RCTs of MT plus usual care and usual care alone as a treatment for patients with AIS due to an LVO. The search identified a total of 544 unique citations, of which 13 citations, describing eight potentially relevant trials (ESCAPE [Goyal 2015]; EXTEND-IA [Campbell 2015]; MR CLEAN [Berkhemer 2015]; REVASCAT [Jovin 2015, Jovin 2013, Davalos 2014a, Davalos 2014b, Davalos 2013 and Urra 2015]; SWIFT PRIME [Saver 2015]; MR RESCUE [Kidwell 2013]; IMS-III [Broderick 2013]; SYNTHESIS [Ciccone 2013]) met the predefined inclusion criteria.

Three trials, presented in four citations (PISTE [Muir 2015]; THRILL [Bendszus 2015] and THERAPY [Khatri 2014 and von Kummer 2013]), were excluded due to no or incomplete results after further review. The PISTE trials was terminated early, following positive results from other RCTs of MT (there were no safety concerns).

Table 12 Summary of identification of RCTs from the published literature search

	MEDLINE/EMBASE	Cochrane Library
Citations retrieved by current search	517	100
Number of unique citations	544	
Citations excluded after title/abstract review:		
— Wrong study type	476	
— Wrong population	23	
— Wrong intervention and/or comparator	19	
TOTAL EXCLUDED	518	
Citations excluded after full text review:		
— Wrong study type	0	
— Wrong population	0	
— Wrong intervention and/or comparator	0	
— No or incomplete data/results	4	
TOTAL EXCLUDED	0	
INCLUDED		
Meta-analyses and systematic reviews	9	
Number of citations of potentially eligible trials	13	
Number of potentially eligible trials	8	

Published systematic reviews/meta-analyses

The search for published literature identified 9 citations representing relevant systematic reviews and/or meta-analyses. Additionally, a further 3 citations were identified via manual searching (Goyal 2016, Campbell 2016 and Sardar 2015). These are listed in Table 13.

Table 13 Relevant systematic reviews and/or meta-analyses identified

Authors	Title	Citation
Badhiwala et al.	Endovascular thrombectomy for acute ischaemic stroke: a meta-analysis.	*JAMA* 314 (17): 1832-1843, 2015.
Balami et al.	A systematic review and meta-analysis of randomized controlled trials of endovascular thrombectomy compared with best medical treatment for acute ischaemic stroke.	*Int J Stroke* 10 (8): 1168-1178, 2015
Birns et al.	A meta-analysis of randomised controlled trials of endovascular treatment for acute ischaemic stroke.	*Stroke* 45, 2014.
Chen et al.	Endovascular vs medical management of acute ischaemic stroke.	*Neurology* 85 (22): 1980-1990, 2015.
Grech et al.	Stent-based thrombectomy versus intravenous tissue plasminogen activator in acute ischaemic stroke: A systematic review and meta-analysis.	*Intervent Neuroradiol* 21(6): 684-690, 2015.
Koh et al.	Safety and efficacy of mechanical thrombectomy with Solitaire stent retrieval for acute ischaemic stroke: a systematic review (Provisional abstract).	*Neurointervention* 7: 1-9, 2012.
Lin et al.	Efficacy and Safety of Mechanical Thrombectomy in Treating Acute Ischaemic Stroke: A Meta-Analysis.	*J Invest Surg*, 2015.
Marmagkiolis et al.	Safety and efficacy of stent retrievers for the management of acute ischaemic stroke comprehensive review and meta-analysis.	*JACC Cardiovasc Interventions* 8 (13): 1758-1765, 2015
Sardar et al.	Effectiveness of endovascular therapy for acute ischaemic stroke-evidence from a meta-analysis of randomized trials.	J Am CollCardiol. 66, B309-B310, 2015
Goyal et al.	Goyal, M., Menon, B. K., van Zwam, W. H et al. (2016). Endovascular thrombectomy after large vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.	*Lancet.* 2016 Apr 23;387
Campbell et al.	B. Campbell, MD. Hill, M Rubiera et al, Safety and Efficacy of Solitaire Stent Thrombectomy Individual Patient Data Meta-Analysis of Randomized Trials.	*Stroke. 2016;*47:798-806.
Sardar et al.	Sardar, P., Chatterjee, S., Giri, J.et al. Endovascular therapy for acute ischaemic stroke: a systematic review and meta-analysis of randomized trials.	*European heart journal,* 36(35), 2373-2380, 2015

Clinical trials registry search

The search of the National Institute of Health (NIH) Clinical Trials Registry (http://clinicaltrials.gov) identified a total of 94 records (see Attachment 1). Of these, 16 records met inclusion criteria (Table 14).

Seven of the trials (NCT01492725, NCT01778335, NCT01657461, NCT01692379, NCT00389467, NCT00359424, NCY01745692) were also identified in the search of the NIH Clinical Trials Registry (EXTEND-IA as Campbell 2015; ESCAPE as Goyal 2015; SWIFT PRIME 2015 as Saver 2015; REVASCAT as Jovin 2015, MR RESUCE as Kidwell 2013,

IMS-III as Broderick 2013 and PISTE as Muir 2015, respectively). The remaining 9 trials did not have data available at the time of the submission.

Table 14 Randomised trials identified in the NIH Clinical Trial Registries with potential to meet inclusion criteria

NCTID	Title	Completion date[1]	Data availability
NCT01492725	Randomized Controlled Trial of Intra-arterial Reperfusion Therapy After Standard Dose Intravenous tPA Within 4.5 Hours of Stroke Onset Utilizing Dual Target Imaging Selection. (Extend-IA)	December 2014	Previously identified as Campbell 2015 (EXTEND-IA)
NCT01778335	Endovascular Treatment for Small Core and Proximal Occlusion Ischaemic Stroke (ESCAPE)	January 2015	Previously identified as Goyal 2015 (ESCAPE)
NCT01657461	Solitaire™ FR With the Intention For Thrombectomy as Primary Endovascular Treatment for Acute Ischaemic Stroke (SWIFT PRIME) Clinical Trial	January 2015	Previously identified as Saver 2015 (SWIFT PRIME)
NCT01692379	RandomizEd Trial of reVascularizAtion With Solitaire FR® Device Versus Best mediCal Therapy in the Treatment of Acute Stroke Due to anTerior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset	December 2015	Previously identified as Jovin 2015 (REVASCAT)
NCT00389467	Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE)	April 2012	Previously identified as Kidwell 2013 (MR RESCUE)
NCT00359424	Interventional Management of Stroke Trial (IMS-III): A Phase III Clinical Trial Examining Whether a Combined Intravenous (IV) and Intra-Arterial (IA) Approach to Recanalization is Superior to Standard IV r-TPA (Activase®) Alone	April 2013	Previously identified as Broderick 2013 (IMS-III)
NCT01745692	A Randomised Controlled Clinical Trial of Adjunctive Mechanical Thrombectomy Compared With Intravenous Thrombolysis in Patients With Acute Ischaemic Stroke Due to an Occluded Major Intra-cranial Vessel. (PISTE)	July 2015	Previously identified as Muir 2015 (PISTE) Study terminated
NCT01869478	Endovascular Arterial Reperfusion vs. Intravenous ThromboLYsis for Acute Ischaemic Stroke (EARLY): A Randomized Pilot Study of Ultra-early (<2 Hours) and Early (2-4.5 Hours) Reperfusion Therapy	September 2015	No data available
NCT01062698	The Contribution of Intra-arterial Thrombectomy in Acute Ischaemic Stroke in Patients Treated With Intravenous Thrombolysis (THRACE)	March 2016	Study terminated
NCT01852201	POSITIVE: PerfusiOn Imaging Selection of Ischaemic STroke Patents for EndoVascular ThErapy	May 2016	No data available
NCT01429350	The THERAPY Trial: The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke	December 2016	No data available

NCTID	Title	Completion date[1]	Data availability
NCT02142283	Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes (DAWN)	July 2017	No data available
NCT02135926	Comparison of Thrombectomy and Standard Care for Ischaemic Stroke in Patients Ineligibility for Tissue Plasminogen Activator Treatment (THRILL)	March 2018	No data av ailable
NCT02216643	EndoVascular Treatment With Solitaire FR® vs. Best Medical Therapy in Acute Ischaemic Stroke (RESILIENT)	March 2018	No data available
NCT02157532	Intra-arterial Thrombectomy as an Acute Treatment Intervention for Stoke: the Endovascular Acute Stoke Intervention (EASI) Trial	January 2020	No data available
NCT02586415	Endovascular Therapy Following Imaging Evaluation for Ischaemic Stroke 3 (DEFUSE 3)	June 2020	No data available

1. Completion dates from Clinicaltrials.gov

Conclusion

The search of published and unpublished literature identified eight potentially eligible randomised trials of MT plus usual care and usual care alone ESCAPE [Goyal 2015]; EXTEND-IA [Campbell 2015]; MR CLEAN [Berkhemer 2015]; REVASCAT [Jovin 2015, Jovin 2013, Davalos 2014a, Davalos 2014b, Davalos 2013 and Urra 2015]; SWIFT PRIME [Saver 2015]; MR RESCUE [Kidwell 2013]; IMS-III [Broderick 2013]; SYNTHESIS [Ciccone 2013]) which met inclusion criteria. The search for published literature identified 9 citations representing relevant systematic reviews and/or meta-analyses. Additionally, a further 3 citations were identified via manual searching (Goyal 2016, Campbell 2016 and Sardar 2015).

B.2.2 Master list of trials

A master list of the eight potentially eligible RCTs meeting initial inclusion criteria, complete with any identified associated reports is presented in Table 15. The reports used as key sources of data in this submission are highlighted in bold text. In most cases, these are the primary publications for the trial plus their supplementary appendices and protocols (included in Appendix B).

Details of these trials are summarised in Table 16. Upon full review of the eight potentially relevant RCTs, three trials were excluded (MR RESCUE, IMS-III and SYNTHESIS), primarily because the intervention was not considered applicable to the current MSAC submission. The precise reasons for excluding these trials are discussed in Section B.2.3, whilst a summary of the characteristics of the excluded trials is presented in Table 16.

Table 15 Master list of RCTs potentially eligible studies identified in the literature

Trial ID	Citations	Pivotal source of data
Included		
ESCAPE	**M. Goyal, A.M. Demchuk, B.K. Menon, et al. Randomized assessment of rapid endovascular treatment of ischaemic stroke. *New Engl J Med*. 372 (11):1019-1030, 2015.**	**Full publication, Protocol, Supplementary Appendix**
EXTEND-IA	**B.C. Campbell, P.J. Mitchell, T.J. Kleinig, et al. Endovascular therapy for ischaemic stroke with perfusion imaging selection. *New Engl J Med*. 372:1009-1018, 2015.**	**Full publication, Protocol, Supplementary Appendix**
MR CLEAN	**O.A. Berkhemer, P.S.S. Fransen, D. Beumer, et al. A randomized trial of intra-arterial treatment for acute ischaemic stroke. *New Engl J Med.* 372 (1):11-20, 2015.**	**Full publication, Protocol, Supplementary Appendix**
REVASCAT	**T.G. Jovin, A. Chamorro, E. Cobo, et al. Thrombectomy within 8 hours after symptom onset in ischaemic stroke. *New Engl J Med.* 372 (24):2296-2306, 2015.**	**Full publication, Protocol, Supplementary Appendix**
	A. Davuls, A. Chamorro, C. Molina, et al. REVASCAT: Randomized trial of revascularization with SolitaireÂ® device versus best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion. *Int J Stroke.* 10:4, 2015.	Abstract only – No results
	T. G. Jovin, E. Cobo, A. Chamorro, et al. Randomized trial of revascularization with Solitaire FR device versus best medical therapy in the treatment of acute stroke due to an anterior circulation large vessel occlusion presenting within 8 hours of symptom onset. *International Stroke Conference 2013.* 2013.	Conference presentation
	A. Davalos, A. Chamorrow, E. Cobo. REVASCAT. RandomizEd trial of reVascularizAtion with Solitaire FR device versus best mediCal therapy i the treatment of Acute stroke due to anTerior circulation large vessel occlusion presenting within 8 hours of symptom onset. *European Stroke Conference 2014.* 2014.	Abstract only
	A. Davalos, A. Chamorro, E. Cobo. Randomized trial of revascularization with Solitaire FR device versus best medical practice therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within 8 hours of symptom onset (REVASCAT). *International Stroke Conference 2014.* 2014.	Abstract only
	X. Urra, A. Chamorro, E. Cobo. Randomized trial of revascularization with Solitaire device versus best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within 8 hours of symptom onset. *International Stroke Conference 2015.* 2015.	Abstract only
SWIFT PRIME	**J.L. Saver, M. Goyal, A. Bonafe, et al. Stent retriever thrombectomy after intravenous tPA vs. tPA alone in stroke. *New Engl J Med*. 372:2285-2295, 2015.**	**Full publication, Protocol, Supplementary Appendix**
Excluded		
SYNTHESIS	A. Ciccone, L. Valvassori, M. Nichelatti, A. Sgoifo, M. Ponzio, R. Sterzi, and E. Boccardi. Endovascular treatment for acute ischaemic stroke. *New Engl.J.Med.* 368:904-913, 2013.	Full publication
MR RESCUE	C.S. Kidwell, R. Jahan, J. Gornbein, et al. A trial of imaging selection and endovascular treatment for ischaemic stroke. *New Engl J Med*. 368:914-923, 2013.	Full publication

Trial ID	Citations	Pivotal source of data
IMS-III	J.P. Broderick, Y.Y. Palesch, A.M. Demchuk, et al. Endovascular therapy after intravenous tPA versus tPA alone for stroke. *New Engl J Med.* 368 (10):893-903, 2013.	Full publication

Key sources of data are in bold text; these are included in Appendix B, whilst other citations are included in the reference folder

B.2.3 Summary of included studies

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 on 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 clinical equipoise (i.e. loss of uncertainty on the relative treatment benefits of MT and comparators – in practice the emerging results from other trials raised ethical concerns about further assignment of patients to the control group), despite the trial's interim results not meeting the pre-specified stopping boundaries.

ESCAPE

The ESCAPE trial was a multicentre, prospective, randomised, open-label, controlled trial with blinded outcome evaluation (PROBE design). ESCAPE was designed to show that rapid endovascular revascularisation amongst radiologically selected patients with ischaemic stroke results in improved outcome compared to patients treated in clinical routine. The study was performed at 22 centres in Canada (11 centres), the United States (6), South Korea (3), Ireland (1), and the United Kingdom (1).

Eligible participants consisted of those with a disabling ischaemic stroke who had been functioning independently in the community (score on the Barthel Index ≥90) before the stroke. Enrolment could occur up to 12 hours after the onset of stroke symptoms. Non-contrast CT and CTA were performed to identify participants. Before and during screening, participants were treated with IV alteplase when clinically appropriate as part of standard care. Participants in the intervention treatment arm underwent rapid endovascular treatment (with any approved endovascular intervention), the majority of which were stent retrievers.

The primary outcome was score on the modified Rankin scale at 90 days after randomisation. Secondary and safety outcomes included early recanalisation and reperfusion, intra-cranial haemorrhage, angiographic complications, neurologic disability at 90 days, and death.

An unplanned interim analysis was conducted after the release of the MR CLEAN results, which showed efficacy of endovascular therapy. The ESCAPE trial was stopped early on the advice of the data and safety monitoring board because the pre-specified boundary for efficacy had been crossed.

EXTEND-IA

The EXTEND-IA trial was an investigator-initiated, multicentre, prospective, randomised, open-label, controlled trial with blinded outcome evaluation (PROBE design). EXTEND-IA study was designed to test the hypothesis that patients with anterior circulation ischaemic stroke will have improved reperfusion and early neurologic improvement when treated with early endovascular thrombectomy after IV administration of alteplase, as compared with the use of alteplase alone. The study was performed in 14 centres in Australia and New Zealand.

Patients were eligible if they could receive IV alteplase within 4.5 hours after the onset of anterior circulation ischaemic stroke. All patients received alteplase at a dose of 0.9 mg per kilogram as standard care. Patients were randomly assigned in a 1:1 ratio to receive either alteplase plus endovascular therapy with the use of the Solitaire stent retriever (endovascular therapy group) or no further therapy (alteplase-only group). Endovascular therapy had to be initiated (groin puncture) within 6 hours after stroke onset and completed within 8 hours after onset.

The co-primary outcomes were a) reperfusion (which was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and imaging at 24 hours), and b) early neurologic improvement (which was defined as a reduction of 8 points or more on the NIHSS or a score of 0 or 1 at 3 days). Secondary outcomes were the score on the modified Rankin scale at 90 days, death due to any cause, and symptomatic intra-cranial haemorrhage, including any subarachnoid haemorrhage associated with clinical symptoms and symptomatic intracerebral haemorrhage.

After the release of the results of the MR CLEAN study, recruitment into the trial was suspended on October 31, 2014, and the data and safety monitoring board reviewed data for the 70 enrolled patients. A pre-specified Haybittle–Peto stopping boundary was applied to the co-primary outcome in the ITT population with the use of Holm's step-down procedure, so that one co-primary outcome was tested at a z value of more than 3.29 and the other at a z value of more than 3. Because the pre-specified boundary for efficacy had been crossed, the data and safety monitoring board stopped the trial for efficacy after this analysis.

MR CLEAN

MR CLEAN was a multicentre clinical trial with randomised treatment allocation, open-label treatment and blinded endpoint evaluation (PROBE design).The study was conducted at 16 centres in the Netherlands. The primary objective of MR CLEAN was to estimate the effect of endovascular treatment on overall functional outcome after AIS.

The trial compared intra-arterial treatment (intra-arterial thrombolysis, mechanical treatment, or both) plus usual care (which could include IV administration of alteplase) with usual care alone (control group). This was considered to be a pragmatic RCT which aimed to consider 'real world' practice; that is, the method of intra-arterial therapy type of mechanical thrombectomy, and to the choice for general anaesthesia was left to the discretion of the local interventionist, Patients were 18 years of age or older (no upper age limit) with AIS caused by an intra-cranial occlusion in the anterior circulation artery.

The primary outcome was the score on the modified Rankin scale at 90 days. Secondary outcomes included the NIHSS score at 24 hours and at 5 to 7 days or discharge if earlier, activities of daily living measured with the Barthel Index, and the health-related quality of life measured with the EuroQoL Group 5-Dimension Self-Report Questionnaire at 90 days. Pre-specified dichotomisations of the modified Rankin score were also examined: 0 or 1 versus 2 to 6, 0 to 2 versus 3 to 6, and 0 to 3 versus 4 to 6.

REVASCAT

REVASCAT was a multicentre, prospective, randomised, and sequential, open-label phase 3 study with blinded evaluation. The study objective was to evaluate the hypothesis that mechanical embolectomy with the Solitaire FR device is superior to medical management alone. Participating sites were four large, designated, comprehensive stroke centres in Catalonia, Spain.

Eligible patients were between the ages of 18 and 80 years, presenting with AIS within 8 hours from symptom onset and whose strokes are attributable to an occlusion of the internal carotid or proximal MCA (M1) arteries. Subjects are either ineligible for IV alteplase or have received IV alteplase therapy without recanalisation.

The primary outcome was the severity of disability at 90 days, according to the distribution of scores on the modified Rankin scale. Secondary outcomes included centrally adjudicated infarct volumes on CT or MRI at 24 hours, the NIHSS score and Barthel Index at 90 days, and health status, as measured on the EQ-5D.

The first interim analysis was performed as planned after 25% patients (174 of the maximum

sample size) had completed 90 days of follow-up. Although the interim results did not reach the pre-specified stopping boundaries, study recruitment was terminated because of emerging results from MR CLEAN, EXTEND-IA and ESCAPE that showed the efficacy of thrombectomy, which raised ethical concerns about further assignment of patients to the control group.

SWIFT PRIME

SWIFT PRIME is an international, multicentre, prospective, randomised, open clinical trial, performed at 39 centres in the U.S. and Europe. The study was designed to test the hypothesis that combined treatment with IV tPA and Solitaire FR will result in lower mRS scores than with treatment with IV tPA alone.

The trial compared IV tPA followed by neurovascular thrombectomy within 6 hours of symptom onset with IV tPA alone in patients with AIS. All patients had confirmed occlusion of the intra-cranial internal carotid artery, the first segment of the middle cerebral artery, or both on vessel imaging and an absence of large ischaemic core lesions.

The primary outcome was the severity of global disability at 90 days. Secondary clinical efficacy outcomes were the rate of death at 90 days, the rate of functional independence (modified Rankin scale score, ≤2) at 90 days, and the change in the NIHSS score at 27 hours after randomisation.

In February 2015, the study was halted when the interim efficacy analysis showed that the pre-specified stopping-criteria boundary (12-percentage- point boundary) for efficacy had been crossed.

EXCLUDED STUDIES

The key exclusion reason for three excluded studies was the absence of use of appropriate imaging to select patients who could benefit from treatment. However, the Applicant is of the view that there are important explanations for differences between the results of early studies and the overwhelmingly positive outcomes observed in recent studies of MT. A brief description and detailed reason for exclusion of each study is discussed below.

SYNTHESIS Expansion (Ciccone et al, 2013) was an open-label RCT that enrolled 362 patients with ischaemic stroke eligible for IV-tPA within 4.5 hours of onset and for whom endovascular treatment was possible within 6 hours. Among the patients who received endovascular treatment, 66% received intra-arterial thrombolysis alone, while in 34% a device was also deployed. Stent retrievers were used in 14% of patients in the intervention

study arm. Thus the study included only a small number of patients that received an intervention considered in this Application. Furthermore, it should be noted that patients in the intervention arm of this study were allowed treatment with IV-tPA after having received MT. This method of administering MT is inconsistent with use in clinical practice guidelines and the prosed intervention in this Application. On this basis, the results of SYNTHESIS are not considered relevant to this submission and the study is not discussed further.

The Interventional Management of Stroke Trial III (IMS-III) (Broderick 2013). was an RCT that enrolled patients with a major ischaemic stroke defined by NIHSS score ≥10 who received IV-tPA within 3 hours and were likely to or known to have occlusion of a major cerebral artery (Broderick et al, 2013). Endovascular therapy was administered in 77% of patients randomised to this treatment group. Intra-arterial thrombolysis alone was used in 41% and a device with or without intra-arterial tPA in 59%; in only 1.5% were stent retrievers used. Once again, the intervention delivered in this study does not reflect the service requested in this submission, which is MT alone or concurrent with IV-tPA treatment.

Mechanical Retrieval and Recanalisation of Stroke Clots Using Embolectomy (MR RESCUE) (Kidwell 2013) was a 2-arm, superiority trial that enrolled 118 patients with large artery occlusion and anterior circulation ischaemic stroke within 8 hours who were ineligible for IV-tPA or had persistent vessel occlusion after IV-tPA (Kidwell et al, 2013). This study enrolled patients up to 8 hours from symptom onset, with a mean time from stroke onset to groin puncture of 6.35 ± 1.2 hours; this is substantially longer than the permissible time in other studies and the recommended use of the IV-tPA (which should be used within 4.5 hours).

In addition to the trial-specific exclusion criteria described above, it should be noted that these early studies of endovascular therapy included older thrombectomy devices with poorer efficacy, often had insufficiently robust imaging selection criteria and had long delays from hospital presentation to reperfusion – this is inconsistent with the proposed service in the current Application In addition most of the recent trials excluded patients with large regions of irreversibly injured brain tissue On this basis, a recently published systematic review of endovascular thrombectomy only included five recent studies that included “modern neurothrombectomy devices” (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND-IA). This approach has been used by other decision-makers (EUnetHTA, 2015) and in the Victorian statewide service protocol for endovascular clot retrieval. The EUnetHTA guideline states “concern has been raised about combining results from the earliest three trials (MR RESCUE, IMS-III, SYNTHESIS Expansion) with the five later trials in meta-analysis, as it is widely acknowledged that there were major methodological differences between these trials, not least of which is that different types of devices were employed”. As

a consequence of methodological differences described above - none of the three excluded studies of showed a clinical or safety benefit of endovascular therapy in comparison to IV-tPA.

On the basis of methodological differences, it was considered appropriate to exclude the three early studies of endovascular therapy (SYNTHESIS, IMS-III and MR RESCUE) from the current MSAC submission.

Table 16 Summary of included studies and characteristics

Trial ID	Design characteristics	Early termination	Primary objective	Compared interventions	Main population characteristics	Main outcomes	
						Primary	Key secondary
Included studies							
ESCAPE	MC, Phase III, PROBE	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	To show that rapid endovascular revascularisation amongst radiologically selected patients with ischaemic stroke results in improved outcome compared to patients treated in clinical routine	N=165 MT (undertaken with any currently available and approved device) N=150 Routine stroke care governed by current guidelines	Adults with a disabling ischaemic stroke who had been functioning independently in the community (score on the Barthel Index ≥90) before the stroke. Enrolment could occur up to 12 hours after the onset of stroke symptoms. Participants were treated with IV alteplase when clinically appropriate as part of standard care	A shift or one or more categories (proportional odds analysis) on the mRS at 90 days	NIHSS score of 0-2 at 30 days and 90 days mRS score of 0-2 at 30 days and 90 days NIHSS score at 90 days mRS score at 90 days BI score at 90 days BI shift at 90 days Health Utilities index at 90 days EQ-5D (EuroQoL) at 90 days Recanalisation of the target arterial occlusive lesion (TICI 3 flow) at the end of the procedure TICI 3 score at the end of the procedure
EXTEND-IA	MC, Phase III, PROBE	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	To test the hypothesis that patients with anterior circulation ischaemic stroke will have improved reperfusion and early neurologic improvement when treated with early endovascular thrombectomy after IV administration of alteplase, as compared with the use of alteplase alone	N=35 Alteplase plus MT with the Solitaire FR stent retriever N=No further therapy (alteplase-only)	Patients were eligible if they could receive IV alteplase within 4.5 hours after the onset of anterior circulation ischaemic stroke	The co-primary outcomes were reperfusion and early neurologic improvement	Score on the modified Rankin scale at 90 days Death due to any cause, Symptomatic intra-cranial haemorrhage

Trial ID	Design characteristics	Early termination	Primary objective	Compared interventions	Main population characteristics	Main outcomes	
						Primary	Key secondary
MR CLEAN	MC, Phase III, PROBE	No	To estimate the effect of endovascular treatment on overall functional outcome after AIS	N=233 Intra-arterial thrombolysis, mechanical treatment, [undertaken with any currently available and approved device] or both, plus usual care [which could include IV alteplase] N=267 Usual care alone	Patients were 18 years of age or older with AIS caused by an intra-cranial occlusion in the anterior circulation artery. Initiation of intra-arterial treatment had to be possible within 6 hours after stroke onset	Modified Rankin scale score at 90 days	NIHSS score at 24 hours Activities of daily living measured with the Barthel Index, HRQoL measured by EQ-5D at 90 days Pre-specified dichotomisations of the modified Rankin score examined: 0 or 1 versus 2 to 6, 0 to 2 versus 3 to 6, and 0 to 3 versus 4 to 6.
REVASCAT	MC, Phase III, PROBE	Study recruitment was terminated because of emerging results MR CLEAN, EXTEND-IA and ESCAPE that showed the efficacy of thrombectomy, which raised ethical concerns about further assignment of patients to the	To evaluate the hypothesis that mechanical embolectomy with the Solitaire FR device is superior to medical management alone	N=103 Solitaire stent retriever (thrombectomy group) N=103 Medical therapy alone (control group).	Patients between 18 and 80 years of age, presenting with AIS within 8 hours from symptom onset Subjects are either ineligible for IV alteplase or have received IV alteplase therapy without recanalisation	Modified Rankin scale score at 90 days	Early dramatic response to treatment (defined as a decrease in the NIHSS score of ≥8 from baseline or an NIHSS score of 0 to 2 at 24 hours), NIHSS score and Barthel Index at 90 days, HRQoL measured by EQ-5D at 90 days Successful vessel revascularisation, which was defined as a grade of 2b or 3 (mTICI) scale

Trial ID	Design characteristics	Early termination	Primary objective	Compared interventions	Main population characteristics	Main outcomes	
						Primary	Key secondary
		control group					
SWIFT PRIME	MC, P, R, OL	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	To test the hypothesis that combined treatment with IV tPA and Solitaire FR will result in lower mRS scores than with treatment with IV tPA alone	N=98 IV tPA plus mechanical thrombectomy performed with the use of the Solitaire FR or Solitaire 2 device stent retriever (intervention group) N=98 IV tPA alone (control group).	All the patients had confirmed occlusion of the intra-cranial internal carotid artery, the first segment of the middle cerebral artery, or both on vessel imaging and an absence of large ischaemic core lesions. Patients were receiving or had received intravenous tPA; and were able to undergo initiation of endovascular treatment within 6 hours after the time that they were last known to be well before the onset of acute stroke symptoms	Measure of disability at 90 days, as assessed by means of the mRS	Rate of death at 90 days Rate of functional independence (mRS ≤2) at 90 days Change in the NIHSS score at 27 hours after randomisation.
Excluded							
SYNTHESIS	PROBE design	No	To investigate whether endovascular treatment, including the options of a mechanical device and intra-arterial tPA, is more effective than the currently	N=181 Endovascular therapy N=181 IV tPA alone	Patients with acute stroke and an age of 18 to 80 years Clearly defined time of stroke onset that	Measure of disability at 90 days, as assessed by means of the	Proportion of patients with a mild neurologic deficit or none (NIHSS score, ≤6)

Trial ID	Design characteristics	Early termination	Primary objective	Compared interventions	Main population characteristics	Main outcomes	
						Primary	Key secondary
			available treatment with intravenous tPA	(control group).	allowed for immediate initiation of intravenous tPA therapy (defined as within 4.5 hours after symptom onset) or for the administration of endovascular treatment as soon as possible (within 6 hours after symptom onset)	mRS	
IMS-III	PROBE design	The study was stopped early because of futility after 656 participants had undergone randomisation	To test the approach of intravenous tPA followed by protocol-approved endovascular treatment, as compared with standard intravenous tPA	N=434 Endovascular therapy N=222 IV tPA alone	Patients aged 18 to 82 years of age Intravenous tPA was started within 3 hours after symptom onset in both groups Moderate-to-severe neurologic deficit (defined as an NIHSS score ≥10	mRS score of 2 or less (indicating functional independence) at 90 days	Distribution of the mRS. NIHSS score of 8 to 19 indicating moderately severe stroke NIHSS score of 20 or more indicating severe stroke
MR RESCUE	PROBE design	No	The presence of substantial ischaemic penumbral tissue and a small volume of predicted core infarct, would identify patients who were most likely to benefit from mechanical embolectomy for the treatment of AIS caused by a LVO up to 8 hours after symptom onset	N=70 Endovascular therapy. The intra-arterial administration of tPA at a dose of as much as 14 mg was allowed as rescue therapy within 6	Patients between the ages of 18 and 85 years NIHSS scores of 6 to 29 Large vessel, anterior circulation ischaemic stroke	Score on the mRS	Scores of 0 to 2 on mRS Successful revascularisation was assessed with TICI scale Partial or complete revascularisation was defined as a TICI score of 2a to 3.

Trial ID	Design characteristics	Early termination	Primary objective	Compared interventions	Main population characteristics	Main outcomes	
						Primary	Key secondary
				hours after symptom onset. N=57 IV tPA alone			

Abbreviations: MC, multicentre; PROBE, prospective randomised open blinded endpoint

B.3 Assessment of the measures taken to minimise bias

B.3.1 Randomisation and blinding

The measures undertaken to minimise bias in the included studies are summarised in Table 17. Overall, the studies employed appropriate methods to minimise the risk of bias through concealment of randomisation and blinding. Outcome assessment at 90 days was blinded in all studies; however it was not possible to conceal treatment allocation from patients after randomisation. Given the non-subjective nature of AIS outcomes and response to therapy, it is unlikely that this would have any impact on treatment efficacy. Methods used to maintain the integrity of randomisation and blinding in each study are described under the headings below.

ESCAPE

Participants were randomly assigned in a 1:1 ratio to receive routine standard stroke care (control group, n=150) or standard care plus endovascular treatment with the use of available thrombectomy devices (intervention group, n=165). Randomisation was performed using a web-based algorithm with treatment assignment allocated by web-based real-time interaction with the site. A minimal sufficient balance method was used to ensure that the patients entered into the trial were matched between control and active treatment arms on key variables, such as age, sex, baseline NIHSS score, baseline NCCT ASPECTS score, location of the symptomatic target arterial occlusive lesion and IV-tPA use.

Treatment assignment was open-label. Blinding of the outcome assessment at 90 days was ensured at the site by having a person who was not involved in the acute treatment period conduct the assessment.

EXTEND-IA

All patients received alteplase at a dose of 0.9 mg per kilogram as standard care, after which patients were randomly assigned in a 1:1 ratio to receive either MT with the Solitaire FR stent retriever (endovascular therapy group, n=35) or no further therapy (alteplase-only group, n=35). Randomisation was achieved by means of a centralised website and stratified according to the site of arterial occlusion: the internal carotid artery or the first or second segment of the middle cerebral artery.

The intra-arterial treatment is open-label. However, all those involved in the subsequent clinical and imaging assessment of outcomes were blinded to treatment allocation. Neurological impairment and functional scores were measured by a healthcare professional trained in their administration and blinded to the treatment assignment.

MR CLEAN

A total of 233 participants were randomised to receive intra-arterial thrombolysis, mechanical treatment, (undertaken with any currently available and approved device) or both, plus usual care (which could include IV alteplase) and 267 participants were randomised to receive usual care alone. The randomisation procedure was computer and web-based permuted blocks. Additionally, randomisation was stratified according to medical centre, use of IV alteplase (yes or no), planned treatment method (mechanical or other), and stroke severity (NIHSS score of ≤14 or >14).

Both patient and treating physician were aware of the treatment assignment. Assessment of outcome on the MRS scale was assessed by those who were blinded to the treatment allocation. Information on treatment allocation was kept separate from the main study database.

REVASCAT

Participants were randomly assigned in equal numbers (1:1) to receive medical therapy (including intravenous alteplase when eligible) and endovascular treatment with the Solitaire stent retriever (thrombectomy group, n=103) or medical therapy alone (control group, n=103). A real-time computerised randomisation procedure was used and patients were stratified according to age (≤70 or >70 years), baseline NIHSS score (6 to 16 or ≥17), therapeutic window (≤4.5 or >4.5 hours), occlusion site (intra-cranial internal carotid artery or M1 segment [main trunk of the middle cerebral artery]), and participating centre.

The primary endpoint of functional independence at 90 days was assessed by a local evaluator blinded to the treatment and a central independent blinded Rankin scale-certified evaluator. All the secondary endpoints including infarct volume and haemorrhage were assessed by those blinded to treatment.

SWIFT PRIME

Once all inclusion/exclusion criteria were satisfied including imaging assessments, subjects were randomised in a 1:1 ratio to either the MT procedure using the Solitaire FR

Revascularisation Device (n=98) or remain on IV tPA therapy only (n=98). Eligible patients were receiving or had received intravenous tPA; and were able to undergo initiation of endovascular treatment within 6 hours after the time that they were last known to be well before the onset of acute stroke symptoms. Subject allocation to treatment was accomplished by using an interactive web response (IWRS) or interactive voice response system (IVRS). The number of treatments and controls were balanced within investigational sites and by baseline NIHSS severity (<= 17 versus >17), age, and occlusion location within site.

The primary endpoint of global disability level at 90 days (mRS), as well as the NIHSS and Barthel Index at 90 days were assessed by an independent evaluator blinded to the treatment. The primary analysis for all baseline characteristics and study outcomes will include all randomised subjects.

Table 17 Summary of the measures undertaken to minimise bias

Trial ID	Concealment of randomisation	Blinding			Basis of analysis	Source
		Participants	Investigators	Outcome Assessors		
ESCAPE	Web-based algorithm with treatment assignment allocated by web-based real-time interaction with the site	NO	NO	YES	ITT population	ESCAPE protocol, p, 29, p.99
EXTEND-IA	Randomisation via a centralised website	NO	NO	YES	ITT population	EXTEND-IA protocol, p. 3-5
MR CLEAN	Randomisation procedure was web-based, with the use of permuted blocks	NO	NO	YES	ITT population	MR CLEAN protocol, p. 22
REVASCAT	Real-time computerised randomisation procedure	NO	NO	YES	ITT population	REVASCAT protocol, p.36-37
SWIFT PRIME	Central telephone randomisation service e.g. IWRS/IVRS	NO	NO	YES	All randomised subjects	SWIFT PRIME protocol, Section 5.10, Section 6.4, Section 9.2.1

Abbreviations: IVRS, interactive voice response system; IWRS, interactive web response system

B.3.2 Handling of missing data

ESCAPE

Any missing data for the primary outcome analysis was imputed by assuming the missing mRS score at 3 months to be unfavourable, i.e. the worst possible score. If the patient was known to be alive, a score of 5 was given. If the patient was not known to be alive or dead, a score of 6 was imputed. At a minimum, 90-day outcome assessments were accepted within a +/-30-day window.

EXTEND-IA

Reperfusion in three patients was unable to be assessed due to clinical deterioration prior to the protocol amendment allowing repeat CT at 24h (all three were randomised to alteplase-only and all died shortly afterwards). These missing data were imputed with a pre-specified 0% reperfusion but sensitivity analysis was also performed using 100% reperfusion in place of missing values. Similarly, the three missing data points for recanalisation were imputed with “recanalisation absent” and sensitivity analysis was also performed to test the effect of classifying the missing data points as “recanalisation present”.

The approach taken to address missing data for the 90-day mRS outcome was not described (this was not the primary outcome); however, it should be noted that the population included in the analysis consisted of all randomised patients.

MR CLEAN

Patients who died within the study period were assigned the worst score on all outcome measures and taken into the analysis.

REVASCAT

If a subject died prior to 90 days, that subject was not considered missing and was assigned the highest mRS score (6) for the 90-day evaluation. The worst score (mRS of 6) was also assigned if the living status of the patient was unknown. For patients known to be alive at 3 months post randomisation in whom follow-up evaluations was not be possible, the discharge mRS was carried forward.

SWIFT PRIME

Since the primary endpoint was defined using mRS, subjects deceased during the study

follow-up were scored a mRS 6 and were counted as failures in the evaluation of functional independence. Other subjects not completing the 90-day follow-up visit were categorised for the primary endpoint using the mRS as of the last available follow-up visit.

B.3.3 Flow of participants

The flow of participants in the included trials is summarised in Table 18. The majority of trials had zero loss to follow-up (EXTEND-IA, MR CLEAN, REVASCAT). In the ESCAPE study four patients were lost to follow-up, while in SWIFT PRIME, 3-month mRS outcomes were unavailable for 5 patients. In each of the studies, there were some patients that did not receive MT. However, since this is also likely to occur in clinical practice, and the results for these patients are still included in the ITT analysis, this is not expected to bias the results in any way.

ESCAPE

A total of 316 participants were enrolled in the study; one participant was excluded owing to improper consent procedures; therefore, 165 participants were assigned to the intervention group, 150 participants were assigned to the control group, one participant in the control group crossed over to receive endovascular treatment. In the intervention group, 14 participants did not receive any interventional therapy. Four participants (1.3%) were lost to follow-up; (1 in the endovascular group and 3 in the control group) missing data on outcomes in these participants was not imputed. Therefore, the primary efficacy analysis included 164 (99.4%) participants in the intervention group and 147 (98%) in the control group.

EXTEND-IA

A total of 70 patients underwent randomisation: 35 were allocated to the endovascular therapy group and 35 were allocated to the alteplase-only group. Eight (22.9%) patients in the endovascular group did not undergo thrombectomy. All 70 participants were included for evaluation at 90 days for the primary outcome.

MR CLEAN

In total, 233 patients (46.6%) were assigned to receive intra-arterial thrombolysis, mechanical treatment, [undertaken with any currently available and approved device] or both, plus usual care [which could include IV alteplase] (intervention group) and 267 patients (53.4%) were assigned to usual care alone (control group). One patient received

intra-arterial treatment after being assigned to the control group. Intra-arterial treatment was never initiated in 17 patients (7.3%) assigned to the intervention group. All 500 participants were included for evaluation at 90 days for the primary outcome.

REVASCAT

A total of 207 patients were enrolled in the study; 1 participants withdrew informed consent, therefore 103 participants were allocated to the Solitaire stent retriever (thrombectomy group) and 103 were allocated to medical therapy alone (control group). No crossovers occurred, however 5 participants in the thrombectomy group did not undergo the thrombectomy procedure. All 206 participants were included for evaluation at 90 days for the primary outcome.

SWIFT PRIME

A total of 196 patients underwent randomisation; 98 were randomised to IV tPA plus MT performed with the use of the Solitaire FR or Solitaire 2 device stent retriever (intervention group) and 98 were randomised to IV tPA alone (control group). Eleven (11.2%) participants in the intervention group did not receive MT; the main reason was due to complete or partial resolution of the target occlusion (n=7). Nine (9.2%) participants in the intervention group and 12 (12.2%) participants in the control group died prior to the 90-day follow-up. Final assessment was unavailable for 5 patients randomised to the control group, therefore the primary efficacy analysis included 98 (100%) participants in the intervention group and 93 (94.9%) in the control group.

Table 18 Flow of participants

Trial ID	Intervention	Randomised N	Received tPA n (%)	Did not receive intervention n (%)	Lost to follow-up n (%)	Died n (%)	Analysed n (%)	Source
ESCAPE	Usual care + MT	165	120 (72.7)	14 (8.5)	1 (0.6)	NR	164 (99.4)	Goyal 2015; Figure S1, p.8.
	Usual care	150	118 (78.7)	1 (0.7)[a]	3 (2.0)	NR	147 (98.0)	
EXTEND-IA	Usual care + MT	35	35 (100)	8 (22.9)	0	NR	35 (100)	Campbell 2015; text, p. 1010, Figure S1, p.15.
	Usual care	35	35 (100)	0	0	NR	35 (100)	
MR CLEAN	Usual care + MT	233	203 (87.1)	17 (2.3)	0	NR	233 (100)	Berkhemer 2015; Table 1, p. 15, Figure S1, p.9.
	Usual care	267	242 (90.6)	1 (0.4)[b]	0	NR	267 (100)	
REVASCAT	Usual care + MT	103	70 (68.0)	5 (4.9)	0	NR	103 (100)	Jovin 2015; Figure S1, p.7.
	Usual care	103	80 (77.7)	0	0	NR	103 (100)	
SWIFT PRIME	Usual care + MT	98	31 (32.0)	11 (11.2)	0	9 (9.2)	98 (100)	Saver 2015; Table 1, p.2288, Figure S2, p.22.
	Usual care	98	35/94 (37.0)	0	0	12 (12.2)	93 (94.9)[c]	

Abbreviations: MT, mechanical thrombectomy; NR, not reported

a. Crossover from control to endovascular
b. Demanded treatment
c. Final assessment unavailable for 5 patients

B.4 Characteristics of the direct randomised trials

B.4.1 Eligibility criteria

The inclusion and exclusion criteria applied in the direct randomised trials are summarised in Table 19.

All five trials recruited patients who were of 18 years of age or older, who had AIS. The EXTEND-IA and SWFIT PRIME trials required that patients received IV tPA within 4·5 hours of stroke onset. In ESCAPE, participants were treated with IV tPA when clinically appropriate as part of standard care. Patients in REVASCAT could be either ineligible for IV alteplase or have received IV alteplase therapy without recanalisation. Patients were required to have functional independence prior to the stroke event defined as a Barthel Index score n> 90 in ESCAPE and mRS ≤ 1 in REVASCAT and SWIFT PRIME. Endovascular treatment initiation was required between 6 and 8 hours of stroke onset in all trials.

Imaging is an important element of patient selection as it can be used to identify the location of the occlusion and size of the penumbra, the extent of the infarct, the presence of collateral circulation and the extent of tissue at risk for irreversible ischaemia. The use of up-to-date non-invasive arterial imaging is one of the factors attributed to the success of recent studies of MT when compared to earlier thrombectomy trials (Vo et al, 2015). In the pivotal studies of MT, imaging of the cerebral parenchyma and vascular imaging was performed using a range of techniques, including CT scan with perfusion and CTA, or by MRI, magnetic resonance diffusion and perfusion and MRA. Overall, angiography using CTA or MRA was the most widely used approach to vascular imaging and detection of LVO – in most cases for the detection of the occlusion and determining the core size. The implications of using different imaging strategies to select patients are discussed in Section C.2.

Table 19 Eligibility criteria in the direct randomised trials

Criteria	ESCAPE	EXTEND-IA	MR CLEAN	REVASCAT	SWIFT PRIME
Inclusion criteria					
Age	Age 18 or greater	Age 18 or greater	Age 18 or greater	Age ≥18 and ≤80	Age 18 – 85
Indication	AIS; onset (last seen well) time to randomisation time < 12 hours	Anterior circulation AIS eligible to receive IV tPA within 4·5 hours of stroke onset	Acute stroke	AIS, where the patient is ineligible or IV thrombolytic treatment or the treatment is contraindicated OR where the patient has received IV thrombolytic therapy with recanalisation after a minimum of 30 min from start of IV-tPA infusion	Clinical signs consistent with AIS; patients receiving or had received intravenous tPA;
Baseline NIHSS	NIHSS > 5 (at the time of randomisation)	NA	NIHSS deficit of 2 points or more	NIHSS score ≥ 6 (prior to randomisation)	NIHSS ≥ 8 and < 30 at the time of randomisation
Pre-stroke independent functional status	Modified Barthel Index >90	NA	NA	mRS ≤ 1	mRS ≤ 1
Imaging diagnosis	Confirmed symptomatic intra-cranial occlusion based on single phase, multiphase or dynamic CTA, at one or more of the following locations: Carotid T/L, M1 MCA or M1-MCA equivalent (2 or more M2-MCAs). Non-contrast CT and CTA for trial eligibility performed or repeated at ESCAPE stroke centre with endovascular suite onsite	Arterial occlusion on CT or MR angiography of the ICA, M1, or M2 Mismatch – using CT or MRI with a Tmax >6 s delay perfusion volume and either CT-rCBF or DWI ischaemic core volume	Intra-cranial arterial occlusion of the distal intra-cranial carotid artery or middle (M1/M2) or anterior (A1/A2) cerebral artery, demonstrated with CTA, MRA or DSA	Occlusion (TICI 0-1) of the intra-cranial ICA (distal ICA or T occlusions), MCA-M1 segment or tandem proximal ICA/MCA-M1 suitable for endovascular treatment, as evidenced by CTA, MRA or angiogram, with or without concomitant cervical carotid occlusion or stenosis	TICI 0-1 flow in the intra-cranial internal carotid artery, M1 segment of the MCA, or carotid terminus confirmed by CT or MR angiography that is accessible to the Solitaire FR Device.

Criteria	ESCAPE	EXTEND-IA	MR CLEAN	REVASCAT	SWIFT PRIME
Inclusion criteria					
Endovascular treatment initiation	Groin puncture within 60 minutes of baseline non-contrast CT with target CT to first recanalisation of 90 minutes	Intra-arterial clot retrieval treatment can commence (groin puncture) within six hours of stroke onset	The possibility to start treatment within 6 hours from onset	Patient treatable within eight hours of symptom onset (treatment start defined as groin puncture). Symptoms onset is defined as point in time the patient was last seen well (at baseline).	Able to undergo initiation of endovascular treatment within 6 hours after the time that they were last known to be well before the onset of acute stroke symptoms. Subject is able to be treated (with minimum 1 deployment of Solitaire FR Device) within 1.5 hours of CTA/PCT or PWI/MRA MRI.
Exclusion criteria					
Current treatment			Intravenous treatment with thrombolytic therapy in a dose exceeding 0.9 mg/kg alteplase or 90 mg Current treatment with oral thrombin antagonists, such as argatroban and dabigatran or treatment with oral selective Factor Xa inhibitors, such as rivaroxaban	Subjects who have received IV tPA treatment beyond 4,5 hours from the beginning of the symptoms.	Warfarin therapy with INR greater than 1. Low molecular Weight Heparins (such as Dalteparin, Enoxaparin, Tinzaparin, Fondaparinux) as deep vien thrombosis (DVT) prophylaxis or in full dose within the last 24 hours from screening. Subject who has received heparin or a direct thrombin inhibitor (e.g. rivaroxaban, Angiomax™, argatroban, Refludan™) within the last 48 hours must have a normal partial thromboplastin time (PTT) to be eligible. Subject who has received factor Xa inhibitor therapy (e.g. dabigatran) within the

Criteria	ESCAPE	EXTEND-IA	MR CLEAN	REVASCAT	SWIFT PRIME
Inclusion criteria					
					past 24 hours must have a normal ecarin clotting time to be eligible. Subject who has received factor Xa inhibitor therapy more than 24 hours ago but less than 48 hours ago must have a normal partial thromboplastin time (PTT) to be eligible.
Stroke history/after stroke presentation				Patients with acute stroke within the first 48 hours after percutaneous cardiac or cerebrovascular interventions and major surgery (beyond 48h they should be randomised in REVASCAT)	History of stroke in the past 3 months Rapid neurological improvement prior to study randomisation suggesting resolution of signs/symptoms of stroke. Previous intra-cranial haemorrhage, neoplasm, subarachnoid haemorrhage, cerebral aneurysm, or arteriovenous malformation Clinical presentation suggests a subarachnoid haemorrhage, even if initial CT or MRI scan is normal
Contraindications		Standard contraindications to intravenous tPA	Intravenous treatment with thrombolytic therapy despite contraindications, i.e. major surgery, gastrointestinal bleeding or urinary tract bleeding within the previous 2 weeks, or arterial puncture at		

Criteria	ESCAPE	EXTEND-IA	MR CLEAN	REVASCAT	SWIFT PRIME
Inclusion criteria					
			a noncompressible site within the previous 7 days		
Imaging diagnosis	Baseline non-contrast CT reveals a moderate/large core defined as extensive early ischaemic changes of ASPECTS 0-5 in the territory of symptomatic intra-cranial occlusion			CT or MR evidence of haemorrhage (the presence of microbleeds is allowed). Significant mass effect with midline shift. Evidence of ipsilateral carotid occlusion, high grade stenosis or arterial dissection in the extracranial or petrous segment of the internal carotid artery that cannot be treated or will prevent access to the intra-cranial clot or excessive tortuosity of cervical vessels precluding device delivery/deployment Subjects with occlusions in multiple vascular territories (e.g., bilateral anterior circulation, or anterior/posterior circulation) Evidence of intra-cranial tumour (except small meningioma)	CT or MRI evidence of haemorrhage on presentation CT showing hypodensity or MRI showing hyperintensity involving greater than 1/3 of the MCA territory (or in other territories, >100 cc of tissue) on presentation CT or MRI evidence of mass effect or intra-cranial tumour (except small meningioma) Angiographic evidence of carotid dissection or complete cervical carotid occlusion Arterial tortuosity, calcification, pre-existing stent, and/or stenosis which would prevent the device from reaching the target vessel and/or preclude safe recovery of the device
Imaging complications	Severe contrast allergy or absolute contraindication to iodinated contrast	Contraindication to imaging with contrast agents			Known serious sensitivity to radiographic contrast agents.
Procedure complications	Groin puncture not possible within 60 mins of the end of	Inability to access the cerebral vasculature in the opinion of the neurointerventional team			

Criteria	ESCAPE	EXTEND-IA	MR CLEAN	REVASCAT	SWIFT PRIME
Inclusion criteria					
	CT acquisition. Very difficult endovascular access resulting in a CTA to recanalisation time that is longer than 90 mins No femoral pulse	or contraindication to use of the Solitaire FR device			
Comorbidities	Patient had severe or fatal comorbid illness that will prevent improvement or follow-up or that would render the procedure unlikely to benefit the patient Suspected intra-cranial dissection	Pre-stroke mRS score of ≥2 (indicating previous disability). Any terminal illness such that patient would not be expected to survive more than one year	Arterial blood pressure >185/110 mmHg. Blood glucose <2.7or >22.2 mmol/L. Laboratory evidence of coagulation abnormalities, i.e. platelet count <40 x 109/L, APTT>50 sec or INR >3.0 (for intended MT) Clinical or laboratory evidence of coagulation abnormalities, i.e. platelet count <90 x 109/L, APTT>50 sec or INR >1.7 (for intended intra-arterial thrombolysis) Cerebral infarction in the distribution of the relevant occluded artery in the previous 6 weeks. History of intracerebral haemorrhage. Severe head injury (contusion) in the previous 4 weeks.	Known haemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR > 3.0 Baseline platelet count < 30.000/µL Baseline blood glucose of < 50mg/dL or >400mg/dl Severe, sustained hypertension (SBP > 185 mm Hg or DBP > 110 mm Hg) Patients in coma (NIHSS item of consciousness >1) Seizures at stroke onset which would preclude obtaining a baseline NIHSS Serious, advanced, or terminal illness with anticipated life expectancy of less than one year. History of life threatening allergy (more than rash) to contrast medium Renal insufficiency with	Uncontrolled hypertension defined as systolic blood pressure > 185 or diastolic blood pressure > 110 that cannot be controlled except with continuous parenteral antihypertensive medication. Known hereditary or acquired haemorrhagic diathesis, coagulation factor deficiency. Baseline lab values: glucose < 50 mg/dL or > 400 mg/dL, platelets < 100,000 or Hct < 25 Renal Failure as defined by a serum creatinine > 2.0 or Glomerular Filtration Rate [GFR] < 30. Subject who requires haemodialysis or peritoneal dialysis, or who have a contraindication to an angiogram for whatever reason. Life expectancy of less than 90 days

Criteria	ESCAPE	EXTEND-IA	MR CLEAN	REVASCAT	SWIFT PRIME
Inclusion criteria					
				creatinine ≥ 3 mg/dl Cerebral vasculitis	Presumed septic embolus, or suspicion of bacterial endocarditis. Presumed pericarditis including pericarditis after acute myocardial infarction. Suspicion of aortic dissection Surgery or biopsy of parenchymal organ within 30 days. Trauma, with internal injuries or ulcerative wounds within 30 days. Severe head trauma or head trauma with loss of consciousness within 90 days. Any active or recent haemorrhage within 30 days. Cerebral vasculitis

B.4.2 Patient baseline characteristics

The baseline characteristics of participants in direct randomised trials are summarised in Table 20.

Baseline demographic characteristics were comparable between the treatment arms of within trials and across trials. The age of participants both within arms and across trials was comparable, ranging from mean of 65.0 to 70.2 years or a median range between 65.7 and 71 years.

The majority of patients (50.6-99%), where reported in each trial had a pre-stroke mRS 0-1 score and the median NIHSS score across treatment arms and trials ranged from 13-18. Due to differences between the trials in terms of patient selection, there were some differences between patients in terms of the site of occlusion. In all trials, the most common location of the occlusion in the first segment of the middle cerebral artery: between 57% and 77% in the intervention treatment arms across the trials and 51% and 71% in the control arms across the trials.

In the EXTEND-IA and SWIFT PRIME trials of the Solitaire device, patients were required to receive IV tPA in both arms; however, in the other included RCTs nominated “usual care” as the main comparator, which may or may not have included IV tPA. Across this latter group of trials, between 68-87% of patients in the intervention treatment arm received treatment with IV-tPA compared with 78-91% of patients in the control arm.

Since the studies were conducted in a range of sites and settings, there were differences between trials in terms of delivery of the intervention. The median time from stroke onset to randomisation was 169-223 mins across the trials for the intervention treatment arm and 172-226 mins across the trials for the control arm. Despite some variation, it should be noted that in all of the trials, the time to delivery of the intervention was well within the recommended timeframe of 4.5 hours for IV tPA and 6-12 hours for MT, as required by the trials. Despite these differences, MT was consistently effective and consistency of treatment effect is supported by the IPD (see Section C.2).

The impact of different baseline characteristics on treatment efficacy is explored in an IPD meta-analysis of data from the five trials (Goyal et al, 2016), presented in Section C.2 of this submission.

Table 20 Baseline characteristics of participants in direct randomised trials

Characteristic	ESCAPE		EXTEND IA		MR CLEAN		REVASCAT		SWIFT PRIME	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
N	165	150	35	35	233	267	103	103	98	98
Age; Mean (SD)	NR	NR	68.6 (12.3)	70.2 (11.8)	NR	NR	65.7 (11.3)	67.2 (9.5)	65.0 (12.5)	66.3 (11.3)
Age; Median (IQR)	71 (60-81)	70 (60-81)	NR	NR	65.8 (54.5-76.0)	65.7 (55.5-76.4)	NR	NR	NR	NR
Gender; n/N (%) male	79/165 (47.9)	71/150 (47.3)	17/35 (49)	17/35 (49)	135/233 (57.9)	157/267 (58.8)	55/103 (53.4)	54/103 (52.4)	54/98 (55)	45/96 (47)
Pre-stroke mRS 0-1; n/N (%)	NR	NR	NR	NR	211/233 (90.5)	243/267 (91.0)	86/103 (83.5)	83/103 (80.6)	96/98 (98)	93/94 (99)
NIHSS score; Median (IQR)	16 (13-20)	17 (12-20)	17 (13-20)	13 (9-19)	17 (14-21)	18 (14-22)	17 (14-20)	17 (12-19)	17 (13-19)	17 (13-20)
ASPECTS on CT; Median (IQR)	9 (8-10)	9 (8-10)	NR	NR	9 (7-10)	9 (8-10)	7 (6-9)	8 (6-9)	9 (8-10)	9 (7-10)
Site of occlusion; n/N (%)										
Internal carotid artery	NR	NR	11 (31)	11 (31)	NR	NR	NR	NR	17/93 (18)	15/94 (16)
Intra-cranial ICA	NR	NR	NR	NR	1/233 (0.4)	3/266 (1.1)	0	1/101 (1.0)	NR	NR
Extracranial ICA	NR	NR	NR	NR	75/233 (32.2)	70/266 (26.3)	NR	NR	NR	NR
ICA with M1	45/163 (27.6)	39/147 (26.5)	NR	NR	59/233 (25.3)	75/266 (28.2)	26/102 (64.7)	27/101 (26.7)	NR	NR
Middle cerebral artery										
M1	111/163 (68.1)	105/147 (71.4)	20 (57)	18 (51)	154/233 (66.1)	165/266 (62.0)	66/102 (64.7)	65/101 (64.4)	72/94 (77)	62/93 (67)
M2	6/163 (3.7)	3/147 (2.0)	4 (11)	6 (17)	18/233 (7.7)	21/266 (7.9)	10/102 (9.8)	8/101 (7.9)	6/94 (6)	13/93 (14)

Characteristic	ESCAPE		EXTEND IA		MR CLEAN		REVASCAT		SWIFT PRIME	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
A1 or A2	NR	NR	NR	NR	1/233 (0.4)	2/266 (0.8)	NR	NR	NR	NR
Ipsilateral cervical carotid occlusion	NR	NR	NR	NR	NR	NR	19/102 (18.6)	13/101 (12.9)	NR	NR
Treatment with IV-tPA; n/N (%)	120/165 (72.7)	118/150 (78.7)	100%	100%	203/233 (87.1)	242/267 (90.6)	70 (68.0)	80 (77.7)	100%	100%
Median time from stroke onset to IV-tPA; min (IQR)	110 (80-142)	125 (89-183)	127 (93-162)	145 (105-180)	NR	NR	117.5 (90-150)	105 (86-137.5)	110.5 (85-156)	117 (80-155)
Median time from stroke onset to imaging; min (IQR)	134 (77-247)	136 (76-238)	NR	NR	NR	NR	192 (129-272)	183 (132-263)	NR	NR
Median time from stroke onset to randomisation; min (IQR)	169 (117-285)	172 (119-284)	NR	NR	204 (152-251)	196 (149-266)	223 (170-312)	226 (168-308)	190.5 (141-249)	188 (130-268)
Median time from stroke onset to groin puncture; min (IQR)	NR	NR	NR	NR	260 (210-313)	NA	269 (201-340)	NA	NR	NR

B.4.3 Interventions compared by the randomised trials

Four of the five trials compared 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 MT and/or intra-arterial thrombolysis. However, the majority of patients in the active treatment arm of this trial were treated with 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). The interventions used for each trial are described below.

ESCAPE

Participants in both treatment groups received IV tPA within 4.5 hours after the onset of stroke symptoms if they met accepted local guidelines for IV tPA treatment. The control group received the current standard of care as described in the Canadian or local guidelines for the management of acute stroke. Whilst standard of care was not defined in the study reports, it usually involves medical management with anti-thrombotic treatment only such as aspirin or anticoagulants.

Subjects in the intervention group received emergency endovascular mechanical revascularisation. Endovascular mechanical revascularisation was undertaken with any currently available and approved device or paradigm and used according to the manufacturers specifications for use. The use of stent retrievers was recommended. Approximately 86% (130/151) of patients received endovascular therapy with a stent retriever; 77% (100/130) had received Solitaire. A cerebral angiogram was obtained. During thrombus retrieval, suction through a balloon guide catheter in the relevant internal carotid artery was also recommended.

EXTEND-IA

All participants in the EXTEND-IA trial received alteplase at a dose of 0.9 mg per kilogram as standard care. Those that were randomised to the control arm of the study received no further treatment (alteplase-group only). Participants randomised to receive endovascular therapy, went on to receive treatment with Solitaire FR. The Solitaire FR device is a retrievable stent delivered at the site of intra-cranial vessel occlusion and then removed while negative pressure aspiration is applied. The use of conscious sedation or general anaesthesia for the procedure was at the discretion of the individual site

neurointerventionalist. Before deploying the Solitaire device, the site of vessel occlusion was confirmed using digital subtraction angiography. Endovascular therapy had to be initiated (groin puncture) within 6 hours after stroke onset and completed within 8 hours after onset.

The Solitaire FR retrievable stent was deployed at the site of intra-cranial vessel occlusion and then removed while negative pressure aspiration was applied. Up to 2 passes were permitted with a second device used for further passes up to a maximum of 3 per arterial segment. An angiogram was performed after each pass of the device. Proximal balloon occlusion was recommended as per manufacturer's instructions. During the procedure, catheters were flushed with heparinised saline (1000units/l heparin). Use of other devices, lytic agents, angioplasty or intra-cranial stenting was not permitted within the protocol.

MR CLEAN

Intra-arterial treatment consisted of delivery of a thrombolytic agent, MT, or both. The method of intra-arterial treatment was left to the discretion of the local interventionist.

The use of alteplase or urokinase for intra-arterial thrombolysis was allowed in this trial, with a maximum dose of 90 mg of alteplase or 1,200,000 IU of urokinase. The dose was restricted to 30 mg of alteplase or 400,000 IU of urokinase if intravenous alteplase was given. Actual intra-arterial therapy (with or without MT) was performed in 196 of the 233 patients in the intervention group (84.1%). Intra-arterial thrombolytic agents were used as monotherapy in 1 of the 233 patients (0.4%). No intervention was given in 37 patients (15.9%)

Only devices that had received U.S. Food and Drug Administration approval and were approved by the steering committee could be used in the trial. One or more members of each intervention team had to have completed at least five full procedures with a particular type of device. Mechanical treatment could involve thrombus retraction, aspiration, wire disruption, or use of a retrievable stent. Mechanical treatment was performed in 195 of the 233 patients (83.7%). Retrievable stents were used in 190 patients (81.5%), and other devices were used in 5 patients (2.1%).

REVASCAT

Patients who had received IV tPA (alteplase) within 4.5 hours after the onset of symptoms without revascularisation after 30 minutes of alteplase infusion or who had a contraindication to intravenous alteplase were eligible for participation in REVASCAT. Participants randomised to medical management received no further no intra-arterial

intervention with drugs or devices. Furthermore, after randomisation, a subject could not be placed on intravenous thrombolytic therapy.

Participants randomised to endovascular therapy received treatment with the Solitaire FR device. All interventional therapy started earlier than eight hours relative to the time the subject was last seen well. Treatment initiation was defined as groin puncture. The duration of the interventional procedure could not exceed three hours. Study sites consisted of certified comprehensive stroke centres that treat more than 500 patients with acute stroke and perform more than 60 mechanical stroke thrombectomy procedures annually and are staffed by trained neurointerventionalists who are required to have performed at least 20 thrombectomies with the Solitaire FR device.

SWIFT PRIME

Entry criteria for SWIFT PRIME required that all participants were receiving or had received IV tPA. Participants randomised to usual care received no further treatment.

Participants who were randomised to receive further intervention proceeded to be treated with MT, performed with the use of Solitaire FR or Solitaire 2 device. Participants were required to be able to undergo initiation of treatment within 6 hours after the time that they were last known to be well before the onset of acute stroke symptoms. All study centres were required to have performed at least 40 MT procedures, including at least 20 procedures with the Solitaire FR stent retriever annually.

B.5 Outcome measures and analysis

B.5.1 Primary outcome

The primary outcomes and the associated statistical analyses in each of the trials included in the comparison are summarised in Table 21. All trials followed-up patients for a minimum of 90 days. In four of the five trials (ESCAPE, MR CLEAN, REVASCAT and SWIFT PRIME), the primary outcome was the modified Rankin scale (mRS) at 90 days, which is a measure of functional independence. This was a secondary outcome in the remaining trial - EXTEND-IA.

For all studies that reported the 90-day mRS score, the primary outcome was assessed as a median score, and as a “shift analysis” of disability scores. While there were some differences in the statistical approaches taken to perform this calculation, all analyses aimed to determine the likelihood (odds ratio) that endovascular treatment would lead to lower mRS values compared to usual care alone.

Table 21 Primary outcomes and statistical analyses of the direct randomised trials

Trial ID	Primary outcome	Method of primary statistical analysis	Source
ESCAPE	NIHSS score of 0-2 OR mRS score of 0-2 at 90 days after randomisation.	The primary analysis was unadjusted and was performed in the intention-to-treat population. P-values of less than 0.05 were considered to indicate statistical significance, and all tests of hypotheses were two-sided. No adjustments were made for multiple comparisons. Adjusted estimates of effect were calculated, with adjustment for age, sex, baseline NIHSS score, baseline ASPECTS, location of occlusion (internal carotid artery plus middle cerebral artery vs. middle cerebral artery only), and status with respect to intravenous alteplase treatment (yes vs. no). The assessment of effect modification (heterogeneity of treatment effect) was performed with the inclusion of multiplicative interaction terms.	Goyal 2015; Goyal 2015 Protocol
EXTEND-IA	1) Median percentage reperfusion at 24 h post-stroke, adjusted for site of arterial occlusion. 2) NIHSS reduction ≥8 points or reaching 0–1 at 3 days (favourable clinical response) adjusted for baseline NIHSS and age.	The primary efficacy analysis was based on an intention-to-treat basis. Two co-primary outcomes were compared using two-sided significance tests. Statistical significance level adjustment was made using the Bonferroni–Holm step-down procedure. For the co-primary outcome analysis: 1) the reperfusion outcomes were compared between treatment and control arms of the trial adjusted for site of baseline arterial occlusion (all three strata) using the van Elteren test (a stratified version of the Wilcoxon rank-sum test); and 2) the proportion of patients with a favourable clinical response indicated by an NIHSS reduction ≥8 points or reaching 0–1 at three-days was compared between treatment and control arms of the trial adjusted for age and baseline NIHSS score using binary logistic regression.	Campbell 2015 Protocol
MR CLEAN	mRS score at 90 days.	All analyses were based on the intention-to-treat principle. The primary effect variable was the adjusted common odds ratio for a shift in the direction of a better outcome on the modified Rankin scale; this ratio was estimated with multivariable ordinal logistic regression. An adjusted odds ratio was calculated for all possible cut-off values on the modified Rankin scale to assess the consistency of effect and the plausibility of proportionality of the odds ratio. Multivariable regression analysis was used to adjust for chance imbalances in main prognostic variables between intervention and control group.	Berkhemer 2015; Berkhemer 2015 Protocol

Trial ID	Primary outcome	Method of primary statistical analysis	Source
REVSACT	Severity of disability at 90 days, according to the distribution of scores on mRS.	All analyses were performed in the intention-to-treat population. The measure of effect size was a cumulative odds ratio as calculated by logistic regression (shift analysis). This analysis relies on the assumption of an odds ratio behind any cut-off point, which has been shown to be robust to minor deviations. The primary analysis was conducted using an ordered logistic regression in order to control for minimisation factors (centre, baseline NIHSS, therapeutic window, age and occlusion site). In addition, r-TPA administration will be included in this model. The statistical significance of the coefficients (β's) were tested using the Wald test. The effect of Solitaire therapy as compared to control therapy (reference therapy) was measured by estimating the odds ratio corresponding to the therapy effect and its 95% confidence intervals by means of the model coefficient and the corresponding Standard Error derived from the ordered logistic regression model.	Jovin 2015; Jovin 2015 Protocol
SWIFT PRIME	Disability at 90 days, according to the distribution of scores on mRS.	For the primary outcome, the score on the modified Rankin scale at 90 days was analysed using simultaneous success criteria of the overall distribution of the score (shift in disability levels) and the proportion of patients who were functionally independent. Both criteria needed to be met in order for the study to be declared positive. The statistical hypothesis on the scale shift was that the distribution over the entire range of scores (except for scores of 5 or 6, which were collapsed into a single group) among patients in the intervention group would be more favourable than the distribution in the control group, as analysed by means of the Cochran–Mantel–Haenszel test. Type I and Type II error will be computed via simulation and overall alpha will be controlled at a one-sided level of 0.025.	Saver 2015; Saver 2015 Protocol

Table 22 provides a description of the statistical power and sample size calculations for the primary endpoint(s).

Table 22 Description of statistical power calculations for the primary outcome

Trial	Description of statistical power calculation for the primary outcome	Source
ESCAPE	The sample size, at 85% power and conventional alpha =0.05, will be 242 evaluable patients (121 in each arm). This provides adequate power to identify a relative risk-benefit of 1.5 and an absolute risk difference of 20%. This would translate to an NNT of 5. The trial was powered to detect a shift in the distribution of scores on the modified Rankin scale at 90 days between the intervention and control groups, with scores of 5 (bed bound with severe disability) and 6 (death) combined, with the assumption that the differential effect would lead to a common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 1.8. A total required sample of 500 participants was anticipated. One formal interim analysis after the enrolment of 300 participants was planned. The stopping rule for efficacy was defined with the use of O'Brien–Fleming boundaries on the binary outcome of a modified Rankin score at 90 days of 0 to 2 versus 3 to 6.	Goyal 2015; Goyal 2015 Protocol
EXTEND-IA	The original sample size estimation is based on the assumption that the patient mix is broadly reflective of population-wide prevalence (i.e. ICA: 30%, M1: 50%, M2:20%). An	Campbell 2015

Trial	Description of statistical power calculation for the primary outcome	Source
	estimated total sample size of 100 patients (with 50 patients in each of treatment and control arms) should yield 80% power to detect both: a) a significant difference of 24% in strata-weighted median reperfusion at 24 h (80% in treatment vs. 56% in control arm) at two-sided statistical significance threshold of P = 0·025; and b) a significant difference of 33% (63% in treatment vs. 30% in control arm) in the proportion of patients with ≥8-point reduction in NIHSS or reaching 0–1 at three-days (favourable clinical response) adjusted for baseline NIHSS and age at two-sided statistical significance threshold of P = 0·025.	Protocol
MR CLEAN	Assuming a 10% crossover rate, a sample of 500 patients (250 patients in each group) would yield a power of 82%, at a significance level of 0.05, to detect a treatment effect that resulted in an absolute increase of 10 percentage points in the proportion of patients with a modified Rankin score of 0 to 3 in the intervention group as compared with the proportion in the control group.	Berkhemer 2015
REVSACT	Enrolment of 690 patients would provide a power of 90% to detect a difference in the distribution of scores on the modified Rankin scale with a one-sided significance level of 0.025 in the analysis of the primary outcome, assuming an expected result of an odds ratio of 1.615. Because of the uncertainty about the size of the treatment effect for the primary outcome, REVASCAT was designed as a sequential study. On the basis of stopping boundaries for the Whitehead triangular test, it was planned to conduct a maximum of four equally spaced reviews when enrolment had reached approximately 25%, 50%, 75%, and 100% of the sample size. We assigned lower individual limits of significance to the four analyses in order to achieve an overall shared one-sided alpha level of 0.025.	Jovin 2015
SWIFT PRIME	With a one-sided alpha level of 0.025, 750 evaluable subjects for this endpoint (i.e., 750 subjects with evaluable mRS) provides 80% power for testing the study's primary effectiveness hypothesis; assuming attrition of 10% for the primary endpoint, the total randomised sample size is up to 833 while the expected randomised sample size under the alternative hypothesis is approximately 522.	Saver 2015 Protocol

B.5.2 Secondary outcomes

Table 23 describes and provides and explanation of the primary method of statistical analysis for secondary outcomes in the included trials.

Table 23 Secondary outcomes and statistical analyses of the direct randomised trials

Trial ID	Secondary outcomes	Method of primary statistical analysis	Source
ESCAPE	Secondary outcomes included early recanalisation and reperfusion, intra-cranial haemorrhage, angiographic complications, neurologic disability at 90 days, and death.	All secondary outcomes were considered exploratory. Post-hoc analyses were conducted. Outcomes were assessed as the proportion of patents who achieved each score. Raw score comparisons were also examined.	Goyal 2015 Protocol

Trial ID	Secondary outcomes	Method of primary statistical analysis	Source
EXTEND-IA	• mRS at 3 months – ordinal full scale analysis • mRS 0–1 and mRS 0–2 • symptomatic intra-cranial haemorrhage [symptomatic intra-cranial haemorrhage includes any subarachnoid bleeding associated with clinical symptoms and symptomatic intracerebral haemorrhage (SICH). SICH is defined as parenchymal hematoma type 2 (PH2) within 36 h of treatment combined with ≥4 point increase in NIHSS from baseline, or the lowest NIHSS value between baseline and 24 h (37)] • death due to any cause	For the secondary outcome analysis, assumption-free, ordinal analysis of mRS was undertaken on the full range (0–6) of the mRS. The proportions of mRS 0–1 and mRS 0–2 outcomes will also be compared between IV-IA and IV only arms of the trial adjusted for age and baseline NIHSS score using a binary logistic regression model.	Campbell 2015 Protocol
MR CLEAN	Secondary outcomes included the NIHSS score at 24 hours and at 5 to 7 days or discharge if earlier, activities of daily living measured with the Barthel Index, and the health-related quality of life measured with the EuroQoL Group 5-Dimension Self-Report Questionnaire at 90 days. We examined the following pre-specified dichotomisations of the modified Rankin score: 0 or 1 versus 2 to 6, 0 to 2 versus 3 to 6, and 0 to 3 versus 4 to 6.	Secondary effect parameters will be the improvement according to the classical dichotomisations of the modified Rankin scale at 0-1 vs 2-6 and 0-2 vs 3-6, the presence of vessel patency on CTA, MRA or DSA at 24 hours, and the score on the NIHSS at 24 hours and 1 week or discharge. With regard to the range of secondary outcome parameters we will use simple 2x2 tables, two-group t-tests, Mann-Whitney tests, and multivariable linear and logistic regression models, where appropriate. In all analyses, statistical uncertainty will be quantified by means of 95%confidence intervals.	Berkhemer 2015; Protocol p 82
REVSACT	• Early response to treatment as determined by a NIHSS drop of ≥8 or NIHSS 0-2 at 24 (-2/12) hours from randomisation or before discharge if patient is discharged prior to the above time limit • MRS shift analysis at 90 days • Dichotomised mRS SCORE (0-3 versus 4-6) at 90 days • NIHSS at 90 days • Dichotomised mRS score (0-2 versus 3-6) at 12 months • Trial Making Test at 90 days • Quality of life measured by EuroQol EQ-5D • Final infarct volume defined as CT lesion volume at 24 hours • Recanalisation status at 24 (-2/+12) hours	Functional independence defined as mRS ≤ 2 at 90 days was analysed via a logistic regression adjusted by minimisation factors. Along with treatment group, the baseline covariates considered in the minimisation process as well as the interventionist will be included in the logistic regression. Recanalisation status will be evaluated at 24 (-2 /+12) hours on CTA/MRA in both and expressed as occluded or patent according to the patency of the initially occluded vessel.	Jovin 2015 Protocol, p. 22-23;

Trial ID	Secondary outcomes	Method of primary statistical analysis	Source
SWIFT PRIME	• Death due to any cause at 90 days • Good neurological outcome at 90 days (defined as mRS score of 0-2, or equal to the pre-stroke mRS, or NIH stroke scale improvement of 10 points or more from presenting NIHSS) • Change in NIH Stroke Scale score at 27± 3 hours post randomisation • Volume of cerebral infarction as measured by a CT or MRI scan 27± 3 hours post randomisation • Arterial reperfusion measured by reperfusion ratio on CT or MRI scan 27± 3 hours post randomisation • Arterial revascularisation measured by TICI 2b or 3 following device use	These endpoints will be presented descriptively. Labelling claims will not be made with reference to these endpoints and multiplicity adjustments will therefore not be performed in statistical analyses.	Saver 2015 Protocol. p.58

B.5.3 Outcomes presented in the submission

A summary of outcomes presented in the included trials and included in this submission is presented in Table 24. Descriptions of each of the outcomes follow.

Table 24 Outcomes analysed for the purposes of this submission

	ESCAPE	EXTEND-IA	MR CLEAN	REVASCAT	SWIFT PRIME
Primary outcome (mRS score at 90 days)					
Median mRS score (odds of improvement of 1 point)	✓	✓	✓	✓	✓
Distribution of mRS scores (0-6) at 90 days	✓	✓	✓	✓	✓
Secondary outcome					
mRS score 0-2 at 90 days	✓	✓	✓	✓	✓
NIHSS	✓	✓	✓	✓	✓
Barthel Index	✓	×	✓	✓	×
TICI score	✓	✓	✓	✓	✓
EQ-5D	✓	×	✓	✓	×
Mortality at 90 days	✓	✓	✓	✓	✓
Safety outcomes					
Any serious adverse events	×	×	✓	×	✓
SICH	✓	✓	✓	✓	✓
Haematoma at access site	✓	✓	×	✓	×
Procedural complications	✓	✓	✓	✓	✓
Parenchymal haematoma	×	✓	✓	✓	✓
Subarachnoid haemorrhage	×	×	✓	✓	✓
New ischaemic stroke	×	×	✓	✓	×

Modified Rankin Scale (mRS)

mRS is a global measure of disability and dependence that categorises the level of functional independence with reference to pre-stroke activities. It is widely applied for evaluating stroke patient outcomes. The scale comprises of seven grades ranging from 0 (no symptoms) to 6 (death). The mRS has excellent test-re-test reliability (K= 0.95) in acute stroke (Wolfe 1991). A minimally clinically important difference has not been established however it is widely accepted that a score ≤2 indicates functional independence. Many AIS studies utilise the mRS dichotomised as 0-1 vs. 2-6 or 0-2 vs. 3-6 to determine treatment success versus failure (Table 25).

Table 25 Modified Rankin Scale (mRS)

0	1	2	3	4	5	6
No symptoms	No significant disability	Slight disability	Moderate disability	Moderately severe disability	Severe disability	Dead
	Able to carry out all usual activities, despite some symptoms	Able to look after own affairs without assistance, but unable to carry out all previous activities	Requires some help, but able to walk unassisted	Unable to attend to own bodily needs without assistance, and unable to walk unassisted	Requires constant nursing care and attention, bedridden, incontinent	
SUCCESS			**FAILURE**			

Mortality at 90 days

Mortality at 90 days is reported in all trials and is captured as an mRS score of 6. Mortality in general can occur as an outcome of stroke or as a side effect of treatment procedure complication (e.g. ICH).

National Institutues of Health Stroke Scale (NIHSS)

The NIHSS is a reliable, valid and responsive tool that quantifies the severity of neurological impairment post-stroke. It was originally developed in 1989 and is now a widely used outcome measure in stroke trials. In the current National Stroke Foundation guidelines, the NIHSS is recommended as a valid tool to assess stroke severity in emergency departments.

The NIHSS is composed of 15-item impairment scale and assesses level of consciousness, extraocular movements, visual fields, facial muscle function, extremity strength, sensory function, coordination (ataxia), language (aphasia), speech (dysarthria), and hemi-inattention (neglect) (Lyden, Lu, & Jackson, 1999).

Each impairment is scored on an ordinal scale ranging from 0 to 2, 0 to 3, or 0 to 4. A score of 0 typically indicates normal function, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0. The MCID of the NIHSS has not been established. Stroke severity may be stratified on the basis of NIHSS scores as shown in Table 26 (Brott et al, 1989).

Table 26 NIHSS scores

Very Severe:	>25
Severe:	15 – 24
Mild to Moderately Severe:	5 – 14
Mild:	1 – 5

Barthel Index

The Barthel Index assesses the ability of an individual with a neuromuscular or musculoskeletal disorder to care for him/herself by measuring the ability to perform the activities of daily living. There are 10 activities of daily living/mobility that the Barthel Index assesses: feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation, and stair climbing. Items are rated based on the amount of assistance required to complete each activity. The index ranges from 0 (severe disability) to 100 (no disability) with a higher score indicating good performance of the activities of daily living. In a Taiwanese sample of patients (n=43), with a mean age of 55.4 years and mean time since stroke of 7.04 days, the minimally clinical important difference was determined to be 1.85 points of the Barthel Index (Hsieh 2007).

Revascularisation

The thrombolysis in cerebral infarction (TICI) grading system (Table 27) is a tool used determining the response of thrombolytic therapy for ischaemic stroke. In neurointerventional radiology it is usually used for patients post endovascular revascularisation. Like most therapy response grading systems, it predicts prognosis. The TICI ranges from grade 0 (no perfusion) to grade 3 (complete perfusion) (Higashida 2003).

A consensus paper from three collaborative groups published in Stroke in 2013, recommended a modified scale, and a change of name from TICI to modified Treatment in Cerebral Infarction (mTICI), to better reflect the increased use of endovascular therapies. Both the TICI and mTICI grading systems are presented in Table 27.

Table 27 Revascularisation grading systems

Grade	TICI	mTICI
Grade 0	No perfusion	No perfusion
Grade 1	Penetration with minimal perfusion. The contrast material fails to pacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion.
Grade 2a	Only partial filling (<2/3) of the entire vascular territory is visualised.	Antegrade reperfusion of less than half of the occluded target artery previously ischaemic territory (e.g. in one major division of the middle cerebral artery (MCA) and its territory).
Grade 2b	Complete filling of all of the expected vascular territory is visualised, but the filling is slower than normal.	Antegrade reperfusion of more than half of the previously occluded target artery ischaemic territory (e.g. in two major divisions of the MCA and their territories).
Grade 3	Complete Perfusion.	Complete antegrade reperfusion of the previously occluded target artery ischaemic territory, with absence of visualised occlusion in all distal branches.

Reperfusion

Substantial reperfusion was defined as reperfusion of at least 50% and a modified TICI score of 2b (50 to 99% reperfusion) or 3 (complete reperfusion). Successful reperfusion was defined as reperfusion of at least 90%, as assessed with the use of perfusion CT or MRI.

EQ-5D

EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. EQ-5D is designed for self-completion by respondents taking only a few minutes to complete.

There are two parts to the EQ-5D questionnaire. The first part is the EQ-5D descriptive system, which comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) that each have 3 levels (no problems, some problems, severe problems). The second part is the EQ visual analogue scale (EQ VAS), which is used to record the respondent's self-rated health on a vertical, visual analogue scale (0-100) where the endpoints are labelled 'Best imaginable health state' (100) and 'Worst imaginable health state' (0).

B.6 Systematic overview of the results of the direct randomised trials

B.6.1 Primary efficacy outcome: mRS score at 90 days

The primary outcome in four of the five included trials (ESCAPE, MR CLEAN, REVASCAT and SWIFT PRIME) was the mRS score at 90 days. This outcome was presented as a secondary outcome in EXTEND-IA. All studies also reported the 90-day mRS score assessed as a "shift analysis" of disability scores.

The median mRS score at 90 days favoured the intervention treatment arms and was statistically significant in all five trials at 90 days compared to the control group, i.e. the lower the mRS score, the lower the degree of disability and increased functional independence (Table 28). Consequently, increased functional independence drives costs saving and benefits to carers.

The analysis of the mRS score at 90 days in four of the five included trials (ESCAPE, MR CLEAN, REVASCAT and SWIFT PRIME) was aimed to determine the likelihood (common odds ratio; cOR) that endovascular treatment would lead to lower mRS values compared to usual care alone. The common odds ratio was estimated from an ordinal logistic regression model and indicates the odds of improvement of 1 point on the modified Rankin scale, with a common odds ratio greater than 1 favouring the intervention. In all trials, this analysis demonstrated a significantly greater likelihood of an improved mRS value as a result of MT treatment. In EXTEND-IA, where the 90-day mRS score was reported as a secondary outcome, the proportions of mRS 0–1 and mRS 0–2 outcomes were compared between IV-IA and IV only arms using a binary logistic regression model.

A post-hoc meta-analysis could not be performed based on the median results or cOR estimates presented in the five individual trials. However, a meta-analysis based on IPD for this outcome, presented in Section C.2, shows a pooled cOR of 2.26 (95% CI: 1.67, 3.06; p<0.0001) (Goyal et al, 2016). The absence of heterogeneity strengthened conclusions about the consistency of effects across major subgroups of age and severity. The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on the mRS for one patient was 2·6.

Table 28 mRS score at 90 days

Trial ID	Intervention Median score [IQR]	Control Median score [IQR]	Common OR[a] [95% CI], p-value	Source
ESCAPE	NR	NR	2.6 [1.7, 3.8], p<0.001	Goyal 2015, Table 2
EXTEND-IA	1 [0 to 3]	3 [1 to 5]	2.1 [1.2 to 3.8], # p=0.006	Campbell 2015, Table 3
MR CLEAN	3 [2, 5]	4 [3, 5]	1.66 [1.21, 2.28], NR	Berkhemer 2015, Table 2
REVASCAT	NR	NR	1.7 [1.04, 2.7], NR	Jovin 2015, Table 2
SWIFT PRIME	2 [1, 4]	3 [2, 5]	2.63 [1.57, 2.91], p<0.001	Saver 2015, Table 2

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; NR, not reported

a Common OR [95% CI], unadjusted, as reported by the source document. The common odds ratio was estimated from an ordinal logistic regression model and indicates the odds of improvement of 1 point on the modified Rankin scale, with a common odds ratio greater than 1 favouring the intervention.

The proportions of mRS 0–1 and mRS 0–2 outcomes were compared between IV-IA and IV only arms of the trial adjusted for age and baseline NIHSS score using a binary logistic regression model

Distribution of scores on the mRS at 90 Days

Figure 4 shows that at 90 days there was a greater proportion of patients in the intervention treatment arm with mRS scores of 0, 1, 2 and 3 compared to the control arm representing a favourable shift in the distribution of global disability scores on the mRS at 90 days across all trials.

Figure 5 is a forest plot representation comparing of the proportion in each mRS category at 90 days between the intervention treatment and control arms in each of the five trials. The results show that patients treated with MT have a greater likelihood of having mRS values 0-2, a similar likelihood of having mRS 3 and a reduced chance of being in the mRS4-6 categories.

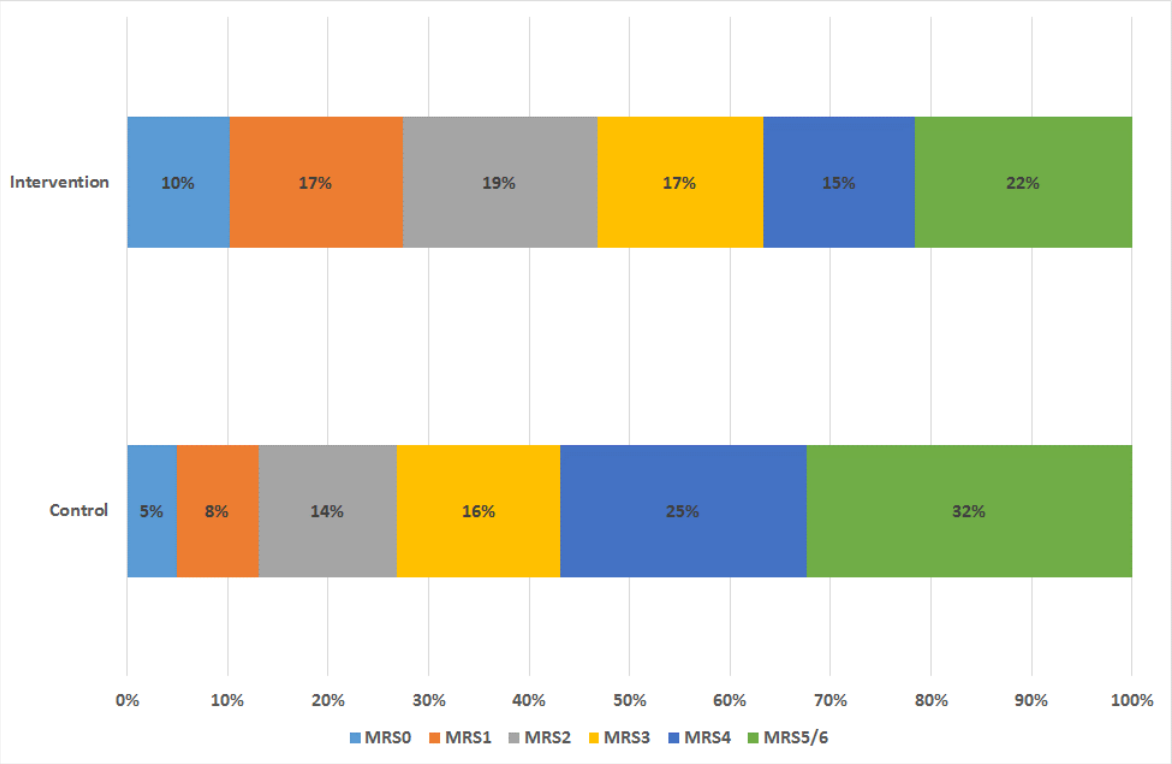


Figure 4 Proportion of patients in each mRS category at 90 days

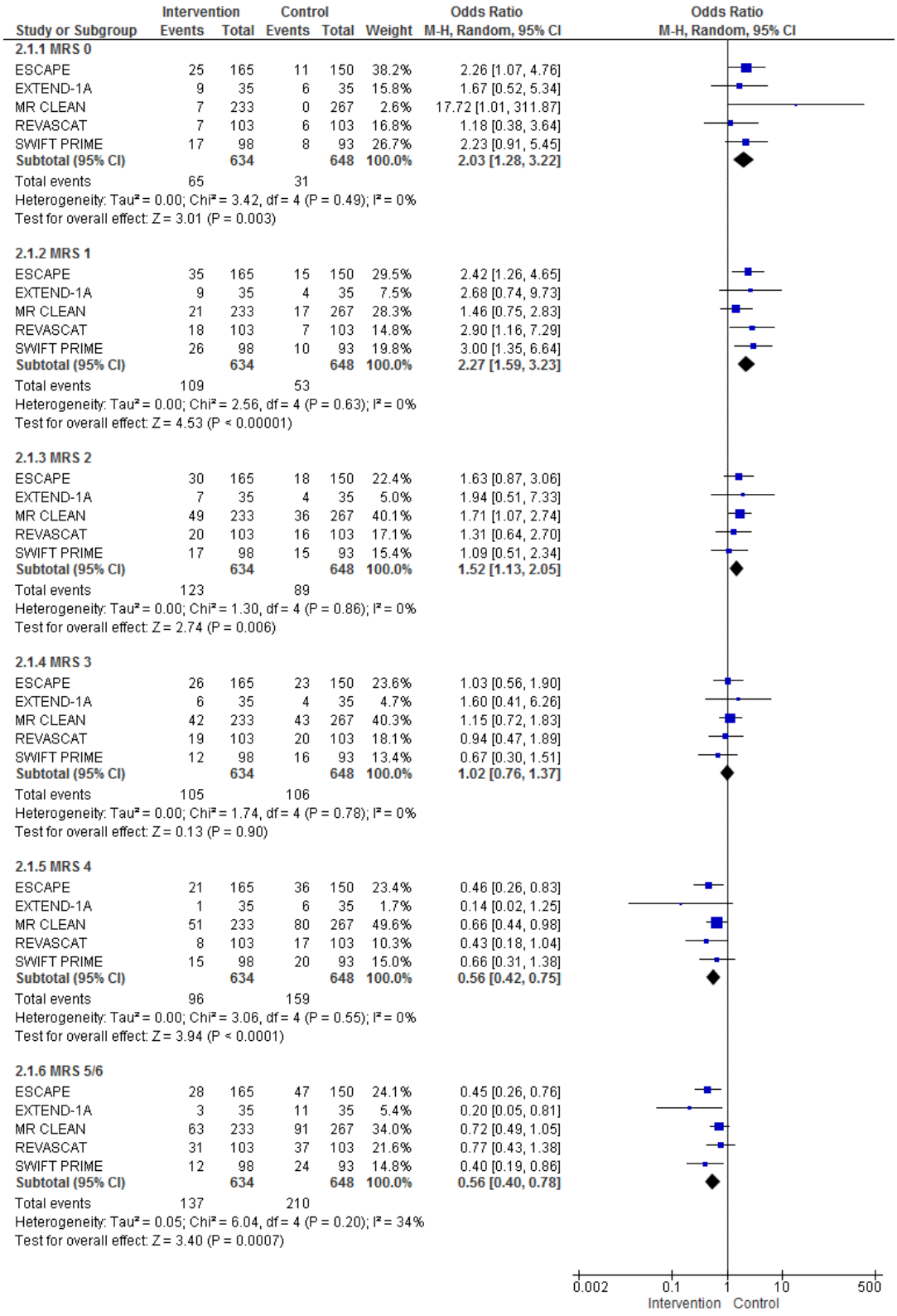


Figure 5 Forest plot representation of the proportion of patients in each mRS category at 90 days

B.6.2 Secondary efficacy outcomes

mRS score 0-2 at 90 days

The proportion of patients with a mRS score 0-2 at 90 days in each trial is presented in Table 29 and Figure 6. A mRS score of 0-2 indicated functional independence. Each of the five trials reported a greater proportion of patients with a mRS score of 0-2 at 90 days in the intervention treatment arm compared to the control arm. Overall, 46.1% of patients in the intervention treatment arm compared to 26.4% of patients in the control arm possessed a mRS score of 0-2 at 90 days. This difference was statistically significant with an OR=2.39 (95% CI: 1.88, 3.04), p<0.0001.

Table 29 mRS score 0-2 at 90 days

Trial ID	Intervention n /N (%)	Control n /N (%)	OR [95% CI][a]	Source
ESCAPE	87/164 (53.0%)	43/147 (29.3%)	2.73 [1.71, 4.37]	Goyal 2015, Table 2
EXTEND-IA	25/35 (71.4%)	14/35 (40.0%)	3.75 [1.38, 10.17]	Campbell 2015, Table 3
MR CLEAN	76/233 (32.6%)	51/267 (19.1%)	2.05 [1.36, 3.09]	Berkhemer 2015, Table 2
REVASCAT	45/103 (43.7%)	29/103 (28.2%)	1.98 [1.11, 3.53]	Jovin 2015, Table 2
SWIFT PRIME	59/98 (60.2%)	33/93 (35.5%)	2.75 [1.53, 4.94]	Saver 2015, Table 2
All trials	292/633 (46.1%)	170/645 (26.4%)	2.39 [1.88, 3.04], p<0.00001	

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio

a) OR [95% CI] calculated using Review Manager 5.3 for this submission.

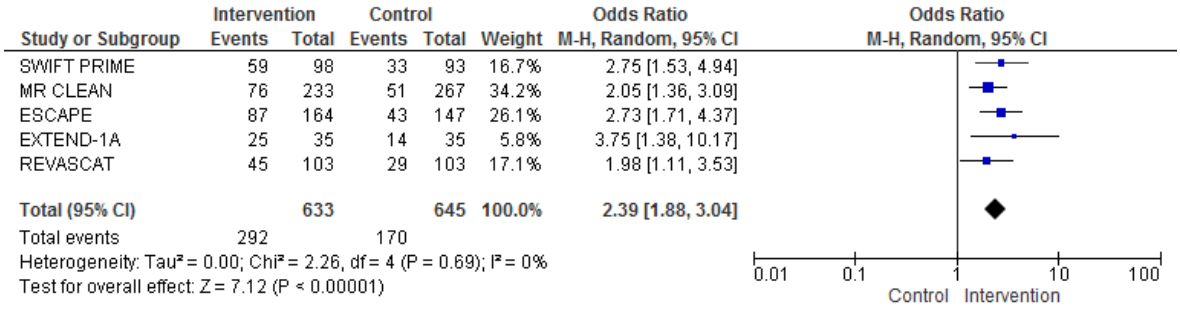


Figure 6 Forest plot representation of the mRS score 0-2 at 90 days

Mortality at 90 days

The mortality rate at 90 days in each trial is presented in Table 30 and Figure 7. Overall, 15.3% of patients in the intervention treatment arm compared to 18.8% of patients in the control arm had died at 90 days. This difference was not statistically significant with an OR=0.78 (95% CI: 0.54, 1.12), p=0.18.

Table 30 Mortality at 90 days

Trial ID	Intervention n /N (%)	Control n /N (%)	OR [95% CI][a]	Source
ESCAPE	17/165 (10.4)	28/147 (19.0)	0.49 [0.26, 0.93]	Goyal 2015, Table 2
EXTEND-IA	3/35 (9)	7/35 (20)	0.38 [0.09, 1.59]	Campbell 2015, Table 3
MR CLEAN	49/233 (21)	59/267 (22)	0.94 [0.61, 1.44]	Berkhemer 2015, Figure 1
REVASCAT	19/103 (18.4)	16/103 (15.5)	1.23 [0.59, 2.55]	Jovin 2015, Table 4
SWIFT PRIME	9/98 (9)	12/97 (12)	0.72 [0.29, 1.79]	Saver 2015, Table 2
All trials	97/634 (15.3)	122/649 (18.8)	0.78 [0.54, 1.12], p=0.18	

Abbreviations: CI, confidence interval; OR, odds ratio

a) OR [95% CI] calculated using Review Manager 5.3 for this submission.

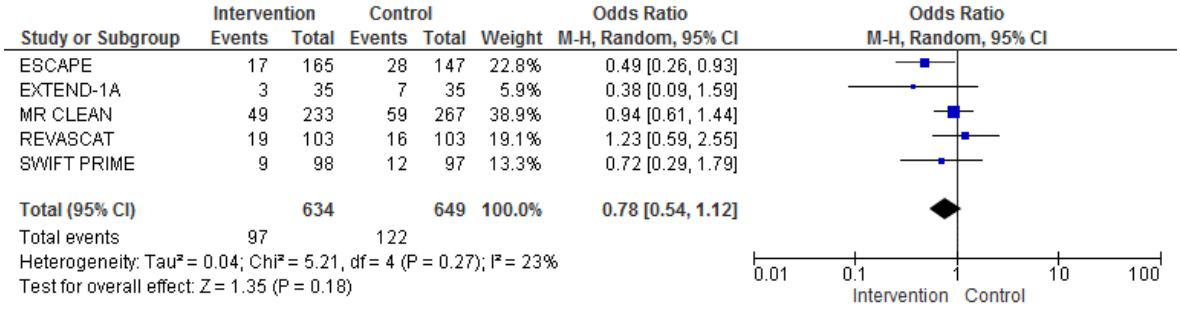


Figure 7 Forest plot representation of mortality at 90 days

NIHSS

One of the co-primary endpoints in the EXTEND-IA trial was early neurologic improvement defined as a reduction of 8 points or more on the NIHSS or a score of 0 or 1 at 3 days. A greater proportion of subjects (80%) in the intervention treatment arm achieved early neurologic improvement compared to the control arm (37%). In ESCAPE, there was a greater proportion of subjects (51.6%) in the intervention treatment arm with a NIHSS score of 0-2 at 90 days, indicating mild impairment post-stroke, compared to the control arm (23.1%), where post-stroke impairment was more severe (Table 31).

Table 31 Proportion of subjects with NIHSS score

Trial ID	Treatment n /N (%)	Control n /N (%)	Definition	Source
ESCAPE	79/153 (51.6)	31/134 (23.1)	NIHSS score of 0–2 at 90 days	Goyal 2015, Table 2
EXTEND-IA	28/35 (80)	13/35(37)	Reduction of 8 points or more on NIHSS score or a score of 0 or 1 at 3 days[a]	Campbell 2015, Table 3

a. Co-primary endpoint in EXTEND-IA.

The median NIHSS score at 24 hours in ESCAPE and MR CLEAN ranged from 2 and 6 in the intervention treatment arm indicating mild impairment post-stroke. In the control arm the median NIHSS score at 24 hours was between 8 and 13, indicating mild to moderately severe impairment. The median NIHSS score at 90 days in ESCAPE and REVASCAT was 2 in the intervention treatment arm indicating mild impairment post-stroke. In the control arm the median NIHSS score at 90 days was between 6 and 8, indicating mild to moderately severe impairment. The median NIHSS score at 5-7 days or at discharge was 8 in the intervention treatment arm and 14 in the control arm (Table 32).

Table 32 Scores on the NIHSS

Trial ID	Intervention Median score [IQR]	Control Median score [IQR]	Definition	Source
ESCAPE	6 (3 - 14)	13 (6 - 18)	NIHSS score at 24 hours	Goyal 2015, Table 2
	2 (1 - 8)	8 (3 - 19)	NIHSS score at 90 days	
MR CLEAN	13 (6 - 20)	16 (12 - 21)	NIHSS score after 24 hours	Berkhemer 2015, Table 2
	8 (2 - 17)	14 (7 - 18)	NIHSS score at 5–7 days or discharge	
REVASCAT	2.0 (0 - 8)	6.0 (2 - 11)	NIHSS score at 90 days	Jovin 2015, Table 2

The change in NIHSS score at 27 hours after randomisation was reported in SWIFT PRIME and was -8.5 (SD=7.1) in the intervention treatment arm and -3.9 (SD=6.2) in the control arm (Table 33). This difference was statistically significant (p<0.001) (Saver 2015, Table 2).

Table 33 Change in NIHSS

Trial ID	Treatment		Control		Definition	Source
	n /N (%)	Mean change (SD)	n /N (%)	Mean change (SD)		
SWIFT PRIME	97/98 (99)	-8.5 (7.1)	92/98 (94)	-3.9 (6.2)	Change in NIHSS score at 27 hr	Saver 2015, Table 2

Barthel Index

The proportion of subjects in ESCAPE and REVASCAT with a Barthel Index score of 95-100 at 90 days was greater in the intervention treatment arm (57.5%), compared to the control arm (30%). Similarly, a greater proportion of subjects (46%) in the intervention treatment arm had a Barthel Index score of 19 or 20 at 90 days compared to the control arm (29.8%) in MR CLEAN (Table 34).

Table 34 Barthel Index

Trial ID	Treatment n /N (%)	Control n /N (%)	Definition	Source
ESCAPE	94/163 (57.7)	49/146 (33.6)	Barthel Index score of 95–100 at 90 days	Goyal 2015, Table 2
MR CLEAN	99/215 (46.0)	73/245 (29.8)	Barthel Index of 19 or 20 at 90 days	Berkhemer 2015, Table 2
REVASCAT	47/82 (57.3)	23/87 (26.4)	Barthel Index score of 95 to 100 at 90 days	Jovin 2015, Table 2

Revascularisation

Across four trials (ESCAPE, EXTEND-IA, MR CLEAN and REVASCAT), between 58.7% and 86% of patients who received MT treatment obtained a TICI score of 2b or 3, which indicates successful perfusion (Table 35).

Table 35 A Thrombolysis in Cerebral Infarction (TICI) score

Trial ID	Treatment n /N (%)	Definition	Source
ESCAPE	113/156 (72.4)	TICI score of 2b or 3 at final angiogram	Goyal 2015, Table 2
EXTEND-IA	11/29 (38) (Grade 2b) 14/29 (48) (Grade 3)	mTICI score of 2b or 3	Campbell 2015, Table 2
MR CLEAN	115/196 (58.7)	mTICI score of 2b or 3	Berkhemer 2015, p.17
REVASCAT	37 (35.9) (Grade 2b) 45/103 (43.7) (Grade 3)	mTICI score of 2b or 3 post-treatment	Jovin 2015 Appendix, Table S5

Reperfusion

One of the co-primary outcomes in EXTEND-IA was median reperfusion at 24 hours, defined as the percentage reduction in the perfusion-lesion volume between initial imaging and imaging at 24 hours (which can be negative if hypoperfusion worsens). There was 100% (IQR: 100 – 100) reduction in the perfusion-lesion volume for patients treated with intervention treatment, compared to 37% reduction for those in the control arm (Table 36).

Table 36 Median reperfusion

Trial ID	Intervention Median score [IQR]	Control Median score [IQR]	OR [95% CI][a]	Source
EXTEND-IA	100 (100 to 100)	37 (−0.5 to 96)	4.9 (2.5 to 9.5) p <0.001	Campbell 2015, Table 3

The proportion of subjects in EXTEND-IA that achieved >90% reperfusion at 24 hr without SICH was higher for those treated with interventional treatment (88.6%) compared to control arm (34.3%). Substantial reperfusion immediately after thrombectomy was achieved in 88.0% of participants in SWIFT PRIME (control arm results not available). Furthermore, successful reperfusion at 27 hours was achieved in 82.8% of participants after MT, compared to 40.4% of participants who only received the control treatment (Table 37).

Table 37 Proprotion of sbjects achieveing reperfusion

Trial ID	Treatment n /N (%)	Control n /N (%)	Definition	Source
EXTEND-IA	88.6%	34.3%	Reperfusion of >90% at 24 hr without SICH	Campbell 2015, Table 3
SWIFT PRIME	88.0%	NA	Substantial reperfusion immediately after thrombectomy	Saver 2015, Table 2
SWIFT PRIME	82.8%	40.4%	Successful reperfusion at 27 hr[b]	Saver 2015, Table 2

a. Substantial reperfusion was defined as reperfusion of at least 50% and a modified TICI score of 2b (50 to 99% reperfusion) or 3 (complete reperfusion).

b. Successful reperfusion was defined as reperfusion of at least 90%, as assessed with the use of perfusion CT or MRI. Data on successful reperfusion were not obtained for all the patients after the adoption of the protocol amendment making penumbral imaging optional.

EQ-5D

The EQ-5D at 90 days ranged between 0.65 and 0.69 for intervention treatment arm and 0.32 to 0.66 for the control arm. The EQ-5D VAS score was higher for intervention treatment compared to control (80 vs. 60) (Table 38).

Table 38 ED-5D scores at 90 days

Trial ID	Intervention Median score [IQR]	Control Median score [IQR]	Definition	Source
ESCAPE	80 (60–90)	65 (50-80)	EQ-5D VAS score at 90 days	Goyal 2015, Table 2
MR CLEAN	0.69 (0.33 to 0.85)	0.66 (0.30 to 0.81)	EQ-5D score at 90 days	Berkhemer 2015, Table 2
REVASCAT	0.65 (0.21 to 0.79)	0.32 (0.13 to 0.70)	EQ-5D score at 90 days	Jovin 2015, Table 2

B.6.3 Safety data

Table 55 summarises the adverse events reported across the five included trials. SICH was reported to be between 3.6% and 7.7% of patient's in the intervention arm compared to 2.7% and 6.4% in the control arm. Hematoma at access site occurred in the intervention arm 1.8-10.7%. Procedural complications were low (<3%). Parenchymal hematoma was reported in between 5% and 11% of patients in the intervention arm compared to 5.8% and 9% in the control arm. Subarachnoid haemorrhage was reported in between 0.9% and 4.9% of patients in the intervention arm compared to 0% and 1.9% in the control arm. Two studies reported the incidence of new ischaemic stroke (MR CLEAN and REVASCAT). In MR CLEAN, patients treated with MT experienced a higher rate of recurrent stroke compared with usual care (5.6% vs 0.4%); however in REVASCAT the rates of recurrent stroke were similar in both study arms (3.9% vs 2.9%). It should be noted that since this outcome was measured within the 90-day duration of the study, any adverse effects on functional outcomes are also captured in the primary outcome (90-day mRS).

Overall, the safety data suggest that MT is associated with an increased risk of certain complications; in particular, procedural complications and hematoma. However, these risks should be balanced against the poor prognosis of many patients with AIS and the net benefits of treatment with MT in terms of functional outcomes.

Table 39 Summary of adverse events

Trial ID	ESCAPE n(%)		EXTEND-IA n(%)		MR CLEAN n(%)		REVASCAT n(%)		SWIFT PRIME n(%)	
Treatment arm	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
N	165	150	35	35	233	267	103	103	98	97
Any serious event at 90 days	NR	NR	NR	NR	110 (47.2)	113 (42.3)	NR	NR	35 (36)	30 (31)
SICH	6 (3.6)	4 (2.7)	0	2 (6)	18 (7.7)	17 (6.4)	7 (6.8)	4 (3.8)	0	3 (3)
Hematoma at access site	3 (1.8)	0	1 (2.9)	0	NR	NR	11 (10.7)	0	NR	NR
Procedural complications	1 (0.6)[a]	0	1 (2.9)[b]	0	26 (11.2)[c]	NR	19 (18.4)[d]	NR	3 (3.1)[e]	3 (3.1)[e]
Parenchymal heamatoma	NR	NR	4 (11)	3(9)	14 (6.0)	16 (5.9)	6 (5.8)	6 (5.8)	5 (5)	7 (7)
Subarachnoid haemorrhage	NR	NR	NR	NR	2 (0.9)	0	5 (4.9)	2 (1.9)	4 (4)	1(1)
New ischaemic stroke	NR	NR	NR	NR	13 (5.6)	1 (0.4)	4 (3.9)	3 (2.9)	NR	NR

a. Perforation of the middle cerebral artery.

b.Bleeding was caused by perforation by a wire during angiography and before deployment of the Solitaire FR stent retriever.

c.Embolization into new territories outside the target downstream territory of the occluded vessel, procedure-related vessel dissections and vessel perforations.

d. Distal embolisation in a different territory, arterial dissection, aterial perforation, groin pseudoaneurysm and vasospasm requiring treatment.

e. Injury, poisoning and procedural complications.

B.7 Extended assessment of comparative harms

There appear to be no long-term follow-up studies documenting adverse events with regards to the use of MT beyond three months. Therefore the long-term safety profile of MT relative to usual care is expected to be similar to the 90-day safety profile reported in the clinical trials.

B.8 Interpretation of the clinical evidence

Efficacy and safety

Overall, 46.1% of patients in the intervention treatment arm compared to 26.4% of patients in the control arm possessed a mRS score of 0-2 at 90 days. A mRS score of 0-2 indicated functional independence. This difference was statistically significant with an OR=2.39 (95% CI: 1.88, 3.04), p<0.0001.

In general, the included trials also demonstrated a greater proportion of subjects who achieved early neurologic improvement, possessed milder impairment post-stroke and higher Barthel Index score compared to the control arm. Additionally, there was 100% reduction in the perfusion-lesion volume for patients treated with intervention treatment, compared to 37% reduction for those in the control arm.

Overall, 15.3% of patients in the intervention treatment arm compared to 18.8% of patients in the control arm had died at 90 days. This difference was not statistically significant with an OR=0.78 (95% CI: 0.54, 1.12), p=0.18.

Outcome	Intervention	Control	OR [95% CI]
	n /N (%)	n /N (%)	
mRS score reduction (shift analysis)	-	-	2.26 (1.67, 3.06) p<0·0001[a]
mRS score 0-2 at 90 days	292/633 (46.1%)	170/645 (26.4%)	2.39 [1.88, 3.04], p<0.00001[b]
Mortality at 90 days	97/634 (15.3)	122/649 (18.8)	0.78 [0.54, 1.12], p=0.18[b]

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; OR, odds ratio

c) Common odds ratio indicating the odds of improvement of one point on the mRS;

d) OR [95% CI] calculated using Review Manager 5.3 for this submission.

Appropriate form of economic evaluation

The evidence presented in Section B clearly demonstrates that treatment with MT in addition to usual care is superior to usual care alone in terms of effectiveness and non-inferior in terms of safety. A modelled cost-utility analysis is presented to support the cost-effectiveness of MT in addition to usual care.

C. TRANSLATING THE CLINICAL EVALUATION TO THE LISTING REQUESTED FOR INCLUSION IN THE ECONOMIC EVALUATION

Summary

- The submission presents subgroup analyses from an IPD meta-analysis of the five eligible RCTs of MT vs usual care. The results show the efficacy of MT is consistent across several key patient/circumstances of use subgroups, supporting the use of an ITT approach in the base case of the economic evaluation.
- For patients who are eligible for IV-tPA, the baseline characteristics of patients in the Australian EXTEND-IA study appear to be similar to those of the meta-analysed IPD population. Patients who are contraindicated to IV-tPA in the pivotal trials are also likely to reflect Australian patients. This further supports the use of an ITT approach in the economic evaluation.
- The base case ICER is expressed in terms of costs per additional QALY. Utility values are identified via a literature review. The base case values are informed by Sturm et al (2002), reporting utility values from the North East Melbourne Stroke Incidence Study (NEMESIS). While providing Australian estimates, this may be conservative; a sensitivity analysis will present an ICER of $8500 (based on Rivero-Arias et al 2010; vs $12,880 in the base case analysis).
- The proposed MBS fee is $3500. The total per-procedural cost is $18,308.49.
- Cost savings as a result of superior functional outcomes offered by MT are estimated based on the published evidence, identified via a literature review. Expectedly, patients with mRS 5 (i.e., bedridden, incontinent, constant care) incur far more costly care ($17,943 per annum) than those who are less dependent (e.g., $1,431 per annum for mRS 0-1) even in the long run (Gloede et al 2014; see Section C.5).
- Extrapolation is an important element of the Section D model because much of the functional benefits offered by MT over usual care at Day 90 (i.e., demonstrated through RCT evidence) will persist into the future. The model accounts for the risk of stroke recurrence and changes in mRS (e.g., “rehabilitation” effects) beyond the trial data availability, as informed by the published evidence (see Section C.6 and C.7).
- The modelling of stroke recurrence and associated mRS transitions adds considerable complexity to the model; it otherwise has a readily understood, pragmatic design (i.e., in principle, simply following post-stroke mRS changes over time). Sensitivity analysis explores alternative model designs without the explicit modelling of recurrent stroke (but the published long-term mRS data are assumed to have already captured the impacts of stroke recurrence); returning ICERs of $8801-$15,953, providing further confidence to MT’s favourable cost-effectiveness of MT (see Section C.7 and Section D).

C.1 Identification of issues to be addressed

Translation issues addressed in Section C are summarised in Table 40 below.

Applicability issues address the relevance of the clinical trial data to the requested MBS listing, and the likely Australian population. These issues are important because, while the overall evidence base from the 5 RCTs as a whole would be able to provide adequate and

applicable clinical evidence for MSAC's consideration, each of these studies individually may raise applicability concerns in terms of patient characteristics and circumstances of use.

Key transformation issues presented in the submission include the identification of utility values and cost data. Because the economic model relies on clinical data that demonstrate improvements in post-stroke functional outcomes, these inputs needed to be reported by post-stroke disability levels (e.g., by mRS scores).

Finally, extrapolation is an important element of the Section D model because the benefits offered by MT over usual care will persist into the future. This is particularly relevant for a fair assessment of MT's cost-effectiveness because all intervention costs are absorbed at baseline, while its cost / health benefits are accrued in the long run. Therefore, the submission includes separate pre-modelling studies to address long-term risk of stroke recurrence and functional outcomes (including mortality).

Table 40 Summary of translation issues

Issue	Identification of issue	Research question	Pre-modelling study
Applicability issues			
Issue 1: Applicability of the clinical trial data to the requested MBS listing (Section C.2)	The targeted population is relatively broad, limited only to "patients with confirmed diagnosis of acute ischaemic stroke caused by large vessel occlusion of the anterior circulation". Despite demonstrating uniformly favourable results for MT relative to usual care, each of the 5 pivotal RCTs had some differences in terms of the populations enrolled and circumstances of use.	What is the relationship between population / circumstances of use variables and the clinical efficacy of MT, and therefore the applicability of the clinical trial evidence to the proposed MBS listing?	The submission presents subgroup analyses from an IPD meta-analysis of the five eligible RCTs of MT vs usual care. The results show the efficacy of MT is consistent across several key patient/circumstances of use subgroups, supporting the use of an ITT approach in the base case of the economic evaluation.
Issue 2: Applicability of clinical trial data to Australian patients with AIS (Section C.3)	Whilst Issue 1 investigates the applicability of the clinical trial data to the proposed MBS listing through assessing the impact of potential clinical effect modifiers, Section C.3 focusses on the applicability of the trial data to Australian patients who would be considered eligible for MT.	Are the patients enrolled in the pivotal clinical trials similar to those who are likely to receive MT in Australian clinical practice?	The pre-modelling study compares the characteristics of all trial participants in the pivotal five RCTs to Australian patients in the EXTEND-IA trial (which was undertaken in solely in Australia and New Zealand). Overall, the baseline characteristics of patients in the EXTEND-IA study appear to be similar to those of the meta-analysed IPD population. Patients who are contraindicated to IV-tPA in the pivotal trials are also likely to reflect Australian patients. This further supports the use of an ITT approach in the economic evaluation.
Transformation issues			

<table>
<tr><th>Issue</th><th>Identification of issue</th><th>Research question</th><th>Pre-modelling study</th></tr>
<tr><td>Issue 3: Selection of utility data
(Section C.4)</td><td>The Section D model employs a Markov model structure and health states are defined according to the mRS state. Two RCTs, MR CLEAN and REVACAST, reported EQ-5D at 90 days. No stratification by post-stroke disability levels was however reported in the aforementioned two RCTs.</td><td>What are the utility values in patients with different mRS values?</td><td>A literature search was undertaken to identify relevant studies. An Australian study by Sturm et al (2002) was selected as the base case source of utility values. Utility values reported in this study are as follows:
<table>
<tr><td>Post-stroke disability by mRS</td><td>Utility score</td></tr>
<tr><td>mRS 0</td><td>0.63</td></tr>
<tr><td>mRS 1</td><td>0.63</td></tr>
<tr><td>mRS 2</td><td>0.40</td></tr>
<tr><td>mRS 3</td><td>0.18</td></tr>
<tr><td>mRS 4</td><td>0.06</td></tr>
<tr><td>mRS 5</td><td>0.02</td></tr>
<tr><td>mRS 6</td><td>0</td></tr>
</table>
These estimates were well corroborated with other estimates in the literature.</td></tr>
<tr><td>Issue 4: Selection of cost data
(Section C.5)</td><td>MT is taken as being “additional” to the care currently provided as usual care.
Management of stroke disability is costly. Functional outcomes are likely to affect the costs of stroke care in acute / mid-term (to 12 months) / long-term (post 12 months), suggesting that MT would offer long-term cost benefits over usual care.</td><td>What is the per procedure cost of MT?
What are the acute/12-month/long-term costs by mRS score?</td><td>The total cost of MT per procedures is $18,308.49.
The cost of stroke care by mRS and time frame (i.e., acute/mid-term/long-term) were derived from the literature.</td></tr>
<tr><td colspan="4">Extrapolation issues</td></tr>
<tr><td>Issue 5: Risk of recurrent stroke
(Section C.6)</td><td>Extrapolation is an important element of the Section D model. To accurately reflect the cost / health implications experienced by patients who have undergone MT (or usual care), the recurrence of stroke among these patients should be considered.</td><td>What is the risk of recurrent stroke among AIS patients?</td><td>A literature search was undertaken. Mohan et al (2011) performed a systematic review which reported the cumulative risk of recurrent stroke was 14.3% at 5 years. The recurrence risk is applied regardless of mRS (no evidence reported that the recurrence risk is mRS dependent).</td></tr>
</table>

Issue	Identification of issue	Research question	Pre-modelling study
Issue 6: Long-term transitions in mRS scores (Section C.7)	Much of the functional benefits offered by MT over usual care at Day 90 (i.e., the availability of RCT evidence) will persist into the future, and for many patients these functional benefits (and thus their QoL and cost implications) are permanent. However, the Section D model should explicitly consider any improvement (i.e., rehabilitation effects) or further deterioration of functional outcomes post Day 90 (i.e., the limit of RCT data availability).	What are long-term functional outcomes in stroke patients by mRS?	A literature search was undertaken. Overall, the observational long-term data in the literature show that patients with poorer functional status (i.e., mRS 4-5) are very unlikely to exhibit any improvement in their functional status, while patients with favourable status are likely to experience "rehabilitation" effects over time or maintain their functional ability. The base case Section D analysis will be informed by Gensicke et al, 2013, a Swiss observational study with 3 year follow-up (n=257).

Abbreviations: MT, mechanical thrombectomy; mRS, modified Rankin score; RCT, randomised control trial; AIS, acute ischaemic stroke.

C.2 Applicability of clinical trial data to the requested MBS listing

The requested MBS listing presented in Section A.2.3 of this submission is as follows:

"*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*".

The evidence base to support this listing consists of efficacy data from five RCTs of MT versus "usual care", with usual care comprising either intravenous tissue plasminogen activator (IV-tPA) for indicated patients, or medical management with anti-thrombotic therapy for patients contraindicated to IV-tPA. The results of these pivotal studies (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME and REVASCAT) demonstrate that mechanical thrombectomy significantly and consistently improves functional outcomes (without compromising safety) in patients with acute ischaemic stroke due to anterior circulation, large artery occlusion, compared with usual care. The meta-analysis of the five studies presented in Section B.6 of this submission showed that the odds ratio (OR) for achieving functional independence (90-day mRS of 0-2) was 2.42 (95% CI: 1.91, 3.08). This analysis was based on a 633 patients that received MT and 650 patients in the control arm.

Despite demonstrating uniformly favourable results for MT relative to usual care, there were some differences between the studies in terms of patient characteristics and circumstances of use represented by each trial. Table 41 below provides a summary of the eligibility criteria for the aforementioned characteristics in each of the five clinical trials presented in Section B. In particular, there was variability between and within the trials in relation to the neurological deficit of patients at baseline (NIHSS score), age, size of the ischaemic core (usually measured by ASPECTS), pre-stroke function (measured by mRS), the site of vessel occlusion, and time from stroke onset to the delivery of the intervention. The majority of trials also included a small proportion of patients who were ineligible of IV-tPA (MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT). In these patients the main comparison of interest for this submission is MT versus usual care (or medical management with anti-thrombotic therapy).

Table 41 Inclusion criteria for eligible RCTs of MT

Study ID	Patient characteristics					Circumstances of use	
	Age (yrs)	Site of occlusion	NIHSS	Pre-stroke function	ASPECTS or core size	Time to randomisation or groin puncture	Includes patients ineligible for IV-tPA
MR CLEAN	>18	ICA, M1, M2 (anterior circulation)	>2	None	None	6 hours to groin	Y
ESCAPE	>18	ICA, M1	>5	Barthel ≥90	ASPECTS 6-10	12 hours to randomisation	Y
EXTEND-IA	≥18	ICA, M1, M2 (anterior circulation)	None	mRS 0-1	Ischaemic core <70mL	6 hours to groin complete in 8 hours	N
SWIFT PRIME	18-80	ICA, M1	8-29	mRS 0-1	Ischaemic core <50 mL (1st 72 or MRI) ASPECTS 6-10 (remaining 125 pts)	6 hours to groin	Y
REVASCAT	18-80 (85)	ICA, M1	≥6	mRS 0-1	ASPECTS 6-10	8 hours to groin	Y

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; CTP, CT perfusion; DWI, diffusion weighted imaging; ICA, internal carotid artery; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale

Based on the aforementioned within-trial eligibility criteria, some clinical practice guidelines have restricted their recommendations for MT to certain subpopulations. For example, the AHA/ASA guidelines (Powers et al, 2015) further recommend limiting the use of MT to patients with pre-stroke mRS score 0–1, 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. This guideline also states there is inadequate data for a recommendation for endovascular therapy in patients with time or non-time based contraindications to IV-tPA (Powers et al, 2015). The EUnetHTA also cites insufficient evidence for this patient group EUnetHTA, 2015). However, in practice, use of mechanical thrombectomy in selected patients beyond six hours of stroke onset may be determined appropriate by treating clinicians - where clinical assessment indicates the patient is likely to benefit from treatment (i.e. evidence of salvageable brain).

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. Hence, the population targeted in this submission is

relatively broad, limited only to "*patients with confirmed diagnosis of acute ischaemic stroke caused by large vessel occlusion*". This reflects the aim of clinical practice: to identify all patients with LVO ischaemic stroke who could potentially benefit from mechanical thrombectomy.

Therefore, this pre-modelling study aims to examine the relationship between population variables and the clinical efficacy of MT, thus establishing the applicability of the clinical trial evidence to the proposed MBS listing. In addition to applicability of the trial population, this Section C issue also addresses important applicability issues around circumstances of use, e.g. concurrent use of IV-tPA, types of pre-procedural imaging tests, and time to the commencement of procedure.

Note that this pre-modelling study examines the applicability of trial evidence to the requested MBS listing by assessing the importance of potential effect modifiers. Another pre-modelling study presented in Section C.3 specifically examines the applicability of the trial population to Australian patients who would likely become eligible for MT under the proposed listing by comparing the patient characteristics in the pivotal RCTs with those in the EXTEND-IA trial (which was undertaken solely in Australia and New Zealand).

C.2.1 Focused analytical plan

Approach to the pre-modelling study

The main approach used in this pre-modelling study is assessing the clinical efficacy of MT in various subpopulations. More specifically, the pre-modelling study presents data from a recently published meta-analysis of IPD from the five eligible studies of MT also presented in Section B of this submission (Goyal et al, 2016). This analysis was performed by the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration, which was funded by Medtronic but conducted independently by investigators from the RCTs included in the meta-analysis. The group's objective was to provide additional information about the degree of precision of adjusted effect size estimates, safety outcome estimates, and estimates by clinical subgroups.

The patient variables considered in this IPD meta-analysis were selected on the basis of qualitative and quantitative differences between the trial protocols. These include demographic characteristics such as age and sex, and disease characteristics such as baseline stroke severity (based on NIHSS), baseline ASPECTS and location of the occlusion (ICA, M1 or M2). The pre-modelling study also compares the imaging techniques used to select patients in the pivotal trials with those likely to be used in the Australian healthcare setting.

Importantly, the IPD meta-analysis includes a subgroup analysis for patients that did and did not receive IV-tPA. This is a particularly relevant issue in the context of this submission, as the proposed MBS population includes patients that are eligible and ineligible for treatment with IV-tPA. The efficacy of MT in this subgroup of patients is further supported by data from registry and observational studies that include a large number of patients receiving mechanical thrombectomy without concomitant IV-tPA.

Methodology of the IPD meta-analysis (Goyal et al, 2016)

The main research question for the IPD meta-analysis was "*Do patients with acute ischaemic stroke and proximal anterior circulation occlusions benefit from additional mechanical thrombectomy compared with standard care (which includes IV-tPA in eligible patients)?*" (Goyal et al, 2016). The full report for the IPD analysis is provided with the submission as Appendix C; however, the methods are summarised below.

The study included controlled trials in endovascular stroke therapy that used brain imaging to identify patients with anterior circulation ischaemic stroke and assessed treatment with modern neurothrombectomy devices. The five studies that fit these criteria are the same five RCTs that are presented in Section B of this submission: MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA. The IPD analysis included pooled patient-level data from each of these trials.

The pre-specified primary outcome in the meta-analysis was the degree of disability on the mRS at 90 days. In statistical modelling of the full mRS, scores of 5 (severe disability) and 6 (death) were merged into a single category.

Pre-specified secondary outcomes were:

- Proportion of patients with functional independence (mRS 0–2) at 90 days
- Stroke severity as measured with the NIHSS at 24 h after stroke onset
- Proportion of patients with NIHSS score 0–2 at 24 h
- Proportion of patients with major early neurological recovery at 24 h, defined as a reduction in NIHSS score from baseline of at least 8 points or reaching 0-1
- Change in NIHSS score from baseline to 24 h
- Technical efficacy was assessed through the degree of revascularisation at the end of the endovascular procedure, defined using the mTICI scale score of 2b or 3 (corresponding to reperfusion of at least 50% of the affected vascular territory)

Safety outcomes were:

- Proportion of patients with symptomatic ICH (as defined by each trial)

- Neuroradiological parenchymal haematoma type 2 (blood clot occupying >30% of the infarcted territory with substantial mass effect) within 5 days
- Mortality within 90 days.

The statistical analyses used a mixed methods ordinal logistic regression with "trial" and “trial*treatment” as random effects variables. Unadjusted and adjusted analyses were presented; the pre-specified covariates included in the adjusted analysis included age, sex, baseline stroke severity, site of occlusion, IV-tPA (yes/no), ASPECTS score, and time to randomisation.

Finally, the IPD meta-analysis aimed to identify treatment effect modifiers by undertaking subgroup analyses based on clinically relevant variables. These were undertaken for the primary outcome (mRS at 90 days) as well as mRS 0-2 vs. 3-6 at 90 days, and mortality at 90 days.

Subgroup analyses for the following variables were reported:

1. Age
    a. Dichotomised at 18-79 vs. 80 and older
    b. More granularly divided as: 18-49, 50-59, 60-69, 70-79, 80 and older
    c. Continuous
2. Sex (Male vs. Female)
3. Baseline Stroke Severity, NIHSS: <10, 11-15, 16-20, >20 Baseline Stroke Severity, NIHSS: continuous
4. Time from onset to endovascular treatment strategy selection (randomisation): 0-300 minutes vs. greater than 300 minutes
5. Baseline ASPECTS as trichotomy – 0-5, 6-8, 9-10
6. Baseline site of thrombi on vascular imaging (trichotomous: ICA, M1, M2) as adjudicated by core lab
7. Concomitant ipsilateral carotid artery occlusion or carotid artery stenosis (yes vs no)
8. IV-tPA (yes vs. no)

The efficacy of MT in the ITT population and relevant subpopulations are discussed in the results section below. The potential clinical effect modifiers are categorised as:

- Population applicability issues, including age and sex, baseline stroke severity based on NIHSS, the size and extent of the infarct based on ASPECTS and location of the occlusion (ICA, M1 or M2); and
- Circumstances of use applicability issues, including time to delivery of the

intervention, eligibility for IV-tPA and type of imaging tests used in patient selection.

Note that the IPD analysis by Goyal et al (2016) did not examine the impact of different imaging strategies to select patients on clinical efficacy. Nonetheless, imaging remains an important element of patient selection; in fact, the use of up-to-date non-invasive arterial imaging is one of the factors attributed to the success of recent studies of MT when compared to earlier thrombectomy trials (Vo et al, 2015). Therefore, the use of different imaging modalities is included as a potential effect modifier despite the fact that it was not explicitly assessed in the IPD meta-analysis by Goyal et al (2016).

C.2.2 Results of the pre-modelling study

Efficacy of MT in the ITT population

The IPD meta-analysis included 1,287 patients including 634 assigned to MT and 653 assigned to usual care. The number of patients assigned to MT corresponds exactly to the number in the combined ITT populations for the five eligible studies presented in Section B of this submission. However, the number of patients assigned to usual care in the IPD meta-analysis is slightly higher than that reported for the five combined studies in Section B (653 vs. 648). The reason for this discrepancy is unclear.

Table 42 presents the efficacy outcomes from the meta-analysis for the ITT population. The primary outcome is reported as a common OR, which indicates the odds that the intervention would lead to improvement of 1 or more points on the mRS in a shift analysis. This analysis shows reduced chance of disability at 90 days in patients assigned to thrombectomy versus those assigned to control (common OR 2·26, 95% CI 1·67, 3·06; p<0·0001).

Similarly, the proportion of patients achieving functional independence (mRS 0-2) at 90 days was higher in the endovascular thrombectomy population than in the control population (common OR 2·35, 95% CI 1.85, 2.98; p<0·0001). This result is very close to the aggregate-level meta-analysis presented in Section B.6.2 of this submission, which reports an OR for functional independence of 2.39 (95% CI: 1.88, 3.04).

The IPD meta-analysis also demonstrated large differences in favour of MT for the proportions of patients with an NIHSS score 0-2 at 24 hrs, and neurological recovery at 24 hrs.

Table 42 Efficacy outcomes from IPD meta-analysis

Outcome	MT (n/N)	Control (n/N)	RD (%)	RR (95% CI)	OR (95% CI)	Adjusted RR (95% CI)	Adjusted OR (95% CI)
Primary outcome							
mRS score reduction (shift analysis)[a]	NA	NA	NA	NA	2·26 (1·67, 3·06) p<0·0001 [a]	NA	2·49 (1·76, 3·53) p<0·0001 [a]
Secondary outcomes							
mRS 0-2 at 90 days	46·0% (291/633)	26·5% (171/645)	19·5	1·7 (1·41, 2·05) p<0·0001	2·35 (1·85, 2·98) p<0·0001	1·73 (1·43, 2·09) p<0·0001	2·71 (2·07, 3·55) p<0·0001
NIHSS score 0-2 at 24 hrs	21·0% (129/615)	8·3% (52/630)	12·7	2·47 (1·79, 3·41) p<0·0001	2·91 (2·06, 4·12) p<0·0001	2·66 (1·92, 3·67) p<0·0001	3·77 (2·49, 5·71) p<0·0001
Early neurological recovery at 24 hrs	50·2% (309/616)	21·2% (134/633)	29·0	2·34 (1·91, 2·87) p<0·0001	4·04 (2·75, 5·93) p<0·0001	2·34 (1·91, 2·87) p<0·0001	4·36 (3·03, 6·27) p<0·0001

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale

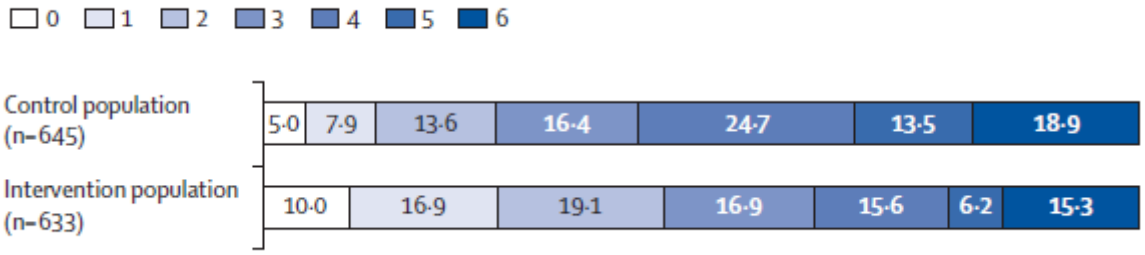
[a] Common odds raio indicating the odds of improvement of one point on the mRS; OR, odds ratio; RD, risk difference; RR, rate ratio

Source: Goyal et al (2016); Table 2

The distributions of patients in different mRS categories at 90 days in the IPD meta-analysis and aggregate-level meta-analysis are presented in Figure 8 and Figure 9, respectively. Overall, the results reported by Goyal et al (2016) are very similar to those presented in Section B of this submission.

It should be noted that IPD meta-analyses can improve the quality of data and produce more reliable results, and for this reason they are considered to be a 'gold standard' for systematic review methodology (Riley et al, 2010). The Cochrane Collaboration notes that the main advantages of adopting an IPD approach relate mostly to improving quality of the data and/or the quality of the analysis. Data quality can be improved through the inclusion of all trials and all randomised participants and detailed checking. Participant level data also allows more comprehensive and appropriate analyses such as time-to-event and subgroup analyses. The collaborative nature of the projects may help achieve a more global and balanced interpretation of the meta-analysis results as well as providing a basis for future collaborations on primary research (Cochrane Collaboration, 2016). On this basis, the results of the IPD meta-analysis were selected for inclusion in the base case economic evaluation presented in Section D of this submission.

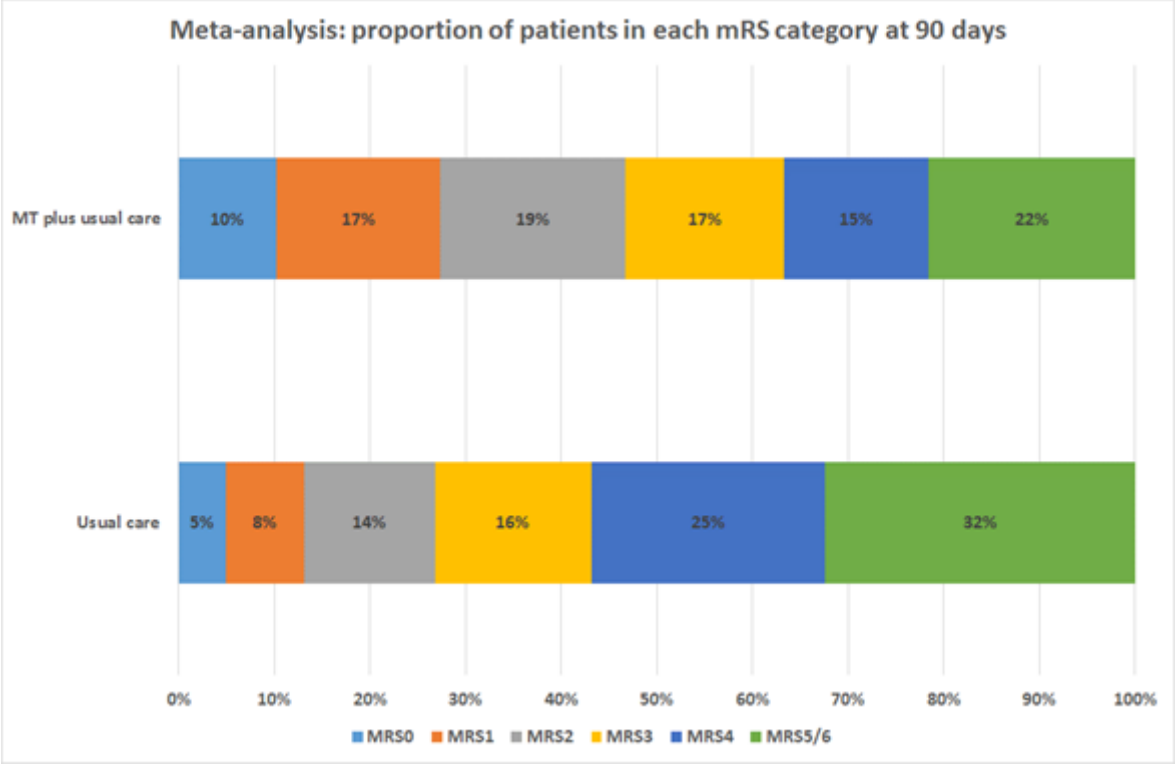
Figure 8 Scores on the mRS in the IPD meta-analysis



Abbreviations: IPD, individual patient data; mRS, modified Rankin Scale

Source: Goyal et al (2016); Figure 1

Figure 9 Scores on the mRS in the aggregate-level meta-analysis



Abbreviations: mRS, modified Rankin Scale

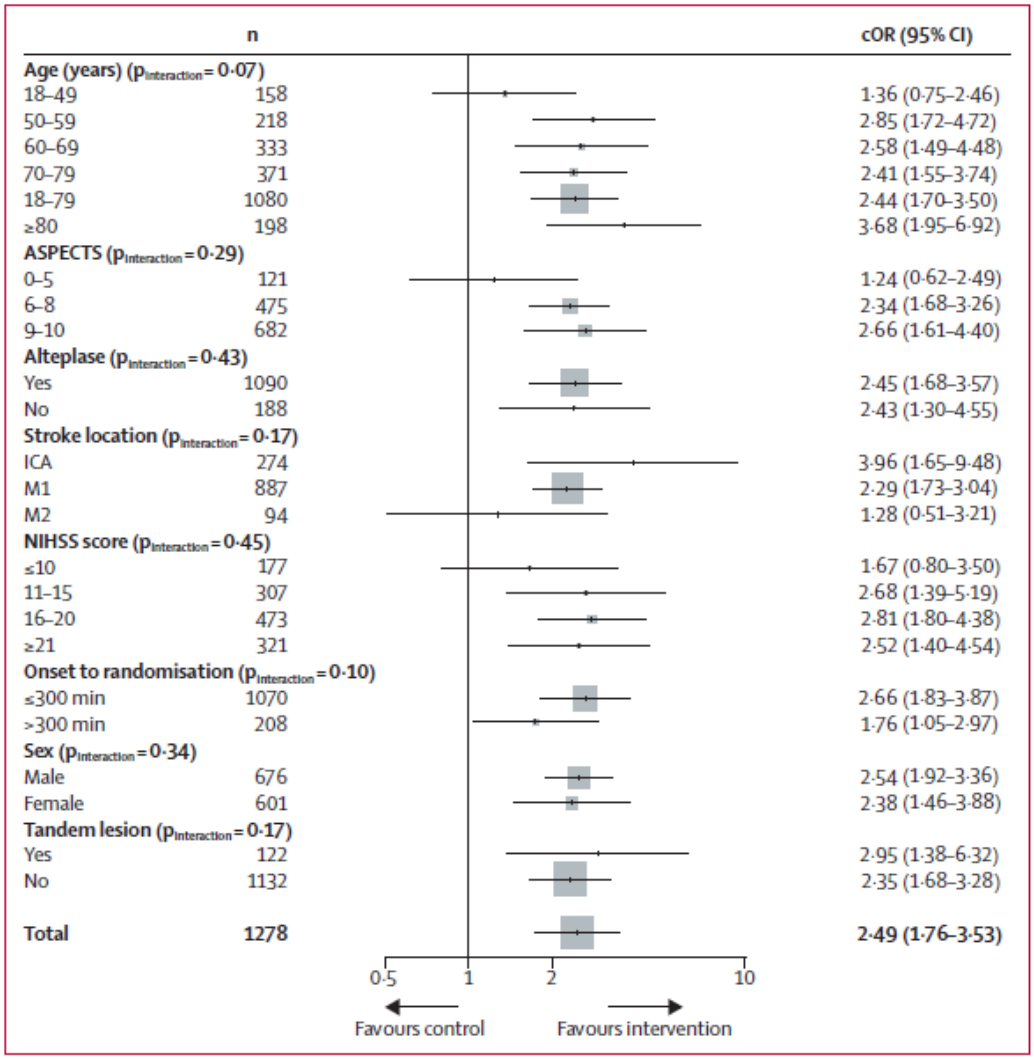
Source: Section B.6.1; Figure 4

Potential clinical effect modifiers

Figure 10 is a forest plot showing the adjusted treatment effect for mRS at 90 days in pre-specified subgroups within the pooled trial populations. The outcomes are reported as a common OR, which indicates the odds that the intervention would lead to improvement of 1 or more points on the mRS in a shift analysis. Overall, the data suggest the efficacy of MT is relatively consistent in patients with different demographic and disease characteristics. None of the potential effect modifiers examined in the IPD analysis were associated with a statistically significant probability of interaction ($p<0.05$).

The impact of various potential clinical effect modifiers are discussed in further detail under the headings below. These include: population characteristics, such as age and sex, baseline stroke severity (based on NIHSS), the size and extent of the infarct (based on ASPECTS) and location of the occlusion (ICA, M1 or M2); and variables related to circumstances of use, including time to delivery of the intervention and eligibility for IV-tPA.

Figure 10 Forest plot showing adjusted treatment effect for mRS at 90 days in pre-specified subgroups (cOR that the intervention would lead to improvement of ≥ 1 point on the mRS)



Abbreviations: cOR, common odds ratio; mRS, modified Rankin scale; ASPECTS, Alberta Stroke Program Early CT score; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale
Source: Goyal et al, 2016; Figure 2

Population applicability issues

Age and sex

Very elderly patients are at a higher risk of poor outcomes compared to younger patients;

and early retrospective studies of thrombectomy reported a high rate of mortality in patients aged over 80 years (Villwock et al, 2014). However, in the recent cohort of RCTs of MT versus usual care, results for the primary outcome were relatively consistent across the different age categories with a trend towards greater clinical efficacy relative to the control in patients aged 80 years or over, and decreased clinical efficacy the relatively small subgroup of patients (n=158) aged 18-49 years. On this basis, age is not considered a treatment effect modifier for MT relative to IV-tPA. Accordingly, clinical practice guidelines recommend that “high age alone is not a reason to withhold mechanical thrombectomy as an adjunctive treatment” (ESO, 2014)

The effects of the intervention were roughly equal in males and females.

Disease characteristics

Contrary to previous studies that have identified patients with most severe strokes (baseline NIHSS score ≥20) as deriving most benefit from MT (Almekhlafi et al, 2014), this IPD analysis shows a similar effect on disability across the entire NIHSS severity range. However, few patients with minor strokes were available for analysis. The authors suggest that in clinical practice, treatment of patients with mild strokes and confirmed LVO should be determined based on specific clinical and radiological features of the individual case, bearing in mind the risk of subsequent clinical deterioration with best medical therapy in patients with LVO.

The extent of pre-treatment infarction on baseline imaging (determined by ASPECTS) has been recognised as a critical predictor of clinical outcome in patients treated with reperfusion therapies. For that reason, most studies exclude patients who present with signs of a large infarct on baseline brain imaging. In the IPD analysis, similar benefits were observed in patients with high baseline ASPECTS (9–10) and those with moderate baseline ASPECTS (6–8). Clinical data from a small subgroup with more extensive irreversible injury (ASPECTS 0-5) found a small benefit associated with endovascular therapy; however, the effect was not statistically significant (common OR 1.24, 95% CI 0.62-2.49).

In terms of location of the occlusion, the results suggest the relative clinical efficacy of MT is greatest in patients with occlusions in the ICA (common OR 3.96, 95% CI 1.65-9.49). Patients with occlusions in the M1 segment of the middle cerebral artery also derive a substantial and statistically significant benefit (common OR 2.29, 95% CI 1.73-3.04), while the benefit in patients with occlusions of the M2 middle cerebral artery segment remains inconclusive due to the small sample size. Three of the five included trials restricted

enrolment to patients with more proximal occlusions and the remaining two enrolled only a few patients with distal occlusions. Furthermore, most of the patients with M2 occlusions included in the IPD analysis were misclassified as having M1 occlusion at the time of enrolment, and were subsequently adjudicated by the core lab as M2 occlusion. These adjusted patients are therefore likely to include a disproportionate proportion of proximal and large M2 occlusions. These off-target enrolments highlight the challenge associated with poor standardisation in distinguishing between M1 and M2 segment stroke.

Circumstances of use applicability issues

Time to delivery of intervention

Table 41 shows that although the majority of trials specified that MT should be administered within 6 hours of stroke onset, one study (ESCAPE) allowed patients to be randomised up to 12 hours after onset, and another permitted groin puncture up to 8 hours after onset (REVASCAT). Aggregate data from REVASCAT and ESCAPE with treatment permitted out to 8 and 12 hours show a benefit, but ESCAPE enrolled too few patients after 6 hours to provide useful data and REVASCAT provides no data about patients who underwent groin puncture between 6 and 8 hours. How much the net benefit in these two trials was driven by those treated at shorter times is unclear (Powers et al, 2015). Of note, the positive effect in the MR CLEAN trial was time-dependent, with adjusted common OR decreasing from 3.0 (95% CI: 1.6–5.6) at 3.5 hours after onset to reperfusion time, to 1.5 (95% CI: 1.1–2.2) at 6 hours (Berkhemer et al, 2015).

The IPD meta-analysis aimed to assess the impact of process times by dichotomising patients according to whether they were randomised before or after 300 minutes. Figure 10 shows the intervention had greater relative clinical efficacy in patients randomised fewer than 300 minutes from stroke symptom onset. This generally corresponds to start of the endovascular procedure less than 8 hours from symptom onset, which is within the 8-hour TGA-approved window for treatment for many endovascular devices, but outside the 6-hour window recommended by the Australian NSF guidelines (NSF, 2010).

Therefore, there remains some uncertainty about the magnitude of the benefit of MT in patients who receive the intervention 8 hours after stroke onset; however it should be noted that even in this subgroup of patients, there remains a statistically significant benefit relative to usual care. These findings underline the necessity to treat as early as possible; and after 6 hours from stroke onset the decision to administer MT should be made in consideration of other patient factors such as imaging identifying salvageable brain, showing likelihood of good neurological outcomes

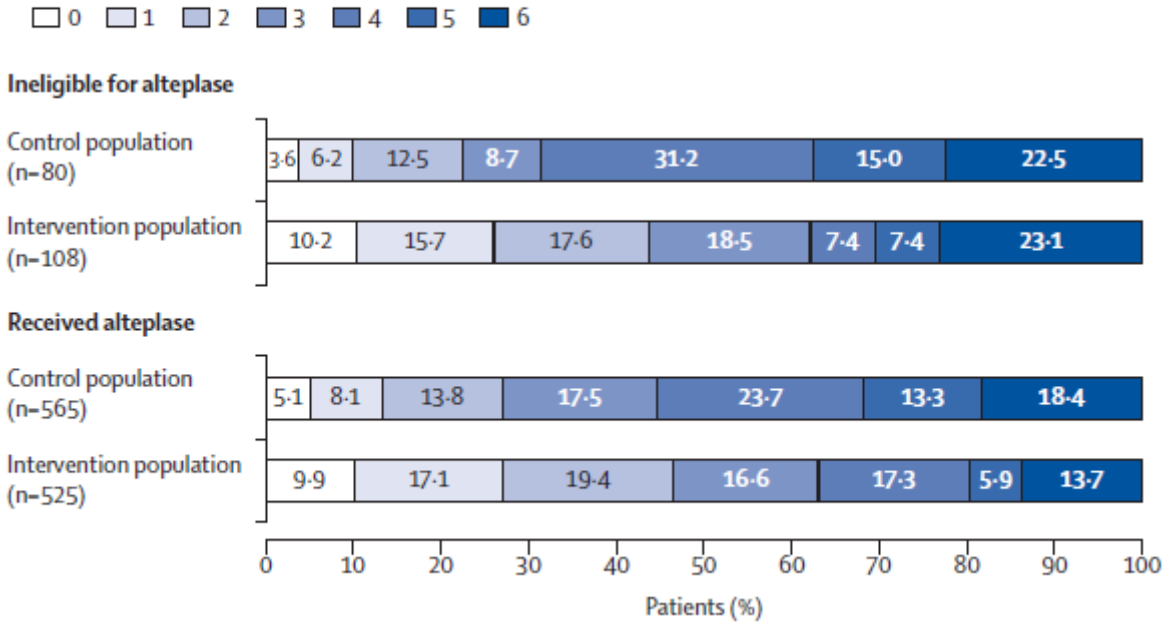
It should also be noted that one of the included studies (REVASCAT) included patients who did not respond to or were contraindicated to V tPA. As such, patients enrolled in the control arm of this studies were essentially "refractory" to IV-tPA, with very low rates of good outcomes. In effect this approach considers whether its possible to minimise unnecessary treatment with MT (i.e. determine whether patient responds to IV-tPA before deciding whether MT is necessary). However, this approach can also cause critical delays in the time to reperfusion (Lee and Demchuk, 2015). On this basis, clinical practice guidelines specifically recommend *"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)"* (Powers et al, 2015).

Eligibility for IV-tPA

Finally, the IPD analysis provides the best available evidence for the relative efficacy of MT in patients that did and did not receive IV-tPA. Whilst four of the five RCTs included in the meta-analysis enrolled some patients that were ineligible for treatment with IV-tPA (SWIFT PRIME, MR CLEAN, ESCAPE and REVASCAT), individually they were not sufficiently powered to assess the benefit of endovascular therapy in this subgroup. By comparison, the IPD meta-analysis of 188 IV-tPA ineligible patients showed a statistically significant benefit in this group of patients, with a similar effect size to that of the ITT population. On the basis of these data, the authors conclude "*this finding does not mean that alteplase should be withheld before thrombectomy in alteplase-eligible patients. Rather, endovascular reperfusion should be pursued for LVO AIS, irrespective of eligibility for alteplase*" (Goyal et al, 2016).

Figure 11 presents the distribution of scores on the mRS after 90 days for patients that were eligible or ineligible for IV-tPA. Notably there are differences between the control arms of the two groups, suggesting that ineligibility for IV-tPA is a risk factor for a very poor outcome (mRS 5-6). However, in both populations, the intervention results in a higher proportion of patients who are functionally independent, with mRS scores of 0-2. As discussed above, this translates to similar odds of an improvement of 1 or more points on the mRS in a shift analysis.

Figure 11 Distribution of scores on the mRS by eligibility for alteplase



Abbreviations: mRS, modified Rankin Scale

Source: Goyal et al (2016); Figure 1

The results reported in the IPD meta-analysis are supported by evidence from observational studies and registries. The Solitaire Flow Restoration Thrombectomy for Acute Revascularization (STAR) study was an international, prospective, single-arm study of MT in patients with large vessel anterior circulation strokes treated within 8 hours of symptom onset (Pereira et al, 2013). The study included a substantial proportion (41%) of patients who were treated directly with MT, i.e. without IV-tPA. At some study sites, primary inclusion of patients to thrombectomy, despite eligibility for IV-tPA, was performed on the basis of local standard stroke treatment protocol. The primary end point was the revascularization rate (thrombolysis in cerebral infarction ≥2b) of the occluded vessel as determined by an independent core laboratory. The secondary end point was the rate of good functional outcome (defined as 90-day modified Rankin scale, 0–2). These results, presented in Table 43 below, also show similar overall rates of efficacy in patients who received MT plus IV-tPA, and MT alone. The overall rates of functional independence at 90 days are slightly higher than those observed in the ITT population of the IPD meta-analysis (57.9% vs. 46%).

Table 43 Efficacy outcomes from STAR study

Outcome	ITT (n/N)	MT + IV-tPA (n/N)	MT (n/N)	p-value
TICI revascularisation				
0	4.7% (9/190)	4.5% (5/110)	5.0% (4/80)	0.989
1	0.5% (1/190)	0.9% (1/110)	0.0% (0/80)	
2a	10.5% (20/190)	10.0% (11/110)	11.3% (9/80)	
2b	29.5% (56/190)	29.1% (32/110)	30.0% (24/80)	
3	54.7% (104/190)	55.5% (61/110)	53.8% (43/80)	
mRS 0-2 at 90 days	57.9% (117/202)	62.2% (74/119)	51.8% (43/83)	0.150

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale

[a] Common odds raio indicating the odds of improvement of one point on the mRS; OR, odds ratio; RD, risk difference; RR, rate ratio

Source: Goyal et al (2016); Table 2

Imaging tests in patient selection

The IPD analysis by Goyal et al (2016) did not examine the impact of different imaging strategies to select patients on clinical efficacy. However, it should be noted that manner used to determine patient eligibility is less important than the actual disease characteristics of the selected population (e.g. in terms of stroke location and severity). As described under the heading above, the efficacy of MT relative to usual care was relatively consistent in patients with varying disease severity, size and extent of the infarct and location of the occlusion.

Nonetheless, imaging remains an important element of patient selection; in fact, the use of up-to-date non-invasive arterial imaging is one of the factors attributed to the success of recent studies of MT when compared to earlier thrombectomy trials (Vo et al, 2015). Therefore, this applicability study compares the imaging techniques used in the pivotal clinical trials of MT those expected to be used in Australian clinical practice.

Table 44 summarises the imaging inclusion criteria of the five RCTs considered eligible for inclusion in this submission. Overall, angiography using CTA or MRA was the most widely used approach to vascular imaging and detection of LVO – in most cases for the detection of the occlusion and determining the core infarct size. This approach is supported by a systematic review by Badhiwala et al (2015), which included earlier RCTs of MT with less advanced imaging strategies (SYNTHESIS, MR RESCUE, IMS-III). This analysis found that functional outcomes were significantly better among patients with angiographic imaging (CTA or MRA) confirming proximal arterial occlusion (OR, 2.24; 95% CI, 1.72-2.90, p for interaction <0.001).

Whilst it is possible to use either CT or MR-based imaging for most parameters, CT-based

modalities have numerous advantages including widespread availability, rapid processing times. A number of studies also used perfusion imaging in order to establish target mismatch and collaterals. These concepts are described in Section A.5.1, in the summary of clinical practice guidelines and Australian protocols.

Table 44 Patient selection for included studies

Imaging	MR CLEAN	ESCAPE	EXTEND-IA	SWIFT PRIME	REVASCAT
Vascular imaging	CTA, MRA, DSA	CTA	CTA, MRA	CTA,MRA	CTA, MRA, DSA
Other imaging (core size, mismatch, collaterals)	~60% CT perfusion	Multiphase CTA or CT perfusion for detection of core size and collaterals	CT/MRI perfusion including "mismatch"	CT perfusion or multimodal MRI to identify target mismatch (first 71 patients) CT or MRI ASPECTS ≥6 for remaining 125 ~83% CT perfusion	CT perfusion, CTA-source or MRI-DWI required if > 4.5 hrs

Abbreviations: CT, computed tomography; CTA, CT angiography; DSA, digital subtraction angiography; DWI, diffusion weighted imaging; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging

As described in Section A.5.1, the recently-developed Victorian statewide service protocol for endovascular clot retrieval recommends routine brain imaging for AIS should include a non-contrast CT brain and CTA from the aortic arch to the vertex. CT perfusion is recommended primarily in patients who are treated 6-8 hours after stroke onset and who are at high risk of "futile" MT. However, it should be noted that this form of advanced imaging is associated with several important limitations, including lack of standardisation, effect of motion and the potential to introduce delays in the decision-making process (Cougo-Pinto et al, 2015). Even where optimised, the use of CT perfusion can consume time (Zerna et al, 2015) – and treatment delays should be avoided to optimise time to reperfusion and likelihood of good neurological outcomes.

On this basis, it is expected that the use of MT in Australia will broadly align with the Victorian protocol which emphasises the use of non-contrast CT and CTA. As discussed above, clinical trial evidence from the five eligible RCTs shows this approach to selecting patients results in a substantial clinical benefit. Furthermore, IPD subgroup analyses show that the relative effect size for MT relative to usual care is consistent across a range of disease characteristics.

C.2.3 Relationship of the pre-modelling study to the economic model

The balance of evidence presented in the current pre-modelling study supports that the efficacy of MT is generally consistent across several key patient/circumstances of use subgroups, demonstrating a satisfactory applicability of the available clinical data to the MBS context overall. This also supports the application of an "ITT" approach as the base

case analysis in generating cost-effectiveness evidence for MT in Section D.

The results of the IPD meta-analysis by Goyal et al (2016) suggest the efficacy of MT is consistent in patients with different demographic and disease characteristics. None of the potential effect modifiers examined in the IPD analysis were associated with a statistically significant probability of interaction ($p<0.05$); however, it is possible that some smaller subgroups may benefit less from therapy, whilst acknowledging uncertain predictive power of these findings due to their small sample sizes. These include patients with a younger age (18-49 years), low ASPECTS (0-5), and those with an occlusion site in the M2 segment of the middle cerebral artery. In addition, it is likely that longer time to the administration of therapy reduces the relative efficacy of MT, highlighting the need to ensure that patients are treated as soon as possible after stroke onset, as outlined in current clinical practice guidelines (NSF, 2010). Of course, these potential negative effect modifications are offset by positive effect modifications observed in their complementary subgroups.

Overall, the diagnostic imaging approaches used in the five eligible RCTs are applicable to the Australian health care setting, where it is expected that eligibility for MT will be established primarily on the basis of non-contrast CT and CT angiography. For some patients, CT perfusion imaging may be used to improve diagnostic sensitivity for ischaemic stroke and identify the extent of irreversible injury. However, the use of this form of advanced imaging should be considered in the context of potential time-delays and a lack of consensus regarding CT perfusion parameters used to assess the extent of salvageable brain tissue (Zerna et al, 2015).

Importantly, the IPD meta-analysis confirms the clinical efficacy of endovascular therapy in the absence of IV-tPA. This conclusion is based on an analysis of 188 patients from four out of the five eligible RCTs. These results suggest the benefits of MT relative to medical management are similar to the benefits of MT plus IV-tPA compared to IV-tPA alone. This observation is supported by the results of the STAR prospective study, including a large proportion of patients who received direct MT (i.e. patients with contraindications to IV-tPA) (Pereira et al, 2013).

It should be noted that IPD meta-analyses can improve the quality of data and produce more reliable results, and for this reason they are considered to be a ‘gold standard’ for systematic review methodology (Riley et al, 2010). In particular, IPD meta-analysis facilitates investigation of specific subgroups of patients and differential treatment effects can be assessed across individuals, which can help reduce study heterogeneity.

As set out above, the clinical data used in the base case Section D model are therefore the meta-analysed IPD of the ITT population. Section D.4 will present all relevant clinical data for the cost-effectiveness analysis. A series of sensitivity analyses will be performed to explore key subgroups and individual RCTs.

Additionally, the control data from the pivotal RCTs are used to inform the usual care arm of the Section D model. *This assumes that the care provided in the control arms of the trials are overall representative of the care likely provided in the absence of MT in the Australian clinical practice.* It is expected that the provision of MT would be restricted to "centres of excellence" in acute stroke care due to the infrastructure and clinical staff requirements (see Section E.1). As discussed in Section A.3.1, the usual care provided in these centres is well standardised (through the use of 'code' stroke teams and protocols) and, importantly, is likely to be generalisable to the high level of care provided in the pivotal RCTs.

C.3 Applicability of clinical trial data to Australian patients with acute ischaemic stroke

C.3.1 Focused analytical plan

The five trials included in Section B of this submission and the IPD meta-analysis presented in Section C.2 were conducted across a range of settings and health care systems. SWIFT PRIME was conducted in 39 centres in the USA and Europe, MR CLEAN was conducted in 16 sites in the Netherlands, ESCAPE was undertaken in 22 sites across Canada, Europe the USA and Asia, REVASCAT was undertaken in four Spanish centres and EXTEND-IA was conducted in nine Australian sites and one centre in New Zealand. Additionally, because the studies were predominantly undertaken by expert, high-throughput, neuroscience-based stroke centres and in highly selected patients raises the possibility of potential selection bias.

Whilst Section C.2 investigates the applicability of the clinical trial data to the proposed MBS listing through assessing the impact of potential clinical effect modifiers, Section C.3 focusses on the applicability of the trial data to Australian patients who would be considered eligible for MT.

To address this issue, this pre-modelling study compares the characteristics of all included trial participants in the pivotal five RCTs to Australian patients in the EXTEND-IA trial (which was undertaken in solely in Australia and New Zealand). EXTEND-IA was the only eligible RCT of MT in which all patients received alteplase treatment in the intervention and comparator arms. Therefore the data from this particular trial are not

applicable to the patient group that is ineligible for treatment with IV-tPA. To address the applicability of population ineligible for IV-tPA, the submission presents a comparison of subgroup data for patients that did and did not receive intravenous alteplase in the MR CLEAN trial. In addition, the pre-modelling study explores the reasons why patients are contraindicated for IV-tPA in the pivotal trials and in clinical practice.

C.3.2 Results of the pre-modelling study

Patients eligible for IV-tPA

The baseline characteristics of the ITT population of the IPD analysis of the five included studies, and those of the EXTEND-IA population alone, are presented in Table 45 (Goyal, 2016; Table 1).

Both populations were well-balanced across the two arms of the analysis. In the IPD meta-analysis, the median age of patients across the five studies is 68 years, with a slightly higher proportion of men than women. Demographic characteristics of the 70 patients included in the EXTEND-IA trial were similar, with a mean age of ~69 years and an almost even number of men and women.

Patients in both analyses had a similar distribution of comorbidities, with over half of the patients with a history of hypertension, a third with a history of atrial fibrillation and a third assessed as recent or current smokers. In terms of clinical characteristics, the mean baseline NIHSS score at baseline was similar in both datasets, as were the distributions of the location of occlusions. The five eligible studies included a range of treatment protocols, and as such, the process times (in particular, time to administration of IV-tPA) ranged from 74 to 140 minutes. By comparison, the process times in the EXTEND-IA study were slightly longer, with a median of 127-145 minutes. Nonetheless, in both groups the median time to alteplase treatment was well within the timeframe of 4.5 hours (270 minutes) recommended by most CPGs (NSF, 2010).

Table 45 Baseline characteristics in the pooled data

Characteristic	IPD ITT population		EXTEND-IA	
	Intervention population (n=634)	Control population (n=653)	Intervention population (n=35)	Control population (n=35)
Demographic characteristics				
Median/mean age (IQR/SD)	68 (57–77)	68 (59–76) (n=650)	70.2 (11.8)	68.6 (12.3)
Men – n (%)	330 (52)	352 (54)	17 (49)	17 (49)
Medical history				
Hypertension – n (%)	352 (56)	388 (59)	23 (66)	21 (60)
Diabetes mellitus – n (%)	82 (13)	88 (13)	8 (23)	2 (6)
Atrial fibrillation – n (%)	209 (33)	215 (33)	11 (31)	12 (34)
Smoking (recent or current) – n (%)	194 (31)	210 (32)	15 (43)	12 (34)
Clinical characteristics				
Baseline NIHSS score – median (IQR)	17 (14–20) (n=631)	17 (13–21) (n=648)	13 (9–19)	17 (13–20)
Baseline blood glucose – median (IQR)	6·6 (5·9–7·8) (n=620)	6·7 (5·9–7·8) (n=644)	7.6 (3.6)	7.1 (2.5)
Imaging characteristics				
ASPECTS on baseline CT	9 (7–10) (n=620)	9 (8–10) (n=644)	NR	NR
Intra-cranial occlusion location – n (%)				
ICA	133 (21)	144 (22)	11 (31)	11 (31)
M1 (MCA)	439 (69)	452 (69)	18 (51)	20 (57)
M2 (MCA)	51 (8)	44 (7)	6 (17)	4 (11)
Other	11 (2)	13 (2)		
Treatment details and process times				
Treatment with IV alteplase – n (%)	526 (83)	569 (87)	35 (100)	35 (100)
Treatment with IV alteplase within 180 minutes – n (%)	442 (70)	462 (71)	NR	NR
Process times (min) – median (IQR)				
Median onset to randomisation	195·5 (142–260) (n=632)	196 (142–270) (n=650)	NR	NR
Median onset to IV alteplase	100 (75–133) (n=598)	100 (74–140) (n=618)	145 (105–180)	127 (93–162)
Median onset to reperfusion	285 (210–362)	NA	NR	NR
Median time from onset to hospital arrival	NR	NR	80 (56–115)	78 (54–112)

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; ICA, internal carotid artery;,National Institute of Health Stroke Scale

Data are median (IQR), n (%), or mean (SD)

Source: Goyal et al, 2016; Table 1

Patients ineligible for IV-tPA

The EXTEND-IA trial required all patients to receive IV-tPA; therefore the comparison presented above does not address the applicability of study participants that were ineligible to IV-tPA to the corresponding Australian population. The main publications for the remaining studies of MT (SWIFT, MR CLEAN, ESCAPE, REVASCAT) did not provide baseline data for the subgroup of patients that were ineligible for IV-tPA. However, a recent publication of the MR CLEAN study performed a subgroup analysis of patients with contraindications for intravenous alteplase treatment (Mulder et al, 2016).

Overall, 55 of 500 patients (11%) in the study were not treated with intravenous alteplase. The baseline characteristics of these patients are presented in Table 46 below. In general patients in the IV-tPA-ineligible cohort were older and more often had atrial fibrillation or other vascular comorbidity. Patients in this group were also much more likely to be taking an anticoagulant, which is consistent with the fact that this is a contraindication for thrombolytic therapy. However, in terms of the location of the occlusion and stroke severity (measured by NIHSS), both groups were very similar.

Despite minor differences between the groups in terms of baseline characteristics, the analysis found no interaction between IV-tPA and treatment effect (p=9.27). In addition, the effect size in patients not treated with IV-tPA was similar to that in patients treated with IV-tPA. Once potential confounders were adjusted for, the common odds ratio for MT in patients treated with IV-tPA was of 1.71 (95% CI: 1.2-2.4) compared to 2.06 (95% CI: 0.7-6.1) in patients that weren't. These results support the conclusions of the IPD meta-analysis presented in Section C.2, suggesting that the efficacy of MT treatment is not modified in patients that are in ineligible for IV-tPA.

Table 46 Baseline characteristics of patients ineligible for IV-tPA in MR CLEAN

Characteristic	IV-tPA eligible (n=55)	IV-tPA ineligible (n=500)
Median/mean age – median (IQR)	65.4 (54.3-76.2)	67.5 (61.5-77.8)
Men – n (%)	257 (58)	35 (64)
Baseline NIHSS score – median (IQR)	18 (14-22)	19 (14-22)
Clinical localization: left hemisphere – n (%)	239 (54)	30 (55)
Atrial fibrillation – n (%)	105 (24)	30 (55)
History of ischaemic stroke – n (%)	43 (10)	11 (20)
History of hypertension – n (%)	194 (44)	33 (60)
History of diabetes mellitus – n (%)	56 (13)	12 (22)
History of myocardial infarction – n (%)	69 (16)	6 (11)
History of peripheral artery disease – n (%)	17 (4)	7 (13)
History of hyperlipidemia – n (%)	116 (26)	13 (24)
Current smoking – n (%)	129 (29)	14 (25)
Current statin use – n (%)	124 (28)	19 (35)
Current antiplatelet use – n (%)	135 (30)	9 (16)
Current anticoagulant use – n (%)	16 (4)	23 (42)
Systolic blood pressure – mean mmHg (SD)	146 (25)	144 (25)
Pre-stroke mRS – n (%)		
0	368 (83)	36 (65)
1	43 (10)	7 (13)
2	18 (4)	7 (13)
3	10 (2)	5 (9)
4	4 (1)	0
5	2 (0)	0
Intra-cranial occlusion location		
ICA	3 (1)	1 (2)
ICA-T	120 (27)	14 (25)
M1 (MCA)	282 (64)	37 (67)
M2 (MCA)	37 (8)	2 (4)
AI	2 (0)	1 (2)
Process times (min) – median (IQR)		
Median onset to IV alteplase	85 (65-110)	NA
Median onset to randomisation	201 (153-262)	191 (134-253)
Onset to IAT	265 (214-315)	242 (200-300)
Median onset to reperfusion	343 (283-394)	310 (242-404)
Duration of procedure	72 (52-97)	67 (43-88)

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; ICA, internal carotid artery;,National Institute of Health Stroke Scale

Data are median (IQR), n (%), or mean (SD)

Source: Goyal et al, 2016; Table 1

The subgroup analysis by Mulder et al (2016) also describes the contraindications and other reasons for no treatment with IV-tPA in the MR CLEAN study (Table 47). The table also presents data from a German retrospective observational study by Dorn et al (2015) which reports the efficacy of MT in a cohort of patients that did not receive IV-tPA. The majority of the reasons for ineligibility in both studies are similar to the PI-defined contraindications for alteplase therapy in Australia (Section A.6).

The reasons for ineligibility are also consistent with the Australian National Stroke Foundation (NSF) clinical practice guidelines, which recommend (Grade A) that IV-tPA should be administered as a first-line therapy in patients with AIS as early as possible, but no later than 4.5 hours after stroke onset (NSF, 2010). Mainly due to the high risk of haemorrhage, tPA is also contraindicated in patients that meet any of the following criteria:

- Severe, uncontrolled hypertension
- Previous surgery; widespread ischaemia
- Patient receiving oral anticoagulants with an international normalised ratio >1.3
- Intra-cranial bleeding
- Previous stroke within the past three months.

Although real world data on the reasons for ineligibility for IV-tPA are not available in an Australian healthcare setting, one can assume from clinical practice guidelines that the protocols used to select patients for this therapy are similar in existing trials of MT and in Australian clinical practice. The comparison of baseline characteristics presented in Mulder et al (2016) shows that this group of patients does not have disease characteristics that are markedly different to those of patients that were eligible for IV-tPA. Finally, the results of the MR CLEAN subgroup analysis and the IPD meta-analysis presented in Section C.2 show that irrespective of any differences between the two patient subgroups, the relative efficacy of MT is largely the same.

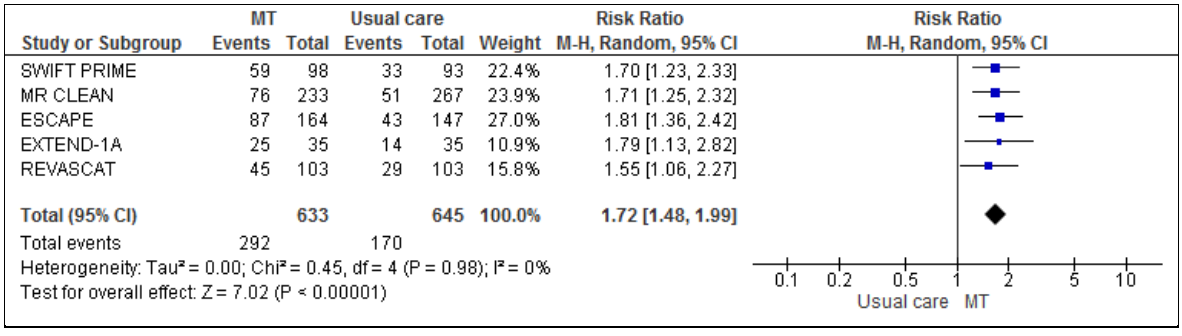
Table 47 Contraindications and other reasons for no treatment with IV-tPA in MR CLEAN

Contraindication	Mulder et al, 2016			Dorn et al, 2015 (n=130)
	Total IV-tPA eligible (n=55)	Intervention (n=30)	Control (n=25)	
INR 1.7-3.0	18 (33%)	12 (40%)	6 (24%)	44 (33.8%)
Platelet count <90 x 10^9/L	2 (4%)	1 (3%)	1 (4%)	NR
Recent surgery or intervention within two weeks prior to event	15 (27%)	7 (23%)	8 (32%)	Recent surgery: 23 (17.7%) Emergency stent-angioplasty: 10 (7.7%)
Recent ischaemic stroke within six weeks prior to event	4 (7%)	3 (10%)	1 (4%)	21 (16.2%)
Use of contraindicated anticoagulants	4 (7%)	2 (7%)	2 (8%)	IV heparin: 6 (4.6%)
Time from onset to arrival exceeds 4.5 hours	5 (9%)	3 (10%)	2 (8%)	NR
Cerebral contusion within four weeks prior to event	1 (2%)	1 (3%)	0 (0%)	NR
Other reasons	6 (11%)	1 (3%)	5 (20%)	26 (20%)

C.3.3 Relationship of the pre-modelling study to the economic model

Overall, the baseline characteristics of patients in the EXTEND-IA study appear to be similar to those of the meta-analysed IPD population, suggesting that the results of the meta-analysis are applicable to Australian patients that are eligible to receive IV-tPA. As shown in Figure 12 below, in the aggregate-level meta-analysis of the five eligible studies, the RR of patients achieving functional independence (mRS 0-2) at 90 days is very similar to the RR for EXTEND-IA alone. In fact, despite some heterogeneity in the study populations (as described in Section C.2) and trial settings, the results across the five included trials are remarkably consistent.

Figure 12 Meta-analysis of functional independence at 90 days



For patients that were ineligible for IV-tPA, this pre-modelling study shows that patients who are ineligible for IV-tPA are more likely to be slightly older and suffer vascular comorbidities; however the clinical efficacy of MT relative to untreated patients remains similar in this subgroup. Although there were no data specific to the Australian healthcare setting, it should be noted that the reasons for contraindication for IV-tPA observed in the trial are consistent with clinical practice guidelines used in Australia. Therefore, the results of the meta-analysis are also applicable to Australian patients that are ineligible to receive IV-tPA.

Collectively, these data further support the conclusion drawn in the previous pre-modelling study justifying the use of the meta-analysed ITT data to inform the base case Section D model for patients who are eligible and ineligible for IV-tPA. The ITT approach may also best reflect the applicability of the model outputs to the MBS population and circumstances of use by capturing the presence of heterogeneity expected to exist in real world.

Taken together, the data presented in this pre-modelling study and in Section C.2 suggest that the efficacy of MT relative to usual care is relatively robust to potential effect modifiers, and varies very little in different clinical settings. This also supports the circumstances of use applicability of the available trial data to the Australian setting. In particular, as also discussed above, it is expected that the provision of MT would be restricted to “centres of excellence” in acute stroke care due to the high infrastructure and clinical staff requirements (see Section E.1).

The usual care provided in these centres is typically would be by and large well standardised (through the use of ‘code’ stroke teams and protocols) and, importantly, is likely to be generalisable to the high level of care provided in the pivotal RCTs.

C.4 Selection of utility data

Two RCTs, MR CLEAN and REVACAST, reported the EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) utility at 90 days. The beta coefficient in the linear regression model of utility was the expected mean difference between two treatments. The adjusted beta coefficients (95% CI) in MR CLEAN (Berkhemer et al 2015) and REVASCAT (Jovin et al 2015) were 0.06 (-0.01 to 0.13) and 0.11 (0.02 to 0.21), respectively, favouring MT.

The Section D model employs a Markov model structure and health states are defined according to the modified Rankin scale (mRS) scores 0 to 5 (plus mRS 6 for death). The source of additional QALYs for MT vs usual care lies in that a greater proportion of

patients are in lower mRS health states in the MT arm over time when compared with the usual care arm (see Section D for further model description). No stratification by post-stroke disability levels was however reported in the aforementioned two RCTs.

Table 48 Modified Rankin Scale (mRS): Disability measurement used to define health states in the Section D cost-effectiveness model

Modified Rankin Scale
0: No symptoms at all
1: No significant disability despite symptoms; able to carry out all usual duties and activities
2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3: Moderate disability; requiring some help, but able to walk without assistance
4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6: Death

The following pre-modelling study clarifies utility inputs employed by the Section D model to inform QALY transformations of clinical outcomes.

C.4.1 Focused analytical plan

Literature review

A search of published literature for utility values was conducted. The search was conducted in PubMed on the 4th of April, 2016. The search strategy and results are provided in Table 49. As expected considering the amount of research that has been conducted in relation to the QoL evaluation of cardiovascular conditions such as stroke, a large number of citations were identified (n=822). The current pre-modelling study hence focused on systematic reviews reported in the literature.

Table 49 Search algorithm for utility values

Search	Query	Items found
#9	#8 AND #7	822 (of these, 69 identified with "Review" filter)
#8	Search stroke	246,487
#7	Search #6 OR #5 OR #4 OR #3 OR #2 OR #1	31,524
#6	Search ("Australian quality of life" or AQoL)	2338
#5	Search (HUI or "health utilities index")	14,769
#4	Search ("time tradeoff" OR "time trade off" OR tto)	1,402
#3	Search ("standard gamble")	720
#2	Search ("Short Form 6D" OR "sf 6d" OR sf6d)	561
#1	Search ("eq 5d" OR eq5d OR EuroQol OR "european quality of life")	13,127

Of the 69 citations identified by the literature search above, there were two systematic reviews (Smith et al 2013 and Post et al 2001). This pre-modelling study will focus on the Smith systematic because it provided far greater details than Post et al (2001). Post et al (2001) was also considered as being outdated.

For the purpose of this pre-modelling study, any utility data that were not preference-based utility values (i.e., health-related QoL scores, VAS scores, utility values that relied on transformations from a HRQoL instrument, or expert opinion) are excluded. In other words, only those utility estimates based on a direct preference elicitation method (time trade off, standard gamble, DCE) or a MAUI (EQ-5D, SF-6D, AQoL and HUI) are included. Importantly, this pre-modelling study will focus on utility values reported by functional levels to match the Section D model structure.

Smith et al (2013) included a total of 52 studies in their review for stroke utility values. According to Table 1 of the publication, the following studies reported utility values by stroke severity, as summarised in Table 50 below.

Table 50 Published evaluation studies that reported utility values by severity

Papers identified through Smith et al 2013; those reporting utility values by disability levels
Adams J, Lee J, Gonzalo F. Deriving utility values from the general population for dronedarone in the treatment of atrial fibrillation. Value Health 14(7), A384 (2011).
Baker R, Robinson A. Responses to standard gambles: are preferences 'well constructed'? Health Econ. 13(1), 37–48 (2004).
Dorman P, Dennis M, Sandercock P. Are the modified "simple questions" a valid and reliable measure of health-related quality of life after stroke? United Kingdom Collaborators in the International Stroke Trial. J. Neurol. Neurosurg. Psychiatry 69(4), 487–493 (2000).
Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Arch. Intern. Med. 156(16), 1829–1836 (1996).
Hallan S, Asberg A, Indredavik B, Wideroe TE. Quality of life after cerebrovascular stroke: a systematic study of patients' preferences for different functional outcomes. J. Intern. Med. 246(3), 309–316 (1999).
Lai SM, Duncan PW. Stroke recovery profile and the Modified Rankin assessment. Neuroepidemiology 20(1), 26–30 (2001).[1]
Murphy R, Sackley CM, Miller P, Harwood RH. Effect of experience of severe stroke on subjective valuations of quality of life after stroke. J. Neurol. Neurosurg. Psychiatry 70(5), 679–681 (2001).
Noto S, Uemura T, Izumi R, Moriwaki K. Construct validity of health utilities index (HUI) Japanese version: Cross-sectional study for stroke in Japan. Value Health 14(3), A45 (2011).
Robinson A, Thomson R, Parkin D, Sudlow M, Eccles M. How patients with atrial fibrillation value different health outcomes: a standard gamble study. J. Health Serv. Res. Policy 6(2), 92–98 (2001).
Shin AY, Porter PJ, Wallace MC, Naglie G. Quality of life of stroke in younger individuals: Utility assessment in patients with arteriovenous malformations. Stroke 28(12), 2395–2399 (1997).
Slot KB, Berge E. Thrombolytic treatment for stroke: patient preferences for treatment, information, and involvement. J. Stroke Cerebrovasc. Dis. 18(1), 17–22 (2009).

Papers identified through Smith et al 2013; those reporting utility values by disability levels
Tengs TO, Lin TH. A meta-analysis of quality of life estimates for stroke. Pharmacoeconomics 21(3), 191–200 (2003).
Tengs TO, Yu M, Luistro E. Health-related quality of life after stroke a comprehensive review. Stroke 32(4), 964–972 (2001).
van Exel NJ, Scholte op Reimer WJ, Koopmanschap MA. Assessment of post-stroke quality of life in cost-effectiveness studies: the usefulness of the Barthel Index and the EuroQoL-5D. Qual. Life Res. 13(2), 427–433 (2004).
Warren JA, Jordan WD, Jr., Heudebert GR, Whitley D, Wirthlin DJ. Determining patient preference for treatment of extracranial carotid artery stenosis: carotid angioplasty and stenting versus carotid endarterectomy. Ann. Vasc. Surg. 17(1), 15–21 (2003).
Identified via supplementary ad-hoc search
Sturm JW, Osborne RH, Dewey HM, Donnan GA, Macdonell RA, Thrift AG. Brief comprehensive quality of life assessment after stroke: the assessment of quality of life instrument in the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2002 Dec;33(12):2888-94.
Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. Med Decis Making. 2010 May-Jun;30(3):341-54.

[1] No actual publication could not be obtained. Data / methodology extracted from the abstract / Smith et al 2013.

In addition, ad-hoc searches identified an Australian utility study performed as a part of the North East Melbourne Stroke Incidence Study (NEMESIS) (Sturm et al 2002) and an UK evaluation study conducted as part of the Oxford Vascular study (OXVASC) (Rivero-Arias et al 2010). NEMESIS is a widely-quoted population-based observational study performed in Melbourne. The Smith review presented only one relevant Australian study (i.e., Adams et al 2011; abstract only) and it had included very limited utility data. To this end, Sturm et al (2002) was also included for further consideration. Rivero-Arias et al (2010) was a relatively recent, large observational study in the UK (OXVASC), providing a full range of EQ-5D utility scores by mRS.

Furthermore, utility estimates employed in other published economic evaluation for mechanical thrombectomy are also explored (Aronsson et al 2016; Ganesalingam et al 2015; Kim et al 2011; Nguyen-Huynh and Johnston 2011; Patil et al 2009). Section D performs a review of cost-effectiveness evaluations of mechanical thrombectomy in the literature.

C.4.2 Results of the pre-modelling study

Findings from the current literature review are summarised in Table 51 below. As expected, there exists a wide range in the reported values relevant to each disability levels, which is attributable to population differences, elicitation methodology and other factors. There nonetheless exists a clear trend where major post-stroke disability (thus very high dependency on care to perform usual everyday activities) is characterised by a

severely compromised QoL with reported utility values as low as -0.23 when evaluated in stroke survivors (Noto et al 2011; HUI3) and <0.00 when evaluated other populations (Murphy et al 2001; SG in patients with AF or "at risk" population). This was reported to be 0.14 when elicited in the general public (Baker and Robinson 2004; SG).

Table 51 Summary of utility values by disability levels in the literature

Study	Population / study design		
Studies included in Smith et al 2013			
Adams et al 2011	General public in Australia (aged 18-69; mean 44). SG with 8 health states (various CV conditions). n=119	Severe stroke and MI 0.41 Mild stroke 0.78	No values reported for severe stroke only or moderate stroke. Abstract only.
Baker and Robinson 2004	General public in UK (mean age = 64). SG with 7 health states (various CV conditions). n=28	Mild stroke 0.55 Severe stroke 0.14	Small study sample.
Dorman et al 2000	Stroke survivors in UK (72 weeks post-stroke; median), enrolled in the International Stroke Trial. EQ5D n=2253 (867 completed EQ5D)	Recovered 0.88 Independent but not recovered 0.71 Dependent 0.31	Subjective questionnaire defining "dependent", "independent but not recovered" and "recovered".
Gage et al 1996	Patients with AF ("at risk") in US. TTO via computer-based interview. n=70	Current health 0.82 mRS 1-2 0.79 mRS3-4 0.39 (0.26 when standard gamble assessment is applied) mRS5 0.11	Only moderate stroke was assessed TTO as well as SG.
Hallan et al 1999	General public in Norway (aged 20-84) and stroke survivors (mRS2-3: 23 subjects; eRS4-5: 18 subjects). TTO and SG n=158 in total	Median utility values from SG /TTO: mRS2-3: 0.91 / 0.88 mRS4-5: 0.61 / 0.51	No mean values reported. No value reported for mRS 0-1. Figure 2 shows a strong skew towards higher values for mRS 2-3.
Lai and Duncan 2001	Stroke survivors in US. Prospective evaluation of changes in mRS and QoL / utility. TTO n=459 (of those, 280 or 62% sifted mRS from baseline to 3 months).	Mean utility gain among those improving at least one mRS scale between 0-3: 0.08-0.09	No actual publication could not be obtained. Data / methodology extracted from the abstract / Smith et al 2013.
Murphy et al 2001	Stroke survivors at 12 months (n=11), patients on anticoagulation (at risk patient; n=22) and medical staff (n=20)	Median utility for survivors/at risk/staff: Current health 0.70/0.85/0.98	No mean values reported. Three separate samples (patients, general public, medical staff).

Study	Population / study design		
	in UK SG via interviews	mRS 1-2: 0.93/0.78/0.88 mRS 3-4: 0.73/0.30/0.68 mRS 5: 0.40/<0.00/0.14	Health states (descriptors) based on Gage et al 1996 (above). Small study sample.
Noto et al 2011	Stroke survivors admitted at 7 hospitals in Japan. HUI3 n=553	mRS 1: 0.62 mRS 2: 0.48 mRS 3: 0.27 mRS 4: 0.00 mRS 5: –0.23	Abstract only.
Robinson et al 2001	Patients with AF at three GP offices in UK. SG n=69	Mild stroke: 0.68 Severe stroke: 0.00	Population is “at risk” patients.
Shin et al 1997	Young stroke survivors (mean age 37l range, 18-57) in Canada, SG n=31	Minor stroke: 0.81 Major stroke: 0.45	Younger patient population. Small study sample.
Slot and Berge 2009	Stroke survivors (n=75; + 1 year ago) and healthy, age-matched control (n=75) in Norway. SG	Median utility for survivors / general public: mRS 1: 0.93 / 0.91 mRS 3: 0.78 / 0.68 mRS 5 :0.18 / 0.11	No mean values reported.
Tengs et al 2001	Literature review	Minor stroke: 0.45-0.92 Moderate stroke: 0.12-0.81 Major stroke: -0.02-0.71	Ranges reported.
Tengs and Lin 2003	Meta-analysis of published evidence. A regression equation developed to estimate utility values by severity.	Minor stroke: 0.87 Moderate stroke: 0.68 Major stroke: 0.52	Regression analysis estimated a coefficient for severe (vs moderate) to be -0.165 and that for mild to be 0.187; based on TTO in general public.
van Exel et al 2004	Stroke survivors (those who achieved hospital discharge) at 2 months (n=364) and 6 months (n=357) in the Netherlands. EQ5D Stroke severity defined by Barthel Index (BI)	Mean utility values at 2 months / 6 months / combined: Independent (BI 20): 0.76 / 0.81 / 0.78 Mild (BI 15-19): 0.61 / 0.56 / 0.58 Moderate (BI 10-14): 0.41 / 0.33 / 0.31 Severe (BI 5-9): 0.06 / 0.09 / 0.08 Very severe (BI 0-4): -0.14 / -0.11 / -0.12	Relatively small changes between 2 months and 6 months.
Warren et al 2003	Prospective patients evaluated for extracranial carotid artery stenosis in US.	Minor non-disabling stoke: 0.797 Major disabling stroke:	“At risk” patients (i.e., extracranial carotid artery stenosis).

Study	Population / study design		
	TTO n=43	0.520	
Identified via supplementary ad-hoc search			
Sturm et al 2002	Stroke survivors (at 3 months) in North East Melbourne Stroke Incidence Study (NEMESIS). AQoL. Stroke severity defined by Barthel Index (BI) n=93	Mean utility values: BI 20 (independent): 0.63 BI 15-19 (mild): 0.40 BI 10-14 (moderate): 0.18 BI 5-9 (severe): 0.06 BI 0-4 (very severe): 0.02	Mean values read from Figure 1.
Rivero-Arias et al 2010	Model-based mapping of mRS to EQ-5D values based on the Oxford Vascular study (OXVASC), a large population-based cohort study in UK. This analysis based on 1283 stroke and TIA patients. EQ-5D	mRS 0: 0.936 mRS 1: 0.817 mRS 2: 0.681 mRS 3: 0.558 mRS 4: 0.265 mRS 5: -0.054	Mapping to utility values by regression models.

Abbreviations: AF, arterial fibrillation; SG, standard gamble; TTO, time trade off; mRS, modified Rankin score; AQoL, Assessment of Quality of Life; BI, Barthel Index; SG, standard gamble; EQ-5D,

Note: Gore et al (1995) also reported utility values by disability (included by Smith et al 2013); but the study was performed in patient treated for acute myocardial infarction (stroke being a complication as a result of thrombolysis). This study was excluded due to significant population differences.

A regression equation developed by Tengs and Lin 2003 (included in Table 51) to estimate utility values by stroke severity suggested an estimated utility value for minor, moderate and severe disability to be 0.87, 0.68 and 0.52, respectively. This analysis was based on a meta-analysis of published evidence for TTO results elicited from the general public (Tengs and Lin 2003).

In a large EQ-5D evaluation study identified via an ad-hoc search (Rivero-Arias et al 2010), utility values for the health states ranged from 0.935 to -0.054, where a mRS score of 5 resulted in a negative utility, indicating that living with a score of mRS 5 is worse than death. As noted above, this trend was observed in other studies as well (e.g., Noto et al 2011 and Murphy et al 2001).

Only two Australian studies were identified (Adams et al 2011 and Sturm et al 2002). Adams et al (2011) was only available as an abstract and the only relevant estimate reported was the utility value for mild stroke (0.78). On the other hand, based on the NEMESIS dataset, Sturm et al (2002) reported a full range of utility values by disability

levels[2] elicited from 93 stroke survivors at three months. Disability level of independent, mild, moderate, severe and very severe was associated with an estimated utility value of 0.63, 0.40, 0.18, 0.06, and 0.02, respectively.

Table 52 below shows that a range of utility data sources had been considered in the cost-effectiveness studies reported in the literature. All studies except Aronsson et al (2016) aggregated mRS groups into two (0-2 and 3-4). It is considered as preferable to include granularity in QALY calculations by having a full range of stroke disability levels (i.e., mRS 0 to 5, individually; as done in Aronsson et al 2016). The values used in the Aronsson analysis are largely in line with but have slightly larger decrements than in Sturm et al (2002); i.e., -0.08 vs 0.02 for severe disability and 0.75 vs 0.63 for independent / slight disability (Aronsson vs Sturm).

Table 52 Utility values considered in the published cost-effectiveness analyses of mechanical thrombectomy

mRS	Aronsson 2016	Ganesalingam 2015	Kim et al 2013 / Nguyen-Huynh and Johnstone 2013	Patil et al 2010
0	0.75	0.74	0.85	0.74
1	0.64			
2	0.40			
3	0.25	0.38	0.27	0.40
4	0.17			
5	-0.08			
Source / methodology	Dewilde et al 2014 Stroke survivors in 10 Swedish hospitals (n=569). EQ5D	Dorman et al 1997 Stroke survivors with no severe communication difficulties in UK (n=146). Face to face interview by a nurse. n=146 Six patients were excluded due to severe communication difficulties. EQ5D	While the authors reference to other cost-effectiveness evaluations, the original source appears to be Gage et al 1993 (abstract only; could not be obtained). It appears Gage et al 1996 (included in Table 51 above) employed a similar methodology.	Hacke et al 2004 (utility values appear to be data on file).

[2] Based on the Barthel Index. Cioncoloni et al (2012) examined the relationship between the BI and the mRS at multiple time points after stroke (n=92); demonstrating that they corroborate well with each other when administered after 3 months post stroke. While approximation, mapping the reported utility estimates by BI to mRS for the purpose of the current Section D model should be considered as reasonable.

Sturm et al (2002) is selected as the base case source of utility values for the current Section D because it offers provides locally-relevant values (providing a superior applicability over other studies). Also, it reported a full range of disability levels, providing granularity in QALY calculations. It is acknowledged that the utility values in this study was stratified by the BI scores (i.e., 0 corresponds to complete dependence, while 20 is equivalent to total independence). It is assumed that the dependency stratification provided by Sturm et al (2002) is applicable to the disability stratification by mRS.

C.4.3 Relationship of the pre-modelling study to the economic model

Table 53 summarises utility values informing the base case analysis presented in Section D. As discussed above, Sturm et al (2002) is selected as the base case source of utility values. Sensitivity analysis will examine other data sources.

It is acknowledged that none of the reported utility values specifically relate to the patient population for which the listing of mechanical thrombectomy is requested. Nonetheless, the QoL of patients should be primarily dependent on the on-going disability levels, and the mode of thrombolysis or other acute care (e.g., mechanical vs pharmacological / medical) should not have persisting impacts; providing support to the employed values.

Table 53 Summary of utility inputs for the Section D cost-effectiveness model

Resource use	Utility input (base case)	Source / notes
Post-stroke disability by mRS		Sturm et al 2002 BI 20 is assumed to correspond to mRS0-1.
0: No symptoms at all	0.63	
1: No significant disability despite symptoms	0.63	
2: Slight disability	0.40	
3: Moderate disability	0.18	
4: Moderately severe disability	0.06	
5: Severe disability	0.02	
6: Death	0	

Abbreviation: BI, Barthel Index; mRS, modified Rankin Score.

C.5 Selection of costing data

The following pre-modelling study clarifies data inputs employed by the Section D model to inform the costing of modelled healthcare resource use. Costs can be broken down into treatment costs, costs in the acute / mid-term phase and long-term phase. Table 54 below summarises modelled resource use items and sources of costing data considered in the current pre-modelling study.

Table 54 Modelled healthcare resource items and sources of costing information

Resource use	Data source	Notes
Modelled interventions (mechanical thrombectomy)	Proposed fee, other relevant MBS service fees, consumables	The proposed fee is $4000. See **Error! eference source not found.** for full details of the associated resource use items.
Acute stroke care / mid-term care (to Day 365)	Published evidence via literature review	Other resource use relevant to in-hospital acute treatment and mid-term out-of-hospital care (e.g., rehabilitation).
Long-term stroke care	Published evidence via literature review	Long-term management costs.

Of note, mechanical thrombectomy is taken as being "additional" to the care currently provided as usual care. Costs of other interventions (including IV-tPA if the patient is eligible) and support care (e.g., nursing, monitoring, bed costs etc) would be captured in "acute stroke care" costs (see Table 54) and they are assumed to exist in both arms, thus largely cancelling out each other. However, it is important to clarify that the use of mechanical thrombectomy improves the rate of revascularisation (reperfusion) during the first critical hours of stroke onset, which in turn reduces the extent / intensity (and thus costs) of other care provided during the acute care phase (to discharge). For example, the use of mechanical thrombectomy has been shown to shorten hospitalisation days, directly contributing to such cost savings (e.g., EXTEND-IA). Similarly, the costs of mid-/long-term rehabilitation can be significant, suggesting that improved functional outcomes offered by mechanical thrombectomy vs usual care would then produce further cost savings post-acute phase. These relationships have been documented in a within-trial cost comparison performed in Australia (Campbell et al 2015) and is adequately captured by the Section D model.

The Applicant acknowledges that the scope of costing exercise in this pre-modelling study is slightly limited than that put forward in Table 11 of the Protocol in terms of costed healthcare resource items. This approach is justified because only incremental cost implications should be captured in cost-effectiveness evaluation. This approach will also reduce the risk of possible double counting, for example, overnight hospitalisation cost for mechanical thrombectomy is unlikely to be separately incurred given the extent / intensity of care provided to these patients during the acute care phase (see Table 11 of the Protocol). This point was clearly raised in the Protocol; "*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" (pg 32).

Of note, Section B.7 above demonstrated that mechanical thrombectomy is associated with a very small risk of procedural complications (<3%). Procedural complications reported in RCTs are summarised in Table 55. Much of the treatment for these procedural complications may also be absorbed into the overall procedural activities and hospitalisation costs, thus not meaningfully producing any additional costs to the healthcare system. *To this end, the base case analysis will not assign specific costs to the management of procedural complications.* It is acknowledged that one outlier is the risk of access site hematoma observed in REVASCAT, which was observed in 10.7% of patients. The REVASCAT protocol defined serious hematoma to be any event requiring greater than 2 units of packed red blood cells transfusion. A sensitivity analysis is performed by applying an estimated cost of $1828 per episode of access site hematoma (based on 2 units of transfusion in Peel et al 2015); effectively increasing the procedural cost $195.60.[3]

Table 55 Summary of adverse events

Trial ID	ESCAPE		EXTEND-IA		MR CLEAN		REVASCAT		SWIFT PRIME	
Treatment arm	MT	Usual care	MT	Usual care	MT	Usual care	MT	Usual care	MT	Usual care
N	165	150	35	35	233	267	103	103	98	97
Procedural complications	1 (0.6)[a]	0	1 (2.9)[b]	0	NR	NR	NR	NR	NR	NR
Hematoma at access site	3 (1.8)	0	1 (2.9)	0	NR	NR	11 (10.7)	0	NR	NR

Abbreviations: MT, mechanical thrombectomy.

a. Perforation of the middle cerebral artery

b. Wire perforation

Other "safety" outcomes explored in Section B included intra-cranial / intracerebral bleeding events as well as mortality. Risks of these events are similar or for the case of mortality more favourable for mechanical thrombectomy vs usual care (see Section B.7). The model considers these outcomes more as "efficacy", and assumed to be captured in the mRS outcomes (i.e., death is captured as mRS of 6). *Hence, any cost and QALY implications associated with these events are captured in the acute treatment costs and utility scores included the model.*

[3] This sensitivity analysis will show that the ICER increases from $12,880 to$13,183; demonstrating no meaningful impact. As an extreme example, when the procedural cost is increased by $5000, the ICER becomes $18,918; reaffirming that the AE management cost is unlikely to have minimal impacts.

C.5.1 Focused analytical plan

Mechanical thrombectomy

Estimation of procedural costs for mechanical thrombectomy is performed in accordance with resource requirements described in the Protocol, supplemented by published evidence and expert inputs.

Costs of stroke care by mRS – acute and mid-/long-term costs

To fully capture the cost implications of improved functional outcomes offered by mechanical thrombectomy vs usual care, the Section D model considers the following three time points:

- In-hospital acute care cost (other than the costs of mechanical thrombectomy, as above)
- Out-of-hospital cost to 12 months – mid-term stroke care costs
- Out-of-hospital cost beyond 12 months – long-term stroke care costs

To identify published cost information, a PubMed literature search was performed on the 15th of April with the following search string; "*Australia* AND (Cost AND Stroke)*"; returning 283 citations. Only observational studies (i.e., non-interventional; unless mechanical thrombectomy and/or usual care including IV-tPA are the studied interventions) performed in Australia are considered for inclusion. To further guide the inclusion / exclusion of papers for further review, a particular focus is then place on studies which reported costs by functional / disability levels. Only one study (Tanny et al 2013) provided cost estimates by post-stroke disability levels.

Table 56 Publications considered in the current pre-modelling study

Study reporting cost information by disability level
Tan Tanny SP, Busija L, Liew D, Teo S, Davis SM, Yan B. Cost-effectiveness of thrombolysis within 4.5 hours of acute ischaemic stroke: experience from Australian stroke center. Stroke. 2013 Aug;44(8):2269-74.
Publications of North East Melbourne Stroke Incidence Study (NEMESIS)
Gloede TD, Halbach SM, Thrift AG, Dewey HM, Pfaff H, Cadilhac DA. Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. Stroke. 2014 Nov;45(11):3389-94.
Cadilhac DA, Carter R, Thrift AG, Dewey HM. Estimating the long-term costs of ischemic and hemorrhagic stroke for Australia: new evidence derived from the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2009 Mar;40(3):915-21.
Dewey HM, Thrift AG, Mihalopoulos C, Carter R, Macdonell RA, McNeil JJ, Donnan GA. 'Out of pocket' costs to stroke patients during the first year after stroke - results from the North East Melbourne Stroke Incidence Study. J Clin Neurosci. 2004 Feb;11(2):134-7.
Dewey HM, Thrift AG, Mihalopoulos C, Carter R, Macdonell RA, McNeil JJ, Donnan GA. Lifetime cost of stroke subtypes in Australia: findings from the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2003 Oct;34(10):2502-7.

Study reporting cost information by disability level
Dewey HM, Thrift AG, Mihalopoulos C, Carter R, Macdonell RA, McNeil JJ, Donnan GA. Informal care for stroke survivors: results from the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2002 Apr;33(4):1028-33.
Dewey HM, Thrift AG, Mihalopoulos C, Carter R, Macdonell RA, McNeil JJ, Donnan GA. Cost of stroke in Australia from a societal perspective: results from the North East Melbourne Stroke Incidence Study (NEMESIS). Stroke. 2001 Oct;32(10):2409-16.
Other studies via supplementary searches[1]
Campbell et al (for the EXTEND-IA investigators) 2015 Endovascular thrombectomy reduces length of stay and treatment costs within 3 months of stroke [conference poster].
Baeten SA, van Exel NJ, Dirks M, Koopmanschap MA, Dippel DW, Niessen LW. Lifetime health effects and medical costs of integrated stroke services – a non-randomized controlled cluster-trial based life table approach. Cost Eff Resour Alloc. 2010 Nov 17;8:21.
Aronsson M, Persson J, Blomstrand C, Wester P, Levin LÅ. Cost-effectiveness of endovascular thrombectomy in patients with acute ischemic stroke. Neurology. 2016 Mar 15;86(11):1053-9.
Ganesalingam J, Pizzo E, Morris S, Sunderland T, Ames D, Lobotesis K. Cost-Utility Analysis of Mechanical Thrombectomy Using Stent Retrievers in Acute Ischemic Stroke. Stroke. 2015 Sep;46(9):2591-8. doi:
Kim AS, Nguyen-Huynh M, Johnston SC. A cost-utility analysis of mechanical thrombectomy as an adjunct to intravenous tissue-type plasminogen activator for acute large-vessel ischemic stroke. Stroke. 2011 Jul;42(7):2013-8.
Nguyen-Huynh MN, Johnston SC. Is mechanical clot removal or disruption a cost-effective treatment for acute stroke? AJNR Am J Neuroradiol. 2011 Feb;32(2):244-9.
Patil CG, Long EF, Lansberg MG. Cost-effectiveness analysis of mechanical thrombectomy in acute ischemic stroke. J Neurosurg. 2009 Mar;110(3):508-13.

[1] Including those identified through a search of published cost-effectiveness studies for Section D.3.1.

Tanny et al (2013) was a cost-effectiveness analysis of IV tPA in an Australian setting. This study employed a decision analytic model with health states defined by mRS[4]. Clinical inputs for this study were based on data from 378 patients with acute ischemic stroke who received IV tPA at Royal Melbourne Hospital Comprehensive Stroke Centre between January 2003 and December 2011.

Cost inputs during the acute in-hospital phase were based on actual expenditure for each of the 378 patients included in the study. These data were sourced from the Clinical Costing Unit of Royal Melbourne Hospital, which assigns detailed, itemised costs to every patient encounter. Out-of-hospital costs were estimated from the North East Melbourne Stroke Incidence Study (NEMESIS; see Dewey et al 2001). The mRS stratification of the out-of-hospital costs were based on discharge destinations of patients included in the study; no further information was reported in the publication. All cost data were analysed by mRS, as required by the health state definitions employed by the model.

[4] The current Section D model fundamentally has the same model structure as the Tan Tanny model.

Tanny et al (2013) hence provides locally relevant "real world" cost data with adequate applicability to the proposed MBS population. It is acknowledged that an adjustment would have to be made for IV tPA costs because not all patients in the usual care arm of the Section D model would receive a concurrent IV tPA (see below).

NEMESIS is also a widely quoted Australian population-based study providing locally relevant "real world" cost information (Dewey et al 2001). Six publications stemming from NEMESIS were also identified by the aforementioned literature search; but none of them reported cost information by disability levels. These studies are presented as supplementary evidence to further support the reasonableness of the Tanny estimates.

In addition, this pre-modelling study explores cost information reported in other relevant cost-effectiveness studies reported in literature (to be reviewed in Section D.3.1) as supplementary evidence.

C.5.2 Results of the pre-modelling study

Mechanical thrombectomy

Error! Reference source not found. below estimates the total cost of mechanical hrombectomy per procedure. Of note, as discussed in Section C.2, pre-procedural imaging tests (CT or MR-based imaging) are a part of the routine diagnostic work-up provided under the current usual care; thus existing in both treatment arms.[5] To this end, these costs are not included here. Based on the local key opinion leader (KOL) inputs, two additional imaging tests are included post procedure; whole head digital subtraction angiography (DSA) to assess for embolisation to new brain territory or other complications and leg angiography and management of groin arteriotomy.

Total cost of stent retriever, catheter and other components related to mechanical thrombectomy is $**redacted**. It is assumed that on average each procedure requires 1.2stent retrievers, meaning up to 20% of patients may require more than 1 stent retriever per procedure (data on file; SWIFT PRIME).

[5] As an extreme example, when the procedural cost is increased by $5000 as a sensitivity analysis, the ICER becomes $18,918.

Table 57 Resource items required to perform mechanical thrombectomy

Resource items	Cost input	Source / notes
Mechanical thrombectomy devices and consumables		
Stent retriever	$**redacted**	Applicant 1.2 units per procedure (unpublished data from SWIFT PRIME study)
Catheter and other consumables	$**redacted**	Applicant
Mechanical thrombectomy procedure (service fee)	$3,500	Proposed MBS fee
Anaesthesia		
General anaesthesia (only relevant to 36% of patients)		Assuming 36% of patients require general anaesthetics, based on EXTEND-IA.
Initiation of management of anaesthesia	$297.00	MBS item 20210
Intra-arterial cannulation with anaesthesia	$79.20	MBS item 22025
Management of anaesthesia	$79.20	MBS items 23041, 23042, 23403; 46 mins to 1 hour
Blood pressure monitoring	$59.40	MBS item 22012, 22014
Assistance	$19.80	MBS item 25015
Subtotal, general anaesthesia	$514.80 or $185.33 on average per patient	Calculated.
Regional anaesthetics for the remaining 64%	$50.05 or $32.03 on average per patient	MBS item 18225
Average anaesthetics cost, per procedure	$224.49	Calculated
Post-operative imaging (radiographer)		
Digital subtraction angiography	$1,376.30	MBS item 60009; Digital Subtraction Angiography, examination of head and neck with or without arch aortography - 10 or more data acquisition runs (K; employing an equipment less than 10 years old).
Leg angiography	$43.10	MBS item 60072; Selective arteriography or selective venography by digital subtraction angiography technique - 1 vessel at $48.10; reduced by $5 according to multiple service rule (Rule A)
Subtotal, post-operative imaging	$1,419.40	Calculated.
Nursing staff	$240.60	$48.12 per hour X 2.5 hours X 2 nurses. The hourly rate based on specialist clinical nurse Grade 2, 2nd year and thereafter[1] 2.5 hours account for 2 hours for in-hours (50% of all cases) and 3 hours for our of hours (1 hour travel; 50% of all cases); based on Campbell et al 2015
Operating theatre cost	$388.00	Intensive care cost at $194 per hour; based on Campbell et al. 2015

Other consumables (drapes, gowns, gloves, sheath etc)	$100.00	KOL inputs / assumptions
Inter-hospital patient transfer	$836.00	Campbell et al. 2015
Total per procedure	$18,308.49	Calculated

[1] Based on "Healthscope and NSWNMA/ANMF – NSW Nurses & Midwives' Enterprise Agreement 2015 – 2019" (http://www.nswnma.asn.au/wp-content/uploads/2013/07/Healthscope-and-NSWNMA-ANMF-NSW-Nurses-Midwives-Enterprise-Agreement-2015-2019.pdf).

The current Application proposes a fee of $3,500 per procedure. The Protocol suggested the proposed MBS fee for mechanical thrombectomy to be referenced to the current MBS benefit amount given to endovascular coiling of intra-cranial aneurisms ($2857.55; MBS item 35412). Further communication with Australian KOLs suggested that when compared with other neurointerventional procedures such as endovascular coiling mechanical thrombectomy for acute ischaemic stroke is:

- Technically more challenging. Traversing occluded vessels in acute ischaemic stroke is more technically challenging – wire/microcatheter navigation requires precision in circumstances where there is no definitive path through an occlusion. Furthermore, stroke patients considered for mechanical thrombectomy are typically elderly. In this patient group, vasculature becomes increasingly tortuous and difficult to navigate; in contrast, the patient demographic for aneurysm is generally younger and vascular access is more straightforward.
- Associated with greater training requirements. Acute ischaemic stroke is a completely different pathophysiological entity to other conditions treated by INRs (e.g. aneurysms) – hence, additional training and expertise is required. In Australia, training relevant to mechanical thrombectomy is described by the Conjoint Committee for Recognition of Training in Interventional Neuroradiology (CCINR).[6] International consensus on training was published recently[7] with CCINR amongst several groups involved in developing this consensus. The comprehensive skills and training requirements necessary to perform mechanical thrombectomy and achieve high quality outcomes illustrate how technically demanding this procedure is.
- More resource intensive. The procedure is usually performed by two operators,

[6] Conjoint Committee Guidelines for Recognition of Training in Interventional Neuroradiology. Available: www.ccinr.org.au/guidelines (Accessed 7th April, 2016)

[7] Training Guidelines for Endovascular Ischemic Stroke Intervention: An International Multi-Society Consensus Document. EJMINT Editorial, 2016: 1607000288 (18th February 2016).

both highly experienced and trained (e.g. Consultants). The fee should be sufficient to ensure that both operators are suitably remunerated.

- Critically urgent. Stroke is a medical emergency and mechanical thrombectomy needs to be provided during the first critical hours of stroke onset. Clinicians providing this service must be able to provide it 'out of hours'. In addition, during normal hospital hours clinicians who can perform the procedure may be called away from scheduled, non-emergency procedures. The need to perform the procedure as soon as possible has significant impacts on clinicians' capacity/availability to perform and be remunerated for other procedures.

In addition, the overall service provision requirements are extensive. In addition to performing mechanical thrombectomy itself, INR provision of the overall proposed service involves the following:

- Pre-procedure:
  - Organise logistics of care when patient arrives at hospital.
  - Review of brain imaging: INR interpretation required.
  - Clinical examination of patient.
  - Check angiography suite or catheterisation laboratory for procedure readiness: prepare where facilities are not ready to receive the patient.
  - INR briefs anaesthetic team on the clinical scenario and the plan for the patient.
- Post procedure:
  - Clinical assessment of the patient
  - Clinical re-assessment of patient
  - Patient transferred to bed and awaken from anaesthesia (if used)
  - Document case in clinical notes and formalisation of results [Note: during Public Consultation respondents advised that centres providing MT should participate in an audit or registry to ensure that minimum performance (outcomes) standards are met]
  - Establish advanced haemodynamic plans for the next 24 hours, particularly anticoagulation regimes and blood pressure control
  - Transfer patient to intensive care unit (ICU) and hand over to ICU team
  - Debrief family

The proposed fee of $3500 is hence considered as well justified and necessary to sufficiently cover a mechanical thrombectomy procedure service.

The use of general anaesthesia appears to vary across centres. In the RCTs, this ranged from 6.7% in REVASCAT (Jovin et al 2015) to 37% in SWIFT PRIME (Saver et al 2015), as shown in Table 58. In EXTEND-IA, general anaesthesia was provided in 36% of patients. While uncertainty remains as to the generalisability of this estimate, the current costing applies 36% based on this trial because it was performed in Australia and New Zealand. Also, the duration of anaesthesia is assumed to be up to 1 hour, roughly informed by 'time from groin puncture to perfusion / completion' reported in the trials, as shown in Table 58. As discussed above (overall service provision requirements), the procedural time criteria assessed and reported in clinical trials do not reflect the overall time commitment required for clinicians to provide the proposed service.

Campbell et al (2015) assumed 2 hours of nursing time in total (per nurse attending the procedure).

Also, the current costing conservatively assumes that 75% of patients receive an inter-hospital transfer to receive mechanical thrombectomy (as also assumed in Campbell et al. 2015). As the uptake of mechanical thrombectomy increases in Australia, it is anticipated that fewer patients will require to be transferred to another facility to receive the procedure in the future.

Table 58 Time from groin puncture to first perfusion / completion and the use of general anaesthesia in RCTs

Study	Definition of procedural time and reported procedural duration (median)	General anaesthetics use	Note
ESCAPE (Goyal et al 2015)	Study CT to first reperfusion (first visualisation of reflow in the middle cerebral artery) = 84 mins (IQR: 65–115) Groin puncture to first reperfusion = 30 mins (IQR: NR)	9.1%	Time from groin puncture to first reperfusion (not to completion).
EXTEND-IA (Campbell et al 2015)	Median time from groin puncture to mTICI 2b or 3 or completion of procedure = 43 mins (IQR: 24-53)	36%	Reported time not fully reflective of time to completion.
MR CLEAN (Berkhemer et al 2015)	NR	38%.	No information provided regarding procedural time.
REVASCAT (Jovin et al 2015)	Time from groin puncture to revascularisation = 59 mins (IQR: 36-95) Time from groin puncture to end of the procedure = 75 mins (IQR: 50-114)	6.7%	75 mins from groin puncture to completion.
SWIFT PRIME (Saver et al 2015)	Groin puncture to first deployment of the stent retriever = 24 mins (IQR: 18-33)	37%	Time from groin puncture to retriever deployment (not to revascularisation or completion).

Abbreviations: CT, computed tomography; IQR, Interquartile range; NR, not reported. mTICI, modified Treatment in Cerebral Ischaemia classification

In total, each procedure is estimated to cost $18,308.49 per procedure. This estimate is applied in the Section D model. the total "staff" cost (i.e., excluding device/consumable costs, theatre cost, patient transfer) is estimated to be $3,965.09 or $5,384.49 with / without the cost of post-operative imaging tests (performed by a radiographer), respectively. The Applicant acknowledges that some uncertainties remain with the employed cost inputs. For example, the time of nursing stuff is costed to reflect the current remuneration for public hospital nurses, which may not be applicable to private centres. A series of sensitivity analyses will be performed in Section D.5.3.

Costs of stroke care by mRS – acute and mid-term costs

Table 59 below summarises inpatient and out-of-hospital cost estimates by mRS (at 90 days), as reported in Tanny et al (2013). The reported values are updated to 2016 values.

As set out above, the estimated acute costs are inclusive of IV-tPA costs. This was reported to be $3465 in Tanny et al (2013). Patients eligible for mechanical thrombectomy include those eligible and ineligible for IV-tPA (see Section A etc.) (see Section A). It is assumed that for those IV-tPA ineligible patients their treatment costs are represented by the reported total costs minus the IV-tPA cost, as shown in Table 59 below. *This is a conservative approach given that they would in practice receive alternatives (but less effective) to IV-tPA. The current approach would omit costs of these treatments.*

It is shown that while inpatient costs are relatively stable across different mRSs, considerable cost differences can be observed after discharge, e.g., $9,795 for mRS 1 vs $22,549 for mRS 5. This is expected considering the extent and types of care required by patients experiencing severely compromised functional ability following stroke during the first 12 months (e.g., rehabilitation, assisted living, allied healthcare, nursing etc).

Table 59 Inpatient and out-of-hospital cost of ischaemic stroke by mRS (to 12 months)

Modified Rankin Scale (taken as at 90 days in the Tanny model)	Applied in Tanny et al 2013		Updated to 2016 values[1]		
	Inpatient cost (median; including $3465 for IV-tPA)	Out-of-hospital cost (to 12 months; median)	Inpatient cost (without IV-tPA cost)	Inpatient cost (with IV-tPA cost)	Out-of-hospital cost (to 12 months; median)
0: No symptoms at all	$20,650	$9,203	$19,605	$23,558	$10,499
1: No significant disability, despite symptoms	$20,895	$11,597	$19,884	$23,837	$13,230
2: Slight disability	$22,503	$13,975	$21,719	$25,671	$15,943
3: Moderate disability	$22,503	$15,375	$21,719	$25,671	$17,540
4: Moderately severe disability	$20,107	$18,208	$18,985	$22,938	$20,772
5: Severe disability	$20,107	$21,186	$18,985	$22,938	$24,169
6: Death	$14,572		$12,671	$16,624	–

Source: Tanny et al (2013)

Note: Table 1 of Tanny et al (2013) notes these cost inputs to be in US$; Aus$ in the 2012-2013 period was roughly at parity with US$. The presented values are hence treated as Aus$ for the purpose of this analysis. A review of other NEMESIS publications below also supports the reasonableness of these cost estimates.

[1] The reported estimates are assumed to be in 2013 values. Price inflator (2013-2016) = 1.1408 (based on Australian Bureau of Statistics, Consumer Price Index - Health, 6401.0).

As noted above, the out-of-hospital cost estimates in Tanny et al (2013) were based on NEMESIS. The literature search identified six publications that reported data from NEMESIS (Gloede et al. 2014, Cadilhac et al. 2009, Dewey et al. 2004, Dewey et al. 2003, Dewey et al. 2002, Dewey et al. 2001). As noted above, no stratification by mRS has been reported in these publications. The NEMESIS data are however presented here as supplementary evidence.

Amongst all the papers identified, Cadilhac et al. (2009) is the paper which was deemed to provide most detailed cost information for acute and on-going treatment for stroke to 12 months. Providing a similar extent of cost information, Gloede et al. (2014) reported longer-term cost data up to 10 years (to be considered in the following section). Apart from the fact these NEMESIS cost studies are basically the only source of "real world" Australian out-of-hospital stroke costs, both studies possess good methodology and are based on unit cost sources consistent with those recommended in the PBAC's *Manual of Resource Items and their Associated Costs*.[8]

[8] http://www.pbs.gov.au/info/industry/useful-resources/manual

Table 60 presents the costs of ischaemic stroke to 12 months by resource category as report by Cadilhac et al. (2009). The acute treatment cost for stroke is assumed to consist of pre-admission costs, acute hospital costs and inpatient rehabilitaiton only, while out-of-hospital cost in the first year represent the total first year cost minus acute inpatient cost. After accounting for inflation, the NEMESIS cost estimates are clearly in line with the Tanny estimates. Again, while the NEMESIS data reflect the "general" ischaemic stroke patient population in Australia as a whole, the Tanny estimates would have a superior applicability to the modelled patient population.

Table 60 Treatment costs of ischaemic stroke by resource category – acute and out-of-hospital phase to 12 months, per patient average

Resource category	Ischaemic stroke (n=27,660)
Pre-admission (GP or ambulance)**	$440
Acute hospitalisation**	$8,644
Inpatient rehabilitation**	$7,087
Aged care facilities	$2,310
Medication costs	$441
GP care	$168
Private allied health	$107
Investigations	$221
Specialist medical care	$175
Outpatient rehabilitation	$672
Community services	$20
Respite care	$307
Hospitalisation for recurrent strokes	$801
Hospitalisation for complications of stroke	$1,442
Ambulance transfers	$116
Emergency department presentations	$33
Aged care assessment teams	$63
Out-of-pocket costs	$545
Caregiver costs	$1,126
Total first year costs (all items), 2004 values	**$24,718**
– Acute costs only	**$16,171**
– Out-of-hospital costs	**$8,547**
Inflated to 2016 prices[a]	
– Acute costs only	**$28,056**
– Out-of-hospital costs	**$14,829**

Source: Cadilhac et al. (2009), Table 3
**Cost items considered as acute and thus excluded from out-of-hospital costs
[a] Price inflator (2004-2016) = 1.7350 (based on Australian Bureau of Statistics, Consumer Price Index - Health, 6401.0).

While not reporting specific cost inputs relevant to the modelled health states (i.e., defined by mRS; see Section D.3), a within-trial cost-effectiveness evaluation of mechanical thrombectomy performed by Campbell et al. (2015; vs IV-tPA, based on EXTEND-IA) reported locally-relevant cost information collected from real world settings, as summarised in Table 61. Inpatient care costs were determined based on the IPD data for length of stay in the acute stroke unit, inpatient fast and slow stream rehabilitation, nursing home and palliative care (Campbell et al. 2015). It should be noted however that these data reflect public hospital costs, which may underestimate the cost benefits offered by mechanical thrombectomy vs usual care in a private hospital setting.

While the 3-month inpatient care costs reported in this study already account for functional outcome differences between the two arms, the reported cost estimates are in agreement with other inpatient cost estimates presented above; however, these values suggest that the acute cost estimates reported by Tanny et al (2013) may underrepresent healthcare resource use for patients treated under usual care. *Of note, importantly, this cost-effectiveness study clearly supports a very favourable health economics profile of mechanical thrombectomy (dominant; cheaper and more effective); to be further discussed in Section D below.*

Table 61 Cost comparison of mechanical thrombectomy vs usual care, based on EXTEND-IA

Costs (first 3 months)	Usual care + MT	Usual care[1]
Alteplase	$3,465	$3,465
Inter-hospital transfer (allow for 75% transferred)	$836	n/a
Endovascular consumables	$10,690	n/a
Endovascular staffing	$3,560	n/a
Inpatient care costs	$23,000 CI95 $15,709-$30,029	$43,000 CI95 $31,290-$54,688
TOTAL	**$41,551**	**$45,465**

Source: Campbell et al 2015, Table 2

[1] IV-tPA eligible patients only.

The base case analysis in Section D will employ estimates for inpatient and outpatient costs reported by Tanny et al (2013), given that this is the only source of locally-relevant stroke costs stratified by functional outcomes. The balance of evidence provided in the current pre-modelling study clearly supports the reasonableness of these estimates. Sensitivity analysis will explore alternative cost assumptions.

Costs of stroke care by mRS – long-term costs (post 12 months)

Gloede et al. (2014) reported longer-term cost data up to 10 years from the NEMESIS dataset, as summarised in Table 62. The reported estimates highlight that ischaemic strokes incur significant on-going costs in the long run ($10,275 each year over a 10 year period).

For the Section D cost-effectiveness evaluation to accurately represent the benefits of the proposed service, it is necessary to capture potential long-term (post 12 months) cost implications because these long-term costs are most likely to be dependent on post-stroke functional outcomes. No relevant information on costs of stroke care by mRS has been reported from the NEMESIS dataset.

Table 62 Long-term stroke costs by resource category, ischaemic stroke (per patient costs)

Resource category	Annual average between 3-5 years	Annual average at 10 years
Aged care facilities	$2,148	$2,337
Medication costs	$690	$928
Community services	$889	$758
Inpatient rehabilitation	$779	$233
General practitioner care	$196	$214
Hospitalisations for complications	$176	$163
Other direct medical costs[1]	$669	$788
Total annual direct medical costs, 2010 values	**$5,545**	**$5,419**
Total annual direct nonmedical costs, 2010 values[2]	**$2,645**	**$2,425**
Total annual direct costs, 2010 values	**$8,190**	**$7,842**
Inflated to 2016 prices[3]		
Total annual direct medical costs	**$7,266**	**$7,100**
Total annual direct nonmedical costs	**$3,465**	**$3,177**
Total annual direct costs	**$10,731**	**$10,275**

Source: Gloede et al. (2014), Table 2 (US values converted to Aus values by using an exchange rate factor of 1.506, as directed by the authors).
[1] Includes specialist care, outpatient rehabilitation, emergency department care, private allied health, respite care, investigations, aids and modifications, ambulance transfers, and aged care assessment teams.

[2] Includes informal care and caregiver out-of-pocket costs.

[3] Price inflator (2010-2016) = 1.3103 (based on Australian Bureau of Statistics, Consumer Price Index - Health, 6401.0).

An additional ad-hoc search identified a Dutch cost-effectiveness analysis of alternative stroke care settings (special stroke care unit vs usual stoke care) (Baeten et al 2010). While cost estimates to 6 months were determined based on the individual patient resource use data from a clinical trial (the EDISSE study – Evaluation of Dutch Integrated Stroke Service Experiments), healthcare costs thereafter were estimated by using a more

aggregated approach on the basis of place of residence data (see Baeten et al 2010 for further information). Cost estimates reported in this study are summarised in Table 63. Although this study represents healthcare costs for stroke in the Netherlands, it illustrates the impact on long-term costs of differences in functional outcomes achieved during the acute treatment phase.

The reported +1 year cost estimates suggest that the costs of care for mRS 4 and 5 are considerably greater than the average cost by a factor of 1.98 and 2.53, respectively (see Table 63). In contrast, patients with mRS 0-1 incur costs that are one fifth of the average. These trends clearly highlight the likely presence of significant long-term cost benefits offered by mechanical thrombectomy vs usual care. Table 63 also shows cost estimates by mRS when these cost multipliers are applied to the mean direct medical cost reported in Gloede et al. (2014; see Table 62).

Table 63 Acute to mid-/long-term stroke care costs in Baeten et al 2010 (€ in 2003 prices)

Modified Rankin Score	0-1	2-3	4	5	Average
0-6 months (in-hospital + out-of-hospital), 6 months total					
Stroke care unit	11,834	16,885	52,671	47,799	37,553
Usual stroke care	13,037	21,471	60,058	68,019	39,656
7-12 months, 6 months total	1,761	4,196	17,824	22,515	9730[a]
+1 year (men, annual)	1,622	2,056	11,994	15,266	6,342[a]
+1 year (female, annual)	1,622	2,056	19,800	25,404	9,751[a]
+1 year (gender standardised[b], annual)[c]	1,622	2,056	15,897	20,335	8,047[a]
Cost multipliers according to mRS (vs average)[c]	0.20	0.26	1.98	2.53	1.00
Callibration to Gloede 2014, annual	$1,431	$1,814	$14,027	$17,943	$7,100 (see Table 62; direct med costs only)

Source: Baeten et al 2013, Table 3

[a] Average for the two arms presented here. Calculated for the purpose of this submission.

[b] The authors ICER calculations suggested a gender split of 50:50. This ratio is applied here.

[c] Calculated for the purpose of this submission; e.g., 0.20 for mRS 0-1 = $1,622 ÷ $8,047. The callibrated Australian value of $1,431 = $7,100 x 0.20

A literature review for other cost-effectiveness studies performed for Section D.3.1 identified five publications. Their long-term cost data are summarised in Table 64, again highlighting large cost differences between patients with no/little disability vs severe disability. As performed above, based on cost multipliers from these publications, the Gloede 2014 estimate is calibrated to different disability levels, as also shown in Table 64 below.

Table 64 Long-term stroke care cost inputs in published cost-effectiveness models

Study	Cost multipliers	Cost inputs used in the original study	Callibration to Gloede 2014 (mean direct med cost of $7,100 per annum; see Table 62)[a]
Aaronson 2016	On-going post 1 year: mRS 0-3 = 0.39 mRS 4-5 = 1	On-going post 1 year (annual; 2015 values): mRS 0-3 = US$3,169 mRS 4-5 = US$8,118	mRS 0-3 = $4,251 mRS 4-5 = $10,899
Ganesalingam 2015	On-going post 3 months: mRS 0-2 = 0.37 mRS 3-5 = 1	On-going post 3 months (3-monthly; 2013 values): mRS 0–2 = US$772 mRS 3-5 = US$2,075	mRS 0-2 = $3,457 mRS 4-5 = $9,342
Kim 2011	On-going post 1 year: mRS 0-2 = 0.11 mRS 3-5 = 1	On-going post 1 year (annual; 2009 values): mRS 0–2 = US$2,885 mRS 3-5 = US $25,960	mRS 0-2 = $1,182 mRS 4-5 = $10,742
Nguyen-Huynh 2011	On-going post ~3 months: mRS 0-2 = 0.11 mRS 3-5 = 1	On-going post ~3 months (annual; 2009 values): mRS 0–2 = US$2,200 mRS 3-5 = US $20,000	mRS 0-2 = $1,182 mRS 4-5 = $10,742
Patil 2009	On-going post 1 year: mRS 0-2 = 0.13 mRS 3-5 = 1	On-going post 1 year (annual; 2008 values): mRS 0–2 = US$5,764 mRS 3-5 = US $45,469	mRS 0-2 = $1,381 mRS 4-5 = $10,620

Note: See respective publications for further information.

[a] Distributions of mRS based on the meta-analysed data of usual care reported in Campbell et al (2016); mRS 1 to 6 = 8%, 10%, 14%, 16%, 21%, 15% and 16%, respectively.

The base case analysis in Section D will employ estimates derived based on Gloede et al (2014), adjusted by mRS cost multipliers reported by Baeten et al. (2010). While this is an approximation and reflects the paucity of locally-relevant published evidence, the resulting estimates by mRS (Table 63) are well supported by the balance of the available evidence explored in the current pre-modelling study. This approach also provides granularity in the cost estimation by mRS in the model.

C.5.3 Relationship of the pre-modelling study to the economic model

Table 65 below summarises all cost inputs employed by the base case cost-effectiveness evaluation presented in Section D.

As discussed above, due to the lack of relevant publish evidence, long-term stroke care costs were estimated by using the mRS cost multipliers in the literature to calibrate the

mean long-term cost from NEMESIS (Gloede et al 2014). While an approximation, this approach is necessary to capture likely long-term stroke care savings offered by mechanical thrombectomy vs usual care as the proposed service provides superior functional outcomes. The base case estimates are based on the cost multipliers from Baeten et al (2013). Sensitivity analysis is performed to explore other estimates (see Table 64).

The intended patient population for the proposed service includes patients eligible and ineligible for IV-tPA. Hence, relevant to the acute stroke costs presented earlier, the proportion of patients who receive concomitant IV-tPA with MT will be considered in the base case Section D model. *The base case Section D model will assume that 50% of all MT procedures are provided along with IV-tPA.*[9] In any case, this assumption will equally affect both arms of the model, thus generating no incremental implications.

Table 65 Summary of cost inputs for the Section D cost-effectiveness model

Resource use	Cost input (base case)	Source / notes
Mechanical thrombectomy	$18,308.49	See **Error! Reference source not ound.**
In-hospital acute stroke care cost by mRS (with / without IV-tPA costs)		Tanny et al 2013, updated to 2016 values. See Table 59. *The base case will assume that 50% of all MT patients receive concomitant IV-tPA.*
mRS 0	$19,605 / $23,558	
mRS 1	$19,884 / $23,837	
mRS 2	$21,719 / $25,671	
mRS 3	$21,719 / $25,671	
mRS 4	$18,985 / $22,938	
mRS 5	$18,985 / $22,938	
mRS 6	$12,671 / $16,624	
Stroke care cost to 12 months by mRS, from Day 90 to Day 365		Tanny et al 2013, updated to 2016 values. See Table 59.
mRS 0	$10,499	
mRS 1	$13,230	
mRS 2	$15,943	
mRS 3	$17,540	
mRS 4	$20,772	
mRS 5	$24,169	
mRS 6	–	
Long-term stroke care costs by mRS, per year		Gloede et al 2014, direct medical

[9] See Section E for further discussion. The Applicant's experience in Germany suggests that 56% of patients received mechanical thrombectomy alone without IV tPA.

Resource use	Cost input (base case)	Source / notes
mRS 0	$1,431	costs only; callibrated according to mRS cost multipliers from Baeten et al 2013. See Table 62 and Table 63
mRS 1	$1,431	
mRS 2	$1,814	
mRS 3	$1,814	
mRS 4	$14,027	
mRS 5	$17,943	
mRS 6	-	

No consideration for indirect / out-of-pocket costs are considered in the current model. From the societal perspective, this may significantly underestimate the value for money of mechanical thrombectomy. The presented cost-effectiveness evidence in Section D should hence be considered as conservative, biasing against mechanical thrombectomy.

C.6 Risk of recurrent strokes

Extrapolation is an important element of the Section D model as much of the functional benefits offered by MT over usual care at Day 90 (i.e., demonstrated through RCT evidence) will persist into the future, and for many patients these functional benefits (and thus their QoL and cost implications) are permanent. From the perspective of a cost-effectiveness analysis of MT, this is particularly important to be accounted for because all costs are accrued at baseline, while the health and economic benefits are spread out over a long period.

In particular, the base case Section D model incorporates the risk of recurrent stroke over time to better reflect the "real world" prognosis for these patients – who having experienced stroke have an increased risk of subsequent stroke compared to someone who has never had a stroke. The following pre-modelling study identifies relevant data informing this process.

C.6.1 Focused analytical plan

A PubMed literature search was performed on the 15th of April with the following search string; *Australia* AND (Recurren* AND (Stroke AND Ischaemic))*; returning 95 citations. Only non-interventional observational studies (unless mechanical thrombectomy and/or usual care including IV-tPA were studied interventions) performed in Australia are considered for inclusion. In addition, an ad-hoc search is also performed to supplement the PubMed search. In total, three Australian cohort data were identified; two reporting on the Perth Community Stroke Study (Hardie et al 2004, Hardie et al 2005) and another study based on a Western Australia data linkage study (Lee et al 2004). In addition, a

systematic review / meta-analysis by Mohan et al (2011) is also identified.

Table 66 Publications reporting risk of recurrent stroke; included for further consideration in the current pre-modelling study

Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke. 2011 May;42(5):1489-94.
Hardie, K, Jamrozik, K, Hankey, GJ, Broadhurst, RJ and Anderson, C (2005) Trends in five-year survival and risk of recurrent stroke after first-ever stroke in the Perth Community Stroke Study. Cerebrovascular Diseases, 19 3: 179-185.
Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke. 2004 Mar;35(3):731-5.
Lee AH, Somerford PJ, Yau KK. Risk factors for ischaemic stroke recurrence after hospitalisation. Med J Aust. 2004 Sep 6;181(5):244-6.

C.6.2 Results of the pre-modelling study

Mohan et al (2011) performed a systematic review which included a total of 13 studies reporting cumulative risk of stroke recurrence in 9115 survivors, as summarised in Table 67 below. The pooled cumulative risk of stroke recurrence was: 3.1% (95% CI, 1.7– 4.4) at 30 days; 11.1% (95% CI, 9.0 –13.3) at 1 year; 26.4% (95% CI, 20.1–32.8) at 5 years; and 39.2% (95% CI, 27.2–51.2) at 10 years after initial stroke.

Table 67 Cumulative risk of stroke recurrence by study

Authors	Country	Initial period	n	Cumulative stroke recurrence risk (%)			
				30 day	1 year	5 year	10 year
Hata et al	Japan	1961–1993	410	.	12.8	35.3	51.3
Petty et al	USA	1975–1989	1111	4.4	12	29.2	39.3
Burn et al	UK	1981–1986	675	.	13.2	29.5	.
Dhamoon et al	USA	1983–1988	655	1.5	7.7	18.3	.
Hardie et al	Australia	1989–1990	328	2	16	32	43
Salgado et al	Portugal	1990–1993	145	.	7	.	.
Rundek et al	USA	1990–1995	611	2.9	9.8	.	.
Kolominsky-Rabas et al	Germany	1994–1998	583	.	11	.	.
Mohan et al	UK	1995–2004	2874	1.1	7.1	16.2	24.5
Modrego et al	Spain	1997–2001	425	2.1	9.5	26	.
Appelros et al	Sweden	1999–2000	377	.	9	.	.
Coull et al	UK	2002–2003	87	15	.	.	.
Xu et al	China	2003–2006	834	5.5	20.6	.	.
Pooled	**–**	**–**	**9115**	**3.1**	**11.1**	**26.4**	**39.2**

Source: Mohan et al 2011. See Mohan et al 2011 for the details of the original sources.
Note: Some studies included haemorrhagic stroke as the index event. However, the authors noted that no differences were identified between studies reporting the cumulative risk of recurrence after ischaemic stroke only compared to studies including haemorrhagic strokes in their analyses.

Mohan et al (2011) identified the presence of substantial heterogeneity between studies at all time points (p<0.0001). Interestingly, and expectedly, the dataset exhibited a temporal reduction in risk of stroke recurrence across the different study populations; that is, more recent studies reported smaller recurrence risk when compared with older studies. This is likely due to the advent and increasing importance given to secondary prevention. The authors developed statistical modelling to demonstrate time trends in risk of stroke recurrence and to predict future trends, which predicted the cumulative risks of stroke recurrence at 1 year and 5 years after first stroke to be 6.49% and 14.3%, respectively, for studies conducted in 2010. This clearly compares favourably to 11.1% and 26.4%, as estimated by a simple pooling of the reported data, as shown in in Table 67 above.

The risk of recurrent stroke observed in the Perth Community Stroke Study (PCSS) cohort was reported in two studies (Hardie et al 2004; Hardie et al 2005). The PCSS registered all episodes of possible acute cerebrovascular disease among residents of a geographically defined segment of Perth, Western Australia, in 1989 to 1990, and the study was repeated in 1995 to 1996 and again in 2000 to 2001. No data relating to the risk of recurrent stroke from the 2000-2001 study appear to have been reported in the literature.

Hardie et al (2004), reporting on the 1989-1990 cohort data, has been included in Mohan et al (2011; see Table 67). Being in line with other studies included in the systematic review, the PCSS 1989-1990 cohort data reported that the risk of recurrent stroke was greatest in the first 6 months at 9% and the risk plateaued thereafter, reaching 16%, 32% and 43% in 1, 5 and 10 years, respectively. Of note, when haemorrhagic stroke was excluded as the index event, the risk was considerably lower than the overall rate in this dataset (28% vs 43%; see Table 67 and Table 68). In PCSS 1989-1990 cohort, recurrent events were predominantly ischaemic with haemorrhagic stroke accounting for less than 5% of all recurrent cases (Table 68).

Table 68 Ten-year cumulative risk of recurrent stroke according to pathological subtype of initial stroke; ischaemic strokes only as the index event

Initial stroke	Recurrent stroke, n			
	Cerebral infarct	Haemorragic	Undetermined	Total (10-year risk)
Cerebral infarction (n=168)	32	2	13	47 (28%)
Large artery occulusion (n=116)	23	1	10	34 (29%)
Lacunar (n=15)	5	0	0	5 (33%)
Cardioembolic (n=28)	3	1	2	6 (21%)
Boundary Zone (n=9)	1	0	1	2 (22%)

Source: Hardie et al 2004, Table 4

The PCSS dataset also demonstrated the temporal reduction in risk of recurrent stroke, as observed in Mohan et al (2011). Hardie et al (2005) reported that the 5-year cumulative risk of first recurrent stroke was 32% (95% CI 25%, 40%; as per Table 67) and 23% (95% CI 16%, 30%) for the 1989-90 and 1995-96 cohorts, respectively (p = 0.07). While not statistically significant, this trend clearly supports the presence of a temporal recurrence reduction among stroke survivors in Australia. Unfortunately, the authors did not report recurrence risks by stroke types (of index events).

Lee et al (2004) performed a retrospective patient data review using the Western Australia (WA) Data Linkage System. First-ever admissions to hospital for ischaemic stroke between 1 July 1995 and 31 December 1999 were included in the study (n=7816). In this dataset, the cumulative risk of having another ischaemic stroke within 6 months of the index event was 5.1% (95%CI, 4.6%-5.7%), increasing to 8.4% (95%CI, 7.6%-9.1%) after 1 year and 19.8% (95%CI, 18.1%-21.4%) after 4 years (Lee et al 2004). These rates are largely in line with the PCSS 1995-96 cohort reported in Hardie et al (2005).

The base case analysis will be informed by the 2010 estimates derived by Mohan et al (2011); i.e., 6.49% during the first 12 months and 14.3% at 5 years. These estimates are slightly lower than older values reported for Australia (Hardie et al 2005, Lee et al 2004), but are considered as more appropriate because they would better capture the expected reduction in recurrent risks than those Australian studies (conducted in the 90's).

C.6.3 Relationship of the pre-modelling study to the economic model

The current pre-modelling study suggested that, also supported by Mohan et al (2010), the risk of stroke recurrence has been declining over time, likely reflecting increasing awareness given to secondary prevention. To capture this, the base case Section D model will apply a recurrence rate of 6.49% during the first year, and a cumulative risk of 14.3% to 5 years (Mohan et al 2011).

In the model, the Day 90 mRS distribution is directly informed by the available RCT evidence. This distribution would have accounted for any impacts due to stroke recurrence occurred to 90 days post the index event. *It was assumed that the monthly probability of stroke recurrence is constant over the first year, allowing the 9-month recurrence risk to be calculated (i.e., between Day 90 to Month 12); i.e., 4.91%. Thereafter, the annual risk is also assumed to be constant at 2.01%, based on the 5-year cumulative risk of 14.30% (as reported in Mohan et al 2011).*

No evidence was identified in the literature review whether disability levels affect the risk

of stroke recurrence. To this end, these recurrent rates are applied regardless of mRS scores in the model.

Sensitivity analysis will be also performed to test other estimates. *The Applicant would like to note that the modelling of recurrent stroke and associated mRS transitions adds considerable complexity to the overall model structure and data requirements. The Excel model provided with the submission incorporates separate analyses that omit the modelling of stroke recurrence, significantly simplifying the model structure. Further discussion is provided in Section C.7.3 below. Findings from this simplified model are presented as a sensitivity analysis in Section D.*5.

C.7 Long-term transitions in mRS scores

As set out above, extrapolation is an important element of the Section D model because the functional benefits offered by MT over usual care will persist into the future. Importantly, a long-term model horizon is also vital to account for the reduction in mortality at Day 90 (i.e., mRS 6) within the calculation of ICER (indeed, a life-time model can only adequately capture this fully). This is particularly relevant for a fair assessment of MT's cost-effectiveness because all intervention costs are incurred at baseline, while its cost / health benefits are accrued in the long run.

The primary outcome in Section B of this submission is the mRS 90 days after the intervention. In each of the five pivotal clinical trials reporting this outcome, this 90-day outcome was also the final efficacy assessment. By comparison, the base case Section D model applies a life-time horizon with the maximum age of 100.[10] During this time, it is possible that patients may improve or deteriorate with respect to functional status. The purpose of this pre-modelling study is to identify long-term clinical data to extrapolate functional outcomes beyond 3 months. The primary source of evidence for this analysis is long-term longitudinal studies that follow patients suffering from acute stroke.

C.7.1 Focused analytical plan

A PubMed literature search was performed on the 20th of April with the following search string; *(mortality OR death OR survival OR prognosis) AND "rankin" AND stroke AND "long-term",* returning 419 citations. A supplementary manual search of reference lists was performed to identify relevant studies not identified through the PubMed search. To be eligible for inclusion, the study had to report long-term functional outcomes (beyond 90

[10] When a shorter-time horizon of 5, 10, or 20 years is used, the ICER increases to $43,542, $22,773, or $14,012, respectively (see Section D.5).

days) for patients with AIS by post-stroke mRS score.

As shown in Table 69, the search identified three relevant studies reporting the association between post-stroke functional status and long-term functional outcomes. An Italian study by Cioncoloni et al (2012) also reported the long-term mRS transitions but only reported data for a mixed stroke population (ischaemic and haemorrhagic) with a relatively small sample size (n=92; 74 and 18 with ischaemic and haemorrhagic, respectively); thus excluded from further consideration.

Table 69 Publications reporting post-stroke functional status and long-term survival

Magalhaes R, Abreu P, Correia M, Whiteley W, Silva MC, Sandercock P. Functional status three months after the first ischaemic stroke is associated with long-term outcome: data from a community-based cohort. Cerebrovasc Dis. 2014;38(1):46-54
Aoki J, Kimura K, Sakamoto Y. Early administration of tissue plasminogen activator improves the long-term clinical outcome at 5years after onset. J Neurol Sci. 2016 Mar 15;362:33-9
Gensicke H, Seiffge DJ, Polasek AE, Peters N, Bonati LH, Lyrer PA, Engelter ST. Long-term outcome in stroke patients treated with IV thrombolysis. Neurology. 2013 Mar 5;80(10):919-25

C.7.2 Results of the pre-modelling study

Table 70 summarises the results for each study identified in the literature search.

Table 70 Results of studies reporting post-stroke functional status and long-term survival

<table>
<tr><th>Study ID</th><th>Population</th><th>Time period / location</th><th>Study design
Follow-up</th><th>Results</th></tr>
<tr><td>Gensicke et al, 2013</td><td>Stroke treated with IV-tPA
N=257</td><td>1998-2007
Switzerland</td><td>Observational study based on IV-tPA registry
Mean age 72 years
Median 3 years (IQR 1-5)</td><td>Long-term outcome at follow-up in 257 patient based on mRS score at baseline
<table>
<tr><th rowspan="2">mRS at 3 months</th><th colspan="8">mRS score at 3 years</th></tr>
<tr><th>mRS 0
n (%)</th><th>mRS 1
n (%)</th><th>mRS 2
n (%)</th><th>mRS 3
n (%)</th><th>mRS 4
n (%)</th><th>mRS 5
n (%)</th><th>mRS 6
n (%)</th><th>Total
n (%)</th></tr>
<tr><td>mRS 0</td><td>26 (67)</td><td>3 (8)</td><td>3 (8)</td><td>0 (0)</td><td>2 (5)</td><td>0 (0)</td><td>5 (13)</td><td>39 (100)</td></tr>
<tr><td>mRS 1</td><td>33 (60)</td><td>4 (7)</td><td>1 (2)</td><td>3 (5)</td><td>4 (7)</td><td>2 (4)</td><td>8 (15)</td><td>55 (100)</td></tr>
<tr><td>mRS 2</td><td>17 (31)</td><td>7 (13)</td><td>10 (18)</td><td>8 (15)</td><td>4 (7)</td><td>2 (4)</td><td>7 (13)</td><td>55 (100)</td></tr>
<tr><td>mRS 3</td><td>3 (18)</td><td>2 (12)</td><td>3 (18)</td><td>3 (18)</td><td>2 (12)</td><td>1 (6)</td><td>3 (18)</td><td>17 (100)</td></tr>
<tr><td>mRS 4</td><td>1 (3)</td><td>0 (0)</td><td>3 (8)</td><td>4 (10)</td><td>11 (28)</td><td>15 (38)</td><td>6 (15)</td><td>40 (100)</td></tr>
<tr><td>mRS 5</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>5 (31)</td><td>11 (69)</td><td>16 (100)</td></tr>
<tr><td>mRS 6</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>35 (100)</td><td>35 (100)</td></tr>
</table>
Source: Gensicke et al, 2013; Figure A</td></tr>
<tr><td>Aoki et al, 2016</td><td>Patients with acute ischaemic stroke who were treated with tPA
N=256 (115 included in the analysis)</td><td>2005 to 2013
Japan</td><td>Prospective registry of consecutive patients
Median age at baseline 79 years (included patients; n=115)
5 years follow-up</td><td>Long-term outcome at 5 years after stroke onset in 115 patient based on mRS score at baseline
<table>
<tr><th rowspan="2">mRS at 3 months</th><th colspan="8">mRS score at 5 years</th></tr>
<tr><th>mRS 0
n (%)</th><th>mRS 1
n (%)</th><th>mRS 2
n (%)</th><th>mRS 3
n (%)</th><th>mRS 4
n (%)</th><th>mRS 5
n (%)</th><th>mRS 6
n (%)</th><th>Total
n (%)</th></tr>
<tr><td>mRS 0</td><td>11 (52)</td><td>3 (14)</td><td>0 (0)</td><td>0 (0)</td><td>1 (5)</td><td>0 (0)</td><td>6 (29)</td><td>21 (100)</td></tr>
<tr><td>mRS 1</td><td>3 (60)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>2 (40)</td><td>5 (100)</td></tr>
<tr><td>mRS 2</td><td>1 (14)</td><td>1 (14)</td><td>4 (57)</td><td>1 (14)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>7 (100)</td></tr>
<tr><td>mRS 3</td><td>0 (0)</td><td>3 (30)</td><td>3 (30)</td><td>0 (0)</td><td>1 (10)</td><td>0 (0)</td><td>3 (30)</td><td>10 (100)</td></tr>
<tr><td>mRS 4</td><td>1 (9)</td><td>0 (0)</td><td>0 (0)</td><td>1 (9)</td><td>0 (0)</td><td>2 (18)</td><td>7 (64)</td><td>11 (100)</td></tr>
<tr><td>mRS 5</td><td>0 (0)</td><td>1 (3)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>4 (12)</td><td>28 (85)</td><td>33 (100)</td></tr>
<tr><td>mRS 6</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td><td>28 (100)</td><td>28 (100)</td></tr>
</table>
Source: Aoki et al, 2016; Figure 1B</td></tr>
</table>

<table>
<tr><th>Study ID</th><th>Population</th><th>Time period / location</th><th>Study design
Follow-up</th><th>Results</th></tr>
<tr><td>Magalhaes et al, 2014</td><td>First-ever ischaemic stroke
N=380</td><td>October 1998 to September 2000
Portugal</td><td>Prospective community-based study.
Median age at baseline 73 years
7 years follow-up</td><td>Distribution of status at 7 years for 3-month survivors
<table>
<tr><th rowspan="2">mRS at 3 months</th><th colspan="4">Status at 7 years</th></tr>
<tr><th>mRS 0-1
n (%)</th><th>mRS 2-3
n (%)</th><th>mRS 4-5
n (%)</th><th>mRS 6
n (%)</th></tr>
<tr><td>mRS 0-1</td><td>45 (37)</td><td>22 (18)</td><td>10 (8)</td><td>46 (37)</td></tr>
<tr><td>mRS 2-3</td><td>15 (14)</td><td>25 (23)</td><td>10 (9)</td><td>58 (54)</td></tr>
<tr><td>mRS 4-5</td><td>0 (0)</td><td>3 (4)</td><td>12 (18)</td><td>53 (78)</td></tr>
</table>
Source: Magalhaes et al, 2014; Table 2</td></tr>
</table>

Abbreviations: ICH, intra-cranial haemorrhage; mRS, modified Rankin Scale; tPA, tissue plasminogen activator; IQR, interquartile range.

The study reported by Gensicke et al (2013) was observational study is based on a registry of patients receiving thrombolytic therapy the University Hospital Basel. The study included 257 patients treated with IV-tPA for stroke. The median time of follow-up was 3.0 years. The analysis of functional status at follow-up by 3-month mRS score suggests that patients with mRS scores of 0-1 are likely to improve or retain the same functional status. Patients with mRS 3 may have a good chance of improving (48%), but some deteriorate (18%) or die (18%), whilst patients with mRS 4 are more likely to remain or deteriorate (28% or 38%, respectively) or die (15%) over the 3-year follow-up. No patients with mRS 5 showed any improvement and remained bedridden (31%) or have died (69%).

Aoki et al (2016) retrospectively reviewed data from a registry of consecutive patients with AIS receiving IV-tPA at a Japanese stroke centre between 2005 and 2013. This study showed that after 5 years, the majority of patients with mRS 0 at three months retained their functional status (52%), a small proportion deteriorated by one mRS point (14%) and about a third died (29%). A large proportion of patients with mRS 1 had improved to mRS 0 by 5 years (60%), whilst the remainder died (40%). As also observed in Gensicke et al (2013), patients with severe mRS scores (4-5) rarely improved, with the majority having died by 5 years (64% and 85%, respectively).

Similar results were observed in the study by Magalhaes et al (2014). This was a prospective community-based study in Northern Portugal run between October 1998 to September 2000, in patients experiencing first-ever ischaemic strokes. Participants were examined at baseline and followed-up at three months, one and seven years. The study included 380 patients with ischaemic stroke, of whom 67 (17.6%) had died at three months. For patients with a relatively good functional status at 3 months (mRS 0-1), there was some deterioration in functional status over the 7-year study duration; however, 37% remained in the mRS 0-1 category, while 37% died after 7 years. For patients with mRS scores 2-3 after 3 months, 14% improved to the mRS category 0-1 after 7 years, 23% remained in the same category and the remainder deteriorated in functional status (9%) or died (54%). Patients with mRS scores 4-5 at 3 months had an extremely high mortality rate of 78% at 7 years. Again, a very small proportion (4.4%) improved in functional status if they were in mRS scores 4-5 at 3 months.

C.7.3 Relationship of the pre-modelling study to the economic model

Overall, the data show that patients with poorer functional status (i.e., mRS 4-5) are very unlikely to exhibit any improvement in their functional status, while patients with favourable status are likely to experience “rehabilitation” effects over time or maintain their functional ability.

Accounting for these rehabilitation effects may be conservative in light of recently released long-term REVASCAT data (unpublished). The 12-month follow up data suggested that the Day 90 functional benefits offered by MT were maintained to 12 months; suggesting there were no clear convergence between the two arms in terms of mRS scores. The common odds ratio of the distribution of mRS scores at 12 months was 1.80 (95% CI 1.10-2.99), similar to the finding at 90 days (common OR 1.71; 95% CI 1.05-2.81). Similarly, the proportion of patients with an mRS score of 0 to 2, indicating functional independence, was higher in the thrombectomy group (43.7% vs 30.1%; adjusted OR 2.14; 95% CI 1.15-3.97), corresponding to a number needed to treat of 7. The finding was similar when looking at Barthel Index scores of 95 to 100.[11]

It should be noted that none of these analyses are adjusted for baseline characteristics, and it is therefore possible that some of the differences in long-term functional outcomes are related to confounding factors such as age or comorbidities prior to stroke. Having acknowledged this, in terms of generalisability to the modelled patient population, Gensicke et al (2013) appears to be preferred over other studies. Aoki et al (2016) included patients considerably older than Gensicke et al (2013); likely explaining greater rates of death observed in this study. Also, this study had a relatively small sample size of 115 patients (more prone to the possible confounding noted above), which made the reported results difficult to interpret and likely unreliable after stratification into 6 mRS groups (e.g., data for patients with mRS 2 at 3 months; see Table 70). Magalhaes et al (2014) was considered as outdated; unlikely to reflect the stroke care currently provided to stroke survivors. Also, it did not provide granularity in terms of mRS transitions that is necessary for the economic model.

Technical issues of incorporating recurrent stroke and 3-year post-stroke transition

As demonstrated above, the only available data for the modelling of mRS transitions post 90 days are based on observational studies with follow-up periods ranging from 3 (Gensicke et al 2013; applied in the base case analysis) to 7 years (Magalhaes et al 2014). Under the Markov cohort design (thus “memoryless”) with 1 year cycle during the post-acute/mid-term phase (see Section D for further details), the modelling of stroke recurrence as well as subsequent modelling of mRS changes based on these data is hence technically demanding.

To retain an otherwise readily understood, pragmatic model design (i.e., the model in principle simply follows post-stroke mRS changes of the modelled cohort over time) and,

[11] Dávalos A, Cobo E, Molina C, et al. Randomized trial of revascularization with Solitaire FR device versus best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within eight hours of symptom onset: REVASCAT trial, final results at 12 months. Presented at: International Stroke Conference; February 18, 2016; Los Angeles, CA.

more importantly, to provide transparency, *it is assumed that the reported 3-year mRS transitions are to be absorbed by 12 months.* This assumption should be reasonable because the majority of mRS changes would generally occur during the mid-term phase (i.e, Day 90 to Day 365).

Based on the above assumption, the derivation of Day 365 mRS distribution is performed through matrix multiplications in order to account for the improvement / deterioration of mRS post 90 days, as demonstrated below.

Table 71 presents the Day 90 mRS distribution applied for the base case analysis, as informed by the published meta-analysis by Goyal et al (2016). Table 72 presents the post Day 90 mRS changes to 3 years as reported by Gensicke et al (2013). *By assuming these mRS changes to have absorbed by 12 months*, a Day 365 mRS distribution can be determined, as shown in Table 73 below. Importantly, the patient cohort in each treatment arm of the model is affected by the same probabilities of mRS improvement /deterioration after Day 90 (thus no recurring treatment effects).

Changes in mRS after stroke recurrence are also similarly performed by assuming that all mRS changes occur within 12 months (to be discussed further in Section D).

Table 71 Expected distribution across mRS health states at Day 90 – the base case Section D model assumption

mRS	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	Dead
At Day 90							
Mechanical thrombectomy + usual care	10.0%	16.9%	19.1%	16.9%	15.6%	6.2%	15.3%
Usual care	5.0%	7.9%	13.6%	16.4%	24.7%	13.5%	18.9%

Abbreviations: mRS, modified Rankin score
Source: Meta-analysed ITT data from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration (Goyal et al, 2016); discussed in Section C.3 above.

Table 72 Transition matrix depicting mRS changes from Day 90 to 3 years as reported by Gensicke 2013 – the base case Section D model assumption

		At 3 years (taken as at 12 months in the model)						
		mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6
At Day 90	mRS 0	66.7%	7.7%	7.7%	0.0%	5.1%	0.0%	12.8%
	mRS 1	60.0%	7.3%	1.8%	5.5%	7.3%	3.6%	14.5%
	mRS 2	30.9%	12.7%	18.2%	14.5%	7.3%	3.6%	12.7%
	mRS 3	17.6%	11.8%	17.6%	17.6%	11.8%	5.9%	17.6%
	mRS 4	2.5%	0.0%	7.5%	10.0%	27.5%	37.5%	15.0%
	mRS 5	0.0%	0.0%	0.0%	0.0%	0.0%	31.3%	68.8%

Abbreviations: mRS, modified Rankin Score
Source: Gensicke et al 2013 (see Table 70)

Table 73 Calculated mRS distribution at Day 365 after rehabilitation effects – the base case Section D model assumption

mRS	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	Dead
At Day 365							
Mechanical thrombectomy + usual care	26.1%	6.4%	8.7%	8.2%	9.4%	10.1%	31.1%
Usual care alone	15.8%	4.6%	7.7%	7.8%	10.5%	15.2%	38.3%

Abbreviations: mRS, modified Rankin score
Note: These distributions relate to patients who do not experience stroke recurrence between Day 90 and Day 365.

The Applicant acknowledges that the above approach is a simplification. Also, the Applicant is aware of a potential double counting of mRS changes because while the modelling of stroke recurrence is explicitly incorporated in the Section D model (see Section C.6), these 3-year mRS changes would also already account for recurrence-related mRS changes.

To this end, sensitivity analysis will present a separate model which omits the explicit modelling of stroke recurrence. As discussed in Section C.6, this alternative model will also address considerable model complexities necessary to capture the mRS transitions caused by stroke recurrence; of note, this model will demonstrate that stroke recurrence has minimal implications to the ICER (see Section D.5.3).[12]

In addition, the Applicant is also aware that the assumption of having all mRS changes absorbed by 12 months affects the way discounting is performed by the model, in particular, the calculation of life years over the model time horizon (life years in the base case).

To this end, sensitivity analysis will present another model which omits the explicit modelling of stroke recurrence and also applies annualised mortality rates based on the 3-year rates (instead of assuming these deaths to occur by 12 months). Transitions among mRS 0 to 5 are still assumed to be absorbed by 12 months in this alternative model.

Table 74 below summarises the post Day 90 mortality rates (or transition rates to mRS 6) employed in this alternative model. It can be seen that the mortality rates for patients with mRS 0 to 4 at Day 90 are relatively similar to each other with a mean annualised value of 5.11%, while the rate for patients with mRS 5 at Day 90 is considerably higher. Given the memoryless nature of the Markov cohort model methodology, it is technically complex to allocate a mortality rate according to the patient's mRS at Day 90 over time. To this end, the mean value is employed to model mortality for patients in mRS 0-4 over time. For patients in mRS 5, the higher reported rate of 32.14% per annum is applied; note that, as discussed

[12] The ICER changes from $12,880 in the base case model to $8801 in this alternative model.

above, patients with severe disability at Day 90 (like mRS5) generally stay at the same compromised functional level (see Table 70 above), providing support to this approach. The model also assumes that these mortality rates are applicable beyond 3 years to the model end.

Table 74 Rates of mortality from Day 90 to 3 years as reported by Gensicke 2013 – explored in an alternative model for sensitivity analysis

mRS at 3 months	% transiting to mRS 6 by 3 years	Annualised mortality (transition to mRS6)	Applied in the model		Note
			Adjusted for Day 90 to Day 365 (i.e., 275 day risk)	Average mRS 0-5, annualised (post Day 365)	
mRS 0	12.8%	4.47%	3.37%	5.11%	The annualised mean value applied post +1 year phase (continue to be applicable till the model end). The Day 90-365 values used to calculate the Day 365 mRS distribution in Table 76 below).
mRS 1	14.5%	5.10%	3.85%	5.11%	
mRS 2	12.7%	4.44%	3.35%	5.11%	
mRS 3	17.6%	6.27%	4.74%	5.11%	
mRS 4	15.0%	5.27%	3.98%	5.11%	
mRS 5	68.8%	32.14%	25.23%	32.14%	Applied post +1 year phase (continue to be applicable till the model end).

Abbreviations: mRS, modified Rankin Score
Source: Gensicke et al 2013 (see Table 70)

The above approach effectively reduces the proportion of patients who die by Day 365 for each mRS from 1 to 5. The transition matrix in Table 72 has to be recalibrated to account for this, as shown in Table 74. The resulting Day 365 mRS distribution is shown in Table 76 below.

Table 75 Transition matrix depicting mRS changes from Day 90 to 3 years as reported by Gensicke 2013, recalibrated to adjust for rates of mortality over time – explored in an alternative model for sensitivity analysis

		At 12 months						
		mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6
At Day 90	mRS 0	73.9%	8.5%	8.5%	0.0%	5.7%	0.0%	3.4%
	mRS 1	67.5%	8.2%	2.0%	6.1%	8.2%	4.1%	3.9%
	mRS 2	34.2%	14.1%	20.1%	16.1%	8.1%	4.0%	3.3%
	mRS 3	20.4%	13.6%	20.4%	20.4%	13.6%	6.8%	4.7%
	mRS 4	2.8%	0.0%	8.5%	11.3%	31.1%	42.4%	4.0%
	mRS 5	0.0%	0.0%	0.0%	0.0%	0.0%	74.8%	25.2%

Abbreviations: mRS, modified Rankin score
Source: Gensicke et al 2013 (see Table 70) and Table 74.
Notes: Distribution across mRS 0-5 at 12 months is adjusted to account for a lower mortality rate (i.e., mRS 6) for each Day 90 mRS by keeping the proportional distribution for these six health states (mRS 0-5) constant.

Table 76 Calculated mRS distribution at Day 365 after rehabilitation effects with no recurrent stroke, adjustment for rates of mortality over time – explored in an alternative model for sensitivity analysis

mRS	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	Dead
Mechanical thrombectomy + usual care	29.23%	7.23%	9.82%	9.33%	10.64%	13.85%	19.91%
Usual care alone	17.73%	5.22%	8.77%	8.81%	11.93%	22.54%	24.99%

Abbreviations: mRS, modified Rankin Score

The Applicant acknowledges that it may be unusual to present three separate models to address uncertainties due to the lack of data inputs that are perfectly compatible to the model design. However, these models share the same core structure (i.e., a 12-month decision tree followed by a Markov cohort design with health stated defined by mRS). And importantly, they are based on the same premise for MT's favourable cost-effectiveness; i.e., the functional benefits demonstrated by the pivotal RCTs at Day 90 vs usual care will persist over long run, which continue to produce on-going cost and QoL benefits. In our opinion, these models are in principle very simple when compared with other cost-effectiveness models presented to MSAC, and thus they would not cause excess evaluation burden.

Possible pros and cons of each model are discussed in

Table 77 below. For convenience, the ICER from each model is also presented to show that the uncertainties being examined by the presentation of alternative models have very limited impacts on the ICER and also highlight that these models together provide a convincing balance of evidence for MT's favourable cost-effectiveness vs usual care (see Section D.5.3 for further discussion).

Table 77 Pros and cons of the three models explored in Section D

Model version	Pros	Cons	ICER (see Section D for further discussion)[1]
Base case model	Cost and LY/QALY implications of stroke recurrence are fully captured. Accurately reflect the full prognosis / natural history of acute ischaemic stroke.	Possible double counting of LY/QALY implications of stroke recurrence. Imperfect discounting of LY/QALY in the first 3 years (due to the assumption all mRS transitions be absorbed by 12 months).	$12,880 per add. QALY
Alternative model 1 – base case model MINUS the modelling of stroke recurrence	Far simpler and more transparent than the base case model without meaningfully compromising the modelling of prognosis / natural history of acute ischaemic stroke.	Underestimation of cost implications of stroke recurrence. Possible underestimation of LY/QALY implications of stroke recurrence (especially post 3 years). Imperfect discounting of LY/QALY in the first 3 years (due to the assumption all mRS transitions be absorbed by 12 months).	$8,801 per add. QALY
Alternative model 2 – Alternative model 1 PLUS better modelling of mortality	Far simpler and more transparent than the base case model. Better captures post-stroke survival (see Section D.5.3).	As per Alternative model 1, but has an improved application of discounting effects on LY/QALY. Slightly more complex than Alternative model 1.	$15,953 per add. QALY

Abbreviations: LY, life year; QALY, quality adjusted life year.

[1] Life-time horizon; no MT for recurrent strokes.

D. ECONOMIC EVALUATION FOR THE MAIN INDICATION

Summary

- A modelled life-time cost-utility analysis is presented to examine the cost-effectiveness of mechanical thrombectomy vs usual care. This analysis affirms a favourable cost-effectiveness of the procedure with the ICER falling below $15,000 per QALY gain.
- This favourable outcome reflects QoL /life year benefits via better functional/survival outcomes offered by mechanical thrombectomy and the associated cost savings. Post-stroke disability and dependency can be extremely debilitating and very costly. The "one-off" procedure hence produces long-term, often permanent, benefits vs usual care.
- A "within-trial" economic evaluation of EXTEND-IA suggested mechanical thrombectomy to be cost saving (thus representing a dominant strategy vs usual care); providing further support for the current Section D results. Similar results have been reported in other published economic evaluations (see Section D.3.1).
- The meta-analysed ITT data (Goyal et al 2016) inform the post-stroke mRS transitions to Day 90. The applicability of this dataset in terms of population / circumstances of use characteristics have been justified in Section C. Individual trials, including subgroup analysis for with/without IV-tPA use, are also examined in sensitivity analysis; further ascertaining the favourable cost-effectiveness (see Section D.5.3).
- Extrapolation is an important and necessary element of the model given the aforementioned long-term/permanent health and economic benefits, while all procedural costs are absorbed at baseline. Needless to say, the mortality benefits demonstrated at Day 90 can only be adequately accounted for by a life-time model. A 5-year model horizon, tested in sensitivity analysis, nonetheless returns an estimated ICER of $43,542 (see Section D.5.3).
- The balance of evidence presented in the current Section D robustly confirms that mechanical thrombectomy under the proposed listing will represent a cost-effective addition to "hyperacute" treatment options. Currently, the provision of the hyperacute stroke care has been criticised as being less than optimal in Australia (see Section E), and the proposed listing will be a welcome addition to improve treatment options for stroke patients.

The proposed procedure involves a mechanical thrombectomy device such as the Solitaire 2 and Solitaire FR™ Revascularization Devices. It is designed to directly remove thrombus, restore blood flow through the occluded vessel and allow reperfusion of the previously ischaemic brain tissue. The clinical benefits achieved with the use of mechanical thrombectomy for treatment of acute ischaemic stroke, either alone or in combination with IV-tPA, have been well established (see Section B). Multiple RCTs have demonstrated that mechanical thrombectomy is safe and effective in restoring blood flow in large vessel occlusions and can significantly improve post-stroke functional outcomes.

As specified in the Protocol and also discussed in Section A, the assessment of mechanical thrombectomy presented in this submission is generic, i.e. considering evidence for all relevant technologies that can deliver endovascular thrombolysis. The presentation of clinical

evidence has been done on this basis, and the following cost-effectiveness analysis will be hence performed accordingly.

D.1 Overview of the economic evaluation

Section B has established that mechanical thrombectomy + usual care (referred to simply as mechanical thrombectomy hereafter) in the target patient population offers superior patient outcomes while offering acceptable safety when compared with usual care. When compared with usual care, mechanical thrombectomy increases the likelihood of successful revascularisation (see Section B and Section C.2 for subgroup analyses). More importantly, it has been demonstrated to provide better functional outcomes during the post-stroke period.

The improvement in post-stroke functional levels offers long-term cost and health / QoL benefits, which will form the basis for the cost-effectiveness evaluation of mechanical thrombectomy in the current Section D.

D.1.1 Type of economic evaluation

The cost-effectiveness evidence presented to support the listing of mechanical thrombectomy under the proposed listing is based on a modelled cost-utility analysis. Extrapolation is an important and necessary element of the current economic evaluation given that the functional benefits offered by mechanical thrombectomy vs usual care have long-term, and likely permanent in many patients, QoL and cost benefits. Needless to say, the mortality benefits demonstrated at Day 90 can only be adequately accounted for a long-term model horizon (indeed, a life-time model can only fully capture this).

Nonetheless, a stepped economic evaluation is also presented, gradually expanding translational / extrapolation scopes from a trial based analysis. This is presented in Section D.5.2. Importantly, there is a published within-trial economic evaluation based on EXTEND-IA (Campbell et al 2015), demonstrating that mechanical thrombectomy represents a “dominant” strategy (i.e., less costly and more effective). This economic evaluation, along with other published modelled evaluations, is reviewed in Section D.3.1.

Table 78 summarises key model inputs for the current cost-effectiveness analysis, as organised by three key time points within the modelled time horizon (see Section D.3.2 for further discussion). Derivation and justification for these estimates have been discussed in Section C.

Table 78 Data inputs and data sources, base case analysis

Data inputs	Data source / notes
Acute phase (to 90 days)	
mRS distributions at discharge and 90 days	Meta-analysed IPD data of RCTs (Goyal et al 2016) Death is captured in mRS6. No other cause deaths are assumed to occur.
Acute stroke treatment cost, by mRS and treatment	*See Section C.2* Mechanical thrombectomy offered in addition to usual care (i.e., complementary service); costing based on the proposed fee and other relevant resource use. Usual care may or may not involve IV-tPA. Costs of acute stroke care by mRS as informed by Tanny et al (2013).
Utility scores, by mRS	*See Section C.4* Utility informed by NEMESIS data (Sturm et al 2002)
Mid-term (90 days to 12 months)	
mRS transitions to 12 months	*See Section C.7* Improvement / deterioration in mRS informed by Gensicke et al (2013). Death is captured in mRS6 (including those triggered by recurrent stroke during this phase). No other cause deaths are assumed to occur.
Mid-term stroke management cost, by mRS	*See Section C.5* Equally applied to both treatment arms; however, better functional outcomes in the MT arm will provide cost savings (via less intensive /costly care). Cost inputs primarily informed by Tanny et al (2013).
Utility scores, by mRS	As per the acute phase.
Risk of recurrent stroke and post-recurrent stroke mRS distribution	*See Section C.6* Risk of recurrence informed by a published met-analysis (Mohan et al 2011), well corroborated with Australian data in the literature (e.g., Hardie et al 2004). Improvement / deterioration in mRS post recurrence are informed by the RCT data and Gensicke et al (2013); *see Section D.4.1 for calculations/assumptions.* Death due to recurrence is captured in mRS6 *Separate Markov models are also presented to investigate the impact of omitting recurrent stroke (see Section D.5.3).* Reasons for this approach are described in Section C.7.3.
Long-term (post 12 months)	
mRS transitions post 12 months	*See Section C.7* The mRS transition data for the mid-term above (to 12 months) are based on a 3-year follow-up (Gensicke et al, 2013). No further change in mRS (i.e., no improvement / deterioration in stroke disability) unless recurrent stroke occurs.

Data inputs	Data source / notes
Long-term stroke management cost, by mRS	*See Section C.5* Equally applied to both treatment arms; however, better functional outcomes in the MT arm will provide cost savings (via less intensive /costly care).
Utility scores, by mRS	As per the mid-term phase.
Risk of recurrent stroke and post-recurrent stroke mRS distribution	As per the mid-term phase. *Separate Markov models are also presented that omits any recurrent strokes (see Section D.5.3).*
Mortality (other causes)	As per the Australian life table.

Abbreviations: MT, mechanical thrombectomy; mRS, modified Rankin scare; NEMESIS, North East Melbourne Stroke Incidence Study.
Note: See Section D.4 for further discussion.

D.2 Population and circumstances of use reflected in the economic evaluation

D.2.1 Demographic and patient characteristics

This has been discussed in Section C.2 and C.3 and the applicability of the trial data to the target population has been justified.

The patient characteristics of the modelled cohort are to match the proposed MBS population. Broadly speaking, they have confirmed occlusions in the proximal anterior intra-cranial circulation. Patients in the mechanical thrombectomy arm are required to be able to undergo initiation of endovascular treatment within 6 hours after symptom onset.

Applicability assessment provided in Section C.2 and C.3 justified that the included pivotal trials generally match the proposed MBS patient population. The baseline patient characteristics, e.g., age and gender, are informed by the meta-analysed RCT data (68 years, 53% male; Goyal et al 2016).

D.2.2 Circumstances of use

Again, this has been discussed in Section C.2 and C.3 and the applicability of the trial data to the circumstances of use likely observed under the MBS funding has been justified.

It is expected that the provision of mechanical thrombectomy would be restricted to “centres of excellence” in stroke care due to the high infrastructure requirements (see Section E.1). The usual care provided in these centres would be by and large well standardised and, importantly, is likely to be generalisable to the care provided in the pivotal RCTs. Section C.2 and C.3 also demonstrated that effect modifications associated with circumstances of use parameters such as the concurrent use of IV-tPA, the types of imaging tests and time to MT are unlikely to be significant, further supporting the applicability of the available trial data for the purpose of this analysis.

Importantly, the control data from the pivotal RCTs inform the usual care arm of the Section D model. The care provided in the control arms of the trials are overall representative of the care provided in the absence of MT in the Australian practice.

D.3 Structure and rationale of the economic evaluation

D.3.1 Cost-effectiveness evidence for mechanical thrombectomy in the literature

To inform formulation of modelling approaches for the current analysis, a review of published cost-effectiveness models comparing mechanical thrombectomy vs usual care is performed. A PubMed search is performed on the 31 of March, 2016, with the following search strategy; *(Cost OR Economic)) AND (Stroke AND Thrombectomy)*. A total of forty-seven citations were identified with five publications considered as relevant for further investigation. Of note, a cost-benefit analysis based on MR CLEAN (Mangla et al 2016) was also identified but excluded from this literature review because of significant methodological / scope differences from the current model (e.g., no use of Markov analysis). A supplementary ad-hoc search also identified a within-trial cost-effectiveness evaluation of EXTEND-IA (Campbell et al. 2015).

Table 79 Published cost-effectiveness models for mechanical thrombectomy

Campbell et al (for the EXTEND-IA investigators) 2015 Endovascular thrombectomy reduces length of stay and treatment costs within 3 months of stroke [conference poster].
Aronsson M, Persson J, Blomstrand C, Wester P, Levin LÅ. Cost-effectiveness of endovascular thrombectomy in patients with acute ischaemic stroke. Neurology. 2016 Mar 15;86(11):1053-9.
Ganesalingam J, Pizzo E, Morris S, Sunderland T, Ames D, Lobotesis K. Cost-Utility Analysis of Mechanical Thrombectomy Using Stent Retrievers in Acute Ischaemic Stroke. Stroke. 2015 Sep;46(9):2591-8. doi:
Kim AS, Nguyen-Huynh M, Johnston SC. A cost-utility analysis of mechanical thrombectomy as an adjunct to intravenous tissue-type plasminogen activator for acute large vessel ischaemic stroke. Stroke. 2011 Jul;42(7):2013-8.
Nguyen-Huynh MN, Johnston SC. Is mechanical clot removal or disruption a cost-effective treatment for acute stroke? AJNR Am J Neuroradiol. 2011 Feb;32(2):244-9.
Patil CG, Long EF, Lansberg MG. Cost-effectiveness analysis of mechanical thrombectomy in acute ischaemic stroke. J Neurosurg. 2009 Mar;110(3):508-13.

The EXTEND-IA analysis is reviewed first separately from other modelled evaluations because this analysis provides cost-effectiveness evidence that is internally consistent with the clinical evidence considered in Section B. It also relies on locally-relevant within-trial resource use data in quantifying the healthcare resource costs. This analysis is hence considered as extremely informative to aid the MSAC's deliberations.

The remaining publications all report modelled economic evaluations of mechanical thrombectomy performed outside of Australia. While their findings may lack direct relevance

for MSAC's evaluation of the cost-effectiveness of MT in Australia, they consistently provide evidence of favourable cost-effectiveness in support of mechanical thrombectomy. They also aid the formulation / validation of modelling strategies for the current model.

EXTEND-IA economic evaluation

A cost-effectiveness analysis was performed on the basis of mRS outcomes at 90 days and within-trial resource use (captured in terms of length of stay in the acute stroke unit, inpatient fast and slow stream rehabilitation, nursing home and palliative care as well as intervention costs). The comparison was made vs IV-tPA. This study was informed by a study of 70 patients recruited across 10 hospitals in Australia and New Zealand. All costing was performed using Australian costs. Hence it is considered that this study provides evidence that is directly relevant to the Australian healthcare setting.

Resource use costs reported in this study are summarised in Table 80 below, demonstrating mechanical thrombectomy to be a cost saving strategy. While complete costing details were not available, a large proportion of cost savings appear to have come from shorter lengths of stay at hospital / inpatient rehabilitation facility (see Figure 13 below).

Table 80 Cost comparison of mechanical thrombectomy vs usual care, based on EXTEND-IA

Costs (first 3 months)	Usual care + MT	Usual care[1]
Alteplase	$3,465	$3,465
Inter-hospital transfer (allow for 75% transferred)	$836	n/a
Endovascular consumables	$10,690	n/a
Endovascular staffing	$3,560	n/a
Inpatient care costs	$23,000 CI95 $15,709-$30,029	$43,000 CI95 $31,290-$54,688
TOTAL	**$41,551**	**$45,465**

Source: Campbell et al 2015, Table 2. Also presented in Section C.5.

[1] IV-tPA eligible patients only.

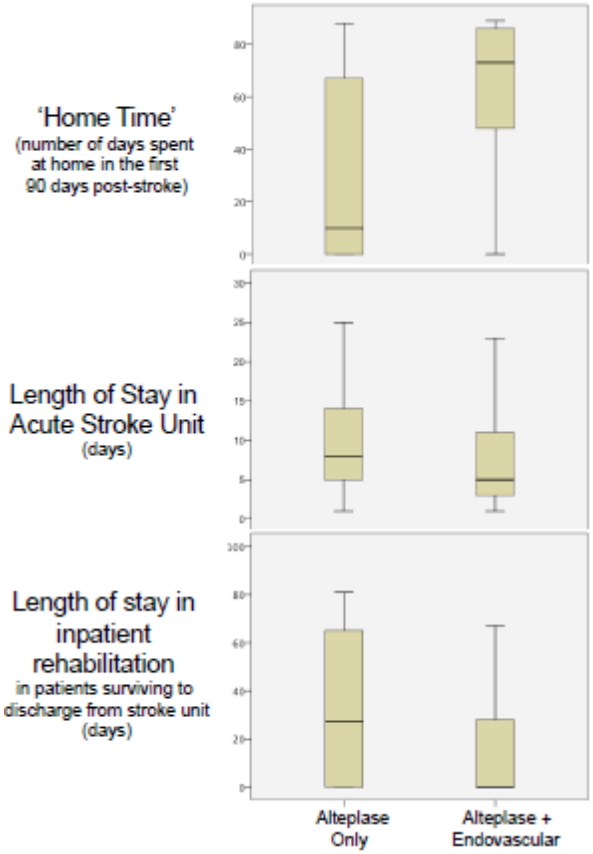


Figure 13 Boxplots of length of stay by treatment group

Source: Campbell et al 2015, Figure 2

The EXTEND-IA economic evaluation provides a strong support for the favourable cost-effectiveness for mechanical thrombectomy; mechanical thrombectomy was shown to represent the dominant strategy over usual care (i.e., more effective and cheaper). It is important to note, in particular, that the savings in the short-term care costs alone (to 90 days) were sufficient to make mechanical thrombectomy a dominant strategy in this analysis (Campbell et al 2015).

The current Section D model will build upon this evidence base but will provide additional flexibility to explore alternative clinical data (thus able to explore wider population / circumstances of use characteristics) as well as cost / utility inputs and longer duration of follow-up post intervention

Other modelled economic evaluations in the literature

Five modelled cost-effectiveness evaluations of mechanical thrombectomy were identified by the aforementioned literature search. Two of them were informed by the five RCTs that were also considered in the current submission (Aronsson et al 2016, Ganesalingam et al 2015), while the remaining three were based on clinical data from the Multi MERCI trial using the

following thrombectomy devices including Merci Retriever X5, X6 and L5 Retriever (Kim et al 2011, Nguyen-Huynh and Johnston 2011, Patil et al 2009). Key characteristics and results from these publications are summarised in Table 81.

All studies consistently suggest a very favourable cost-effectiveness of mechanical thrombectomy; ranging from mechanical thrombectomy being "dominant" (Aronsson et al 2016) to US$16,001 per additional QALY (Kim et al 2011; 2009 values).

All models employed mRS as the criteria to define post-stroke levels with a long-term time horizon (generally life-time). Aronsson et al (2016) for example assumes that mRS distributions of the modelled cohort do not change over time post 90 days (that is, all patients maintain their disability levels at 90 days *or improvement / deterioration cancel out each other over time, keeping the average mRS constant over time*). The authors note this assumption to be conservative, as based on the trend of declining functional status observed in a US follow-up study of +500 stroke survivors (Dhamoon et al 2009).

These published models are very similar to the current Section D model in model structure / methodology, providing support to the current Section D model. The current Section D model has the following features that would mean a more conservative view on the cost-effectiveness of mechanical thrombectomy being presented to the MSAC:

- The base case analysis will apply "rehabilitation effects" whereby patients' mRS distributions overall improve from 90 days to 12 months.
- The risk of recurrent stroke over time is captured.

The model structure and methodologies are further described and discussed in the following section.

Table 81 Modelled cost-effectiveness evaluations of mechanical thrombectomy

Study / perspective	Clinical data source	Modelling approach and key assumptions	Key results
Aronsson 2016 / Swedish healthcare system	Meta-analysis of 90 day mRS scores from ESCAPE, EXTEND-IA, MR CLEAN, REVASCAT and SWIFT PRIME.	A life-time Markov model with health states defined by mRS (1-6, individually). Disability levels at 90 days assumed to remain constant over time (unless recurrent stroke / death experienced). Disability post-recurrent stroke can only be the same or worse than pre-recurrent stroke. Discount rate = 3%	ICERs (per QALY gain; US$) by source of clinical data (mRS at 90 days) are presented: Meta-analysis = dominant (saving of $223) ESCAPE = $2,780 EXTEND-IA = $256 MR CLEAN = $1,662 REVASCAT = dominant (saving of $7,793) SWIFT PRIME = dominant (saving of $2,996)
Ganesalingam 2015 / UK	Meta-analysis of 90 day mRS scores from ESCAPE,	A 20-year Markov model with three health states defined by mRS (0-2,	US$11,651 per additional QALY (2013 values).

Study / perspective	Clinical data source	Modelling approach and key assumptions	Key results
healthcare system	EXTEND-IA, MR CLEAN, REVASCAT and SWIFT PRIME.	3-5, 6). The model captures recurrent stroke / death. Disability post-recurrent stroke can only be the same or worse than pre-recurrent stroke. Discount rate = 3.5%	
Kim 2011 / US Medicare/Medicaid system	Multi-MERCI for mechanical thrombectomy. Published evidence for IV-tPA.	Comparison of mechanical thrombectomy (+ thrombolysis if indicated) vs IT tPA. A life-time Markov model with three health states defined by mRS (0-2, 3-5, 6) but conditional upon +/- vessel occlusion on angiogram & +/- successful revascularisation & +/- ICH. Discount rate = 3%	US$16,001 per additional QALY (2009 values).
Nguyen-Huynh 2011/ US Medicare/Medicaid system	Multi-MERCI for mechanical thrombectomy. Published evidence for IV-tPA.	Model structure/ approaches similar to Kim 2011 above	US$9,368 per additional QALY (2009 values).
Patil 2009 / US Medicare/Medicaid system	Multi-MERCI for mechanical thrombectomy. PROACT II and other published evidence for IV-tPA.	Model structure/ approaches similar to Kim 2011 above	US$12,120 per additional QALY (2008 values).

D.3.2 Structure of the economic evaluation and justification

Overview of the model structure

The model takes a form of “decision tree” analysis to 12 months, following by a Markov model structure. The model is split into three phases; an acute phase from 7 to 10 days from onset or discharge (taken as 7 days for convenience hereafter) to 90 days, a mid-term phase from 91 days to 12 months and a long-term phase spanning from +1 year up to the end of the patients’ life with the maximum age of 100. The model had a total of seven health states based on mRS scores 0 to 6. The diagrammatic depiction of the acute/mid-term model structures for the base case can be found Figure 14 and Figure 15.

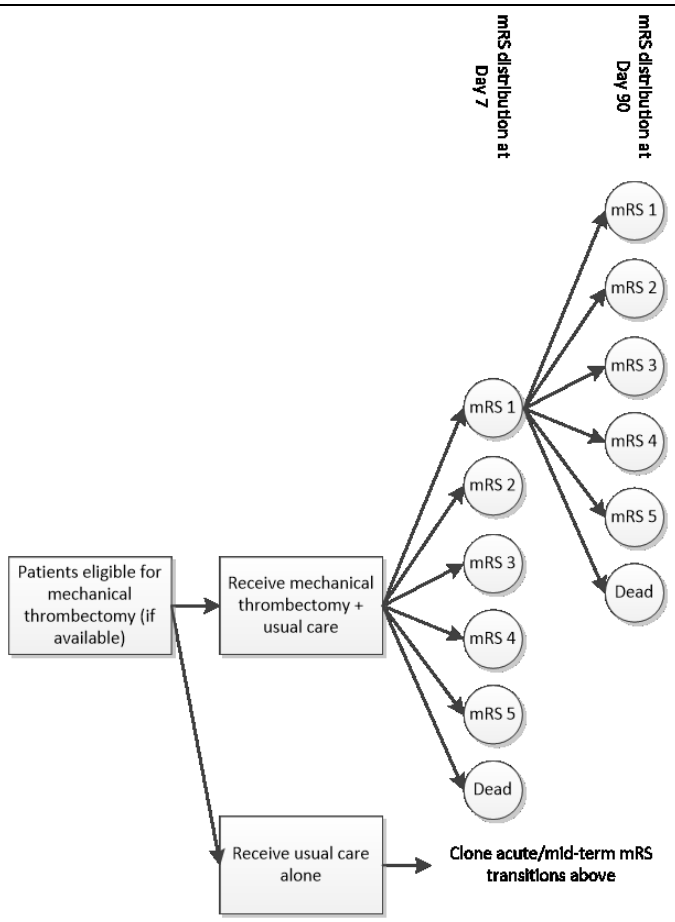


Figure 14 Decision tree structure for the acute phase (to Day 90)

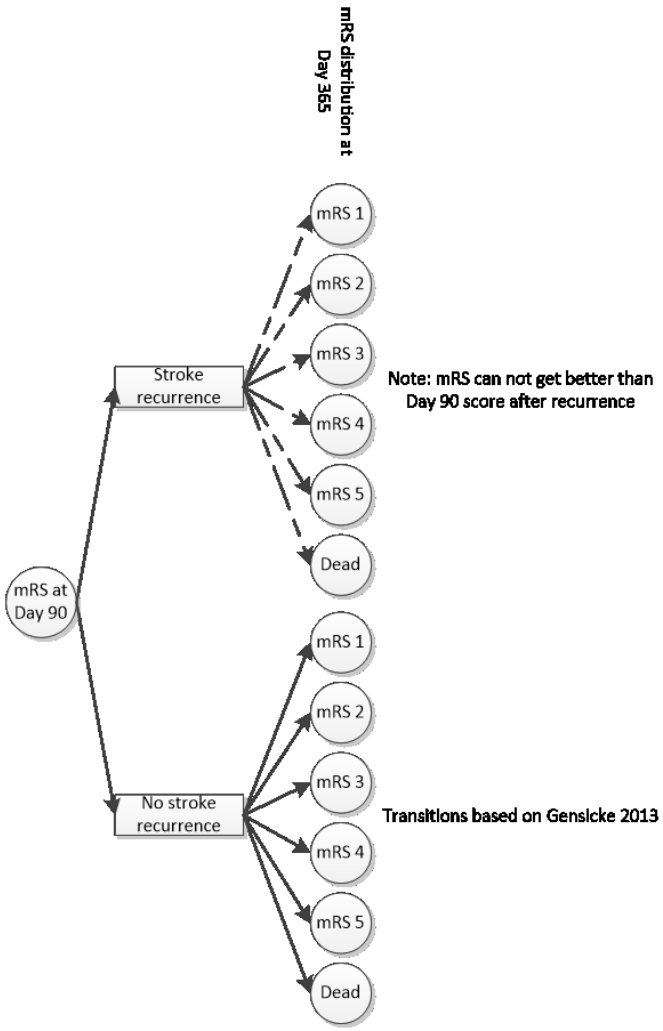


Figure 15 Decision tree structure for the acute phase (to Day 365)

The long-term Markov model (i.e., post 12 months) under the base case follows the occurrence of other cause deaths and stroke recurrence. Transitions in mRS are only triggered by these events. Of note, the 12-month mRS distribution in the model are informed by the 3-year observational study (Gensicke et al 2013; as discussed in Section C.7); this is a simplification but tested in sensitivity analysis.

Notes to the evaluators / MSAC

As described in Section C.7.3, the modelling of recurrent stroke and associated mRS transitions adds considerable complexity to the overall model structure and data requirements. The Excel model provided with the submission incorporates separate models that omit the risk of recurrent stroke. Findings from these simplified models are presented as sensitivity analysis in Section D.5. These simplified model demonstrate that the omission of stroke recurrence has minimal impacts on the ICER; $12,880 in the base case and $8,801/$15,953 based on the models with no stroke recurrence (see Section D.5.3 for further discussion).

This economic analysis is conducted assuming an Australian healthcare provider perspective and a life-time time horizon is considered. Health outcomes and future costs are discounted

at 5%.

Notable assumptions are italicised in describing the model approach and structure in the following sections.

Acute phase (to Day 90)

The acute phase modelled patients from symptom onset to 90 days post-stroke. *All treatment effects are assumed to occur within the acute phase.* The diagrammatic representation of the acute model structure can be found in Figure 14.

Patients are first assigned to a treatment arm, either mechanical thrombectomy or usual care alone, with equal probability. Patients are then assigned a mRS at 7 days and at 90 days. Of note, no data for mRS at stroke onset were available. For the purpose of QALY calculations, *the model assumes the Day 7 mRS distribution to be applicable from the time of stroke onset.* This is a simplification but only has a very limited relevance in terms of QALY calculations (3.5 days if half-cycle correction is applied).

In distributing the cohort across mRS scores at Day 7, the Applicant acknowledges the absence of relevant data from RCTs, except for SWIFT PRIME; i.e., only Day 90 mRS data are available from other four RCTs. To address this data gap, when the meta-analysed data or data from other RCTs are used *a Day 90 mRS distribution is also applicable at Day 7.*

The above assumption is unlikely to have a notable impact on the ICER estimation.[13] Table 82 below presents SWIFT PRIME data where data for both time points are available. It is shown that the direction / extent of mRS changes between Day 7 and Day 90 in each of the treatment arms are by and large consistent with each other; thus this assumption will equally affect both treatment arms. Also, the period for which this assumption becomes relevant is very limited, especially after half-cycle correction.

Table 82 mRS at Day 7 and at Day 90; SWIFT PRIME

mRS	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	Dead
At Day 7							
Mechanical thrombectomy + usual care	16.33%	19.39%	9.18%	11.22%	14.29%	27.55%	2.04%
Usual care	5.38%	7.53%	6.45%	10.75%	24.73%	39.78%	5.38%
At Day 90							
Mechanical thrombectomy + usual care	17.35%	25.51%	17.35%	12.24%	15.31%	3.06%	9.18%
Usual care	8.60%	10.75%	16.13%	17.20%	21.51%	12.90%	12.90%

Abbreviations: mRS, modified Rankin Score; SoC, standard of care.

[13] Sensitivity analysis will demonstrate that when the Day 90 data from SWIFT PRIME are used to inform the Day 7 mRS distribution, the ICER changes from $10,972 to $10,832; indicating that this assumption has a very limited overall impact on the ICER.

It is also assumed that *a patient is at no risk of recurrent stroke in this 90-day period.*

Mid-term phase (Day 91 to Day 365)

The mid-term phase directly follows the acute phase and spans from 91 days up to 365 days (12 months; see Figure 14). Improvement / deterioration of post-stroke functional outcomes (or "rehabilitation effects"), represented by allocation into a different mRS from Day 90, are captured in this phase (as informed by Gensicke et al 2013; see Section C.7 for further discussion and justification). Probabilities informing this process are same in both treatment arms. That is, as noted above, *no persisting treatment effects directly attributable to the treatment itself exist post 90 days.*

Sensitivity analysis explores a scenario where no further changes in mRS exist post 90 days.[14]

Patients are subject to risk of recurrent stroke during this phase. The mechanical thrombectomy arm of the model has an option of giving mechanical thrombectomy or usual care alone to patients experiencing a recurrent stroke. *The base case analysis assumes that all recurrent strokes are managed on usual care with no mechanical thrombectomy.* This assumption is well justified because the chance of a patient presenting with acute ischaemic stroke receiving a mechanical thrombectomy procedure is very low overall due to stringent patient eligibility selection and service availability (see Section E).

Section D.4.1 below will describe the way in which the model performs mRS allocation after recurrent stroke. To put it simply, *the patient's mRS can only be worse than his / her mRS at Day 90*. Also, regardless the timing of the recurrence stroke, *his /her mRS at the end of the mid-term phase is assumed to have exhausted all possible mRS improvements / deteriorations during the first 12 months of the recurrence stroke onset*. As an extreme example, even if a patient experience a recurrent stroke on the 364th day from baseline, his / her mRS on Day 365 in the model would reflect what would have been arrived to after the acute care and rehabilitations.

To avoid double counting, *no "other cause" deaths are captured in the acute / mid-term phases*. All deaths are hence due to index stroke and recurrent stroke (represented by an allocation to mRS6).

Long-term phase (post Month 12)

The base case analysis will take a life-time duration with the maximum age of 100 years. The

[14] This analysis will demonstrate that the cost-effectiveness of mechanical thrombectomy is extremely favourable, producing cost savings and additional health outcomes (i.e., dominant).

life-time model is the only way to adequately capture the mortality benefits offered by mechanical thrombectomy over usual care (15.3% vs 18.9% at Day 90; see Section D.4.1 below).[15]

The long-term phase of the model is built on the Markov methodology. The model applies annual cycles and health state transitions can only be triggered by recurrent stroke in the base case model (causing changes in mRS; see Section C.6). Again, patients in the mechanical thrombectomy arm can have an option of having another mechanical thrombectomy or receiving usual care for the treatment of recurrent stroke. *As per the mid-term phase, the base case analysis assumes that all recurrent strokes are managed on usual care with no mechanical thrombectomy.* Other cause deaths are also captured during the long-term period.

Notes to the evaluators / MSAC
As described in Section C.7.3, Alternative Model 2 (presented in sensitivity analysis) assumes a constant mortality rate to be applicable throughout the long-term phase (as informed by Gensicke et al 2013); providing an estimated ICER of $15,953. Section D.5 will demonstrate that this model better captures the post-stroke survival in the long run.

D.3.3 Calculation of healthcare costs and outcomes

Half-cycle correction is incorporated into the model as cycles have been adopted to estimate patient's transitions between health states. This approach ensures that patients move between states mid-way through each cycle, rather than at the beginning or end of the cycle. As noted above, *the model assumes that the mRS distribution immediately after the onset of index stroke is represented by the Day 7 distribution (with no half-cycle correction)*.

The cost of mechanical thrombectomy is captured at baseline (with no half-cycle correction) and as occurs again upon the incidence of recurrent stroke over time (if applicable). As described in Section C.5, the stroke management costs by mRS are accrued at Day 90 (acute costs), at Day 365 (mid-term costs) and annually thereafter (long-term costs). *For simplicity, each episode of recurrent stroke attracts a non-mRS dependent acute / mid-term treatment cost, based on the mean 12-month cost across mRSs ($35,651; see Section C.5).*

All health and cost outcomes are discounted at 5%, as required.

D.3.4 Justification of the model structure

The model structure is designed to offer transparency without compromising necessary complexities vital in examining the cost-effectiveness of mechanical thrombectomy.

The primary goal of the model is to capture long-term functional benefits offered by

[15] When a shorter-time horizon of 5, 10, or 20 years is used, the ICER increases to $43,542, $22,773, or $14,012, respectively (see Section D.5).

mechanical thrombectomy vs usual care. The extent of post-stroke disability, as defined by mRS, is a relevant patient outcome, if not the most relevant, that has direct implications to the patient QoL and healthcare costs. It also has direct implications for indirect costs – e.g. reduced workforce participation arising from family carer responsibilities. As described in Section D.3.1 above, all Markov models reported for the cost-effectiveness assessment of mechanical thrombectomy used mRS to define health states.

The overall model structure is a “two step” form; a 12-month decision tree analysis followed by a long-term Markov model. A decision tree analysis is considered as simpler and easier to depict how the modelled cohort progresses through the acute phase from stroke onset to Day 90 and through the mid-term phase from Day 91 to Day 365. This approach aims at improving transparency; in particular, all “treatment dependent” changes in mRS are absorbed within the first 12 months covered by the decision tree analysis.

The employed model structure is also largely consistent with other published models considered in Section D.3.1.

It is understood that the extrapolation of mRS outcomes into the future introduces uncertainty. A long-term model time horizon is nonetheless necessary and appropriate because ischaemic strokes often have a long-term and permanent, impact on the patient’s functional ability. The functional benefits offered by mechanical thrombectomy over usual care at 90 days will hence produce QALY / cost benefits that extend far into the future. The model is also able to capture “rehabilitation” effects. Importantly, as discussed above, a life-time model horizon only can capture the mortality benefits offered by mechanical thrombectomy over usual care. A series of sensitivity analysis will be presented to explore various time horizons.

As set out above, it is acknowledged that the modelling of recurrent stroke, while it has a clear and justifiable clinical and economic relevance to the modelling of stroke prognosis, adds considerable complexities to the overall model structure and data requirements. The Excel model provided with the submission incorporates two separate models that omit the risks of recurrent stroke (see Table 83 below). Findings from these simplified models are presented as a sensitivity analysis in Section D.5.

D.3.5 Software package

The model is built in Microsoft Excel (“MT MSAC June 2016 Section D.xlsx”; provided with the submission document). All included worksheets and their main purpose are summarised in Table 83.

Table 83 Excel worksheets included in the submitted cost-effectiveness model

Worksheet title	Purpose and contained information
Results - SUMMARY	Presentation of all relevant model outputs. Results from the three models are presented for convenience (i.e., base case, alternative model 1, alternative model 2; see Section D.5.3).
Clinical inputs	Summarises all clinical inputs. Allows a selection of mRS distributions at Day 7 and 90 (5 RCTs plus one meta-analysed data; IV-tPA eligible and IV-tPA ineligible patients). Allows a selection of mRS transitions post 90 days.
Cost inputs	Summarises all cost inputs.
Utility inputs	Summarises all utility inputs.
Other variables	Baseline patient demographics / discount rates / model horizon / % use of mechanical thrombectomy for stroke recurrence. Australian life table. Data storage for data selection.
Trace_MT	Computation of decision tree analysis (to 365 days; rows 22-59) and long-term Markov model for the base case analysis.
Trace_Control	
Trace_MT no recurrence	Computation of decision tree analysis (to 365 days; rows 18-42) and long-term Markov model for Alternative Model 1 (no recurrence).
Trace_Control no recurrence	
Trace_MT Obs data based	Computation of decision tree analysis (to 365 days; rows 18-57) and long-term Markov model for Alternative Model 2 (no recurrence and post-stroke survival based on constant mortality risks by mRS throughout the long-term phase).
Trace_Control Obs data based	

D.4 Variables in the economic evaluation

D.4.1 Clinical inputs

Distribution of mRS scores during the acute phase

As per the health state definitions in the long-term Markov model, clinical efficacy data are measured by mRS scores and are taken at Day 7 and at Day 90. Efficacy data used within the base case model can be found in Table 84 below. Section C.2 has justified the application of an ITT approach based on the meta-analysed IPD data provided by the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration (Goyal et al, 2016). Sensitivity analysis will explore other data sources.

As discussed above, the meta-analysed data could not inform the Day 7 mRS distribution. As shown in Table 84, *this is hence supplemented by the available Day 90 data.*

Table 84 mRS at Day 7 and at Day 90; meta-analysed RCT data

mRS	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	Dead
At Day 7[1]							
Mechanical thrombectomy + usual care	10.0%	16.9%	19.1%	16.9%	15.6%	6.2%	15.3%
Usual care	5.0%	7.9%	13.6%	16.4%	24.7%	13.5%	18.9%
At Day 90							
Mechanical thrombectomy + usual care	10.0%	16.9%	19.1%	16.9%	15.6%	6.2%	15.3%
Usual care	5.0%	7.9%	13.6%	16.4%	24.7%	13.5%	18.9%

Abbreviations: mRS, modified Rankin Score

[1] Assumed to be same as the Day 90 distribution. As noted above, the Day 7 data are available only in SWIFT PRIME. Sensitivity analysis will demonstrate that when the Day 90 data from SWIFT PRIME are used to inform the Day 7 mRS distribution (vice versa), the ICER changes from $10,972 to $10,832; indicating that this assumption has a very limited overall impact on the ICER.

Distribution of mRS scores during the mid-term phase (to Day 365)

Patients are able to improve or deteriorate from their Day 90 mRS scores. The transition probabilities used in this phase are taken from Gensicke et al (2013), as shown in Table 85 below.

Table 85 Transition matrix depicting mRS changes from Day 90 to 12 months as informed by Gensicke 2013

		At 12 months						
		mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6
At Day 90	mRS 0	66.7%	7.7%	7.7%	0.0%	5.1%	0.0%	12.8%
	mRS 1	60.0%	7.3%	1.8%	5.5%	7.3%	3.6%	14.5%
	mRS 2	30.9%	12.7%	18.2%	14.5%	7.3%	3.6%	12.7%
	mRS 3	17.6%	11.8%	17.6%	17.6%	11.8%	5.9%	17.6%
	mRS 4	2.5%	0.0%	7.5%	10.0%	27.5%	37.5%	15.0%
	mRS 5	0.0%	0.0%	0.0%	0.0%	0.0%	31.3%	68.8%

Abbreviations: mRS, modified Rankin Score
Source: Gensicke et al 2013 (see Section C.7)

Risk of recurrent stroke

Section C.6 estimated the risk of recurrent stroke during this phase to be 4.91% (Mohan et al 2011).

Derivation of Day 365 mRS distribution (after mRS changes during the mid-term phase)

All clinical inputs relevant to the modelling of mRS distributions to Day 365 have been presented above.

The employed cost-effectiveness model during the acute / mid-term phases takes the form of

decision tree analysis, as shown in Figure 14. While visually represented in a "decision tree" form, the derivation of Day 365 mRS distribution is performed through a series of matrix multiplications in order to account for the improvement / deterioration of mRS as well as the incidence of recurrent stroke (thus in turn leads to further functional deterioration in these patients). This process is described here.

Day 365 mRS distribution for patients who do not experience recurrent stroke between Day 90 and Day 365

For those who do not experience a recurrent stroke, their mRS changes between Day 90 and Day 365 are simply informed by the observational study data to account for the "rehabilitation effects" (see Section C.7). Matrix multiplication relevant for this process involves Table 84 (Day 90 values only) and Table 85. The resulting mRS distribution at Day 365 is presented in Table 86. For example, the mRS 0 figure for the mechanical thrombectomy arm is derived as 26.1% = 66.7%*10.0% + 60.0%*16.9% + 30.9%*19.1% + 17.6%*16.9% + 2.5%*15.6% + 0.0%*6.2%; which accounts for patients staying at mRS 0 from Day 90 and those improving from mRS 1-5 during the mid-term phase.

Table 86 mRS at Day 365 after rehabilitation effects, no recurrent stroke

mRS	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	Dead
Mechanical thrombectomy + usual care	26.1%	6.4%	8.7%	8.2%	9.4%	10.1%	31.1%
Usual care alone	15.8%	4.6%	7.7%	7.8%	10.5%	15.2%	38.3%

As extensively discussed in Section C.7.3, the mRS transition data reported by Gensicke et al (2013) are based on a follow-up period of three years. To retain an otherwise very simple model design (i.e., the model in principle simply follows post-stroke mRS changes of the modelled cohort over time) and, more importantly, to provide transparency, *it is assumed that the reported 3-year mRS transitions are to be absorbed by 12 months.* This assumption should be reasonable because the majority of mRS changes would generally occur during the mid-term phase (i.e, Day 90 to Day 365).

Day 365 mRS distribution with the risk of stroke recurrence between Day 90 and Day 365

As discussed above, for simplicity, the mRS distribution for patients experiencing a recurrent stroke is calculated based on the Day 365 mRS distributions in Table 86. This is a conservative approach because recurrent stoke is generally associated with a poorer prognosis than that for a first-ever stroke (Lee et al 2004). *This approach assumes that all mRS changes caused by a recurrent stroke (including acute as well as rehabilitation effects) would be completed by Day 365 regardless of the timing of recurrence onset.*

Table 87 below presents a transition matrix depicting possible mRS changes between Day

90 and Day 365 after accounting for the risk of stroke recurrence. Again, *usual care is given to treat all recurrent strokes under the base case assumption.*

An important assumption in this process is that the probability of a patient remaining in their previous mRS state following a recurrent stroke was equal to the probability of remaining in the same health state and the sum of all probabilities of entering a lower disability mRS state. That is, patients cannot improve on their pre-recurrence mRS. The probabilities of a recurrent stroke resulting in any states with higher disability remained the same as for the first stroke. For example, if a patient had mRS 4 before experiencing a recurrent stroke, the probability of moving to mRS 5 or to mRS 6 would be the same as for their first stroke in the analysis, and the probability of remaining in mRS 4 would be equal to the sum of probabilities of having mRS 0, 1, 2, 3 and 4 following their first stroke.

Table 87 Transition matrix depicting possible mRS changes between Day 90 and Day 365 after accounting for the risk of stroke recurrence (usual care given to treat all recurrent strokes)

		At Day 365 (stroke recurrence at 4.91%)						
		mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6
At Day 90 (no stroke recurrence so far)	mRS 0	95.9%	0.2%	0.4%	0.4%	0.5%	0.7%	1.9%
	mRS 1	-	96.1%	0.4%	0.4%	0.5%	0.7%	1.9%
	mRS 2	-	-	96.5%	0.4%	0.5%	0.7%	1.9%
	mRS 3	-	-	-	96.9%	0.5%	0.7%	1.9%
	mRS 4	-	-	-	-	97.4%	0.7%	1.9%
	mRS 5	-	-	-	-	-	98.1%	1.9%
	mRS 6	-	-	-	-	-	-	100.0%

Note: See "Clinical inputs" worksheet of "MT MSAC June 2016 Section D.xlsx". For example, the probability of remaining mRS0 (95.7%) = (1 - 4.91%) + 4.91% x 15.8% (see Table 86; all recurrent events receive usual care under the base case assumption).

Table 88 below hence summarises the Day 365 mRS distributions for the modelled treatment arms after accounting for the risk of recurrent stroke; derived as a product of matrix multiplication using Table 86 and Table 87. Again, the base case analysis assumes that all recurrent cases will receive usual care.

Table 88 mRS at Day 365 after rehabilitation effects and after accounting for the risk of recurrent stroke (usual care given to treat all recurrent strokes)

mRS	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	Dead
Mechanical thrombectomy + usual care	25.0%	6.2%	8.5%	8.1%	9.4%	10.3%	32.4%
Usual care alone	15.1%	4.5%	7.6%	7.6%	10.5%	15.3%	39.5%

Note: See "Clinical inputs" worksheet of "MT MSAC June 2016 Section D.xlsx". For example, the probability of being mRS1 in the mechanical thrombectomy arm (6.2%) = (26.1% x 0.2%) + (6.4% x 96.3%) (see Table 86 and Table 87; all recurrent events receive SoC under the base case assumption).

As set out above, sensitivity analysis will explore an alternative scenario where recurrent stroke in the mechanical thrombectomy can receive another mechanical thrombectomy procedure. The calculation of the Day 365 mRS distribution under this assumption is done in the same manner but accounting for the efficacy (i.e., mRS scores) of mechanical thrombectomy. *This is a simplification because in reality these recurrent cases may not meet eligibility criteria.*

The modelling of recurrent stroke adds considerable complexity to the presented economic model. As discussed above, the presented Excel worksheet also includes two separate models without the stroke recurrence modelling. Results from these simplified model are presented in Section D.5.3 as sensitivity analysis.

Transition in mRS health states during the long-term phase

Health state transitions during the long-term Markov phase of the model can only be triggered either by a recurrent stroke or deaths.

The mRS health state transitions following a recurrent stroke are informed by the transition matrix presented in Table 88; only applicable to those experiencing a stroke recurrence (otherwise no transitions except for death). Again, *usual care is given to treat all recurrent strokes under the base case assumption.*

The risk of death during this phase is informed by the Australian life table. Relevant data inputs are presented in Section D.4.4 below. *As noted above, Alternative Model 2 will assume a constant mortality rate to be applicable throughout the long-term phase (as informed by Gensicke et al 2013).*

D.4.2 Utility inputs

Section C.4 has detailed utility estimates applied to inform QALY transformations in the economic model. All base case utility scores are presented in Table 89. As described above, utilities are assigned to each mRS health state. Utility values for the health states ranged from 0.63 to 0.02 (Sturm et al 2002).

Of note, while providing Australian data, the balance of evidence provided in Section C.4 suggested that these base case utility values are relatively conservative, likely biasing against mechanical thrombectomy in the assessment of its relative cost-effectiveness (i.e., underestimation of incremental QALYs vs usual care). For example, a large EQ-5D evaluation study (Rivero-Arias et al 2010) demonstrated that utility values for the health states ranged from 0.935 to -0.054, where a mRS score of 5 resulted in a negative utility, indicating that living with a score of mRS 5 is worse than death. This trend was observed in other studies reviewed in Section C.4 (e.g., Noto et al 2011 and Murphy et al 2001). These

values are considered in sensitivity analysis.[16]

Table 89 Utility inputs considered in the base case analysis

Rankin score	Utility	Reference
mRS 0	0.630	Sturm et al 2002
mRS 1	0.630	
mRS 2	0.400	
mRS 3	0.180	
mRS 4	0.060	
mRS 5	0.020	
mRS 6	0.000	

Note: See "Utility inputs" worksheet of "MT MSAC June 2016 Section D.xlsx".

D.4.3 Cost inputs

Section C.5 has detailed cost inputs applied to quantify the costs of resource use in the economic model. All base case cost inputs are presented in Table 90.

The treatment of stroke recurrence incurs additional cost. *The model conservatively assumes that for stroke recurrence in the mid-term phase (i.e., Day 90 to Day 365) only acute treatment cost is applied*. For simplicity, a simple mean of the acute costs by mRS is employed for this purpose ($21,057; see Table 90). For stroke recurrence occurring during the long-term phase, the total acute / mid-term cost is accrued. Again, a simple mean value is calculated and applied (a total of $35,651 = $21,057 + $17,025; see Table 90).

Table 90 Cost inputs considered in the base case analysis

Resource use	Cost input (base case)	Source / notes
Mechanical thrombectomy	$18,308.49	See Section C.5
In-hospital acute stroke care cost by mRS		Tanny et al 2013, updated to 2016 values. Rate of concomitant IV-tPA use assumed to be 50%. Average cost across mRS applied for recurrent strokes to 12 months. See Section C.5
mRS 0	$21,581	
mRS 1	$21,861	
mRS 2	$23,695	
mRS 3	$23,695	
mRS 4	$20,962	
mRS 5	$20,962	
mRS 6	$14,647	
Average across all mRS scores	$21,057	
Mid-term stroke care cost by mRS (to Day 365)		Tanny et al 2013, updated to 2016 values.
mRS 0	$10,499	

[16] A sensitivity analysis based on Rivero-Arias et al 2010 returns an estimated ICER of $8500 (see Section D.5.3).

Resource use	Cost input (base case)	Source / notes
mRS 1	$13,230	Average cost across mRS applied for recurrent strokes. See Section C.5
mRS 2	$15,943	
mRS 3	$17,540	
mRS 4	$20,772	
mRS 5	$24,170	
mRS 6	–	
Average across all mRS scores	$17,025	
Long-term stroke care costs by mRS, annual		Gloede et al 2014, direct medical costs only; callibrated according to mRS cost multipliers from Baeten et al 2013. See Section C.5
mRS 0	$1,431	
mRS 1	$1,431	
mRS 2	$1,814	
mRS 3	$1,814	
mRS 4	$14,027	
mRS 5	$17,943	
mRS 6	–	

Note: See "Cost inputs" worksheet of "MT MSAC June 2016 Section D.xlsx".

It is noted that no indirect costs such as productivity loss, carer's time costs and transportation costs etc are not considered. While this is in line with the application guidelines, this will be a severely conservative approach, underestimating the true economic and broader societal value of post-stroke disability benefits offered by mechanical thrombectomy.

D.4.4 Other inputs

Age-specific all-cause mortality is applied to patients in the long-term phase of the model (beyond one year) to model deaths. Mortality data from the Australian life table are used (ABS, Life table 3302.0.55.001). *According to the Goyal meta-analysis, the baseline age is set to 68 years with 53% being male.*

It is acknowledged that patients with stroke history face an elevated mortality risk (e.g., Slot et al 2009). It is assumed that this has been already captured by the mid-/long-term mRS transition probabilities (to mRS 6). Accounting for the elevated mortality again would cause double counting, thus not performed here. Considering that patients with more severe post-stoke disability have higher risks of death (Slot et al 2009), then this is a conservative approach, biasing against mechanical thrombectomy in the current model. As noted above, Alternative Model 2 will be based on a different way of capturing the long-term post-stroke mortality as informed by a 3-year observational study of stroke survivors (Gensicke et al 2013).

D.5 Results of the economic evaluation

D.5.1 Base case analysis

The current Section D model demonstrates a very favourable cost-effectiveness of mechanical thrombectomy vs usual care under the proposed listing. The base case ICER is estimated to be $12,880 per QALY gain.

The net cost in the mechanical thrombectomy arm vs the usual care arm is estimated to be $10,666 in total. The higher cost associated with the proposed procedure is in part offset by the cost savings resulting from lower stroke care costs due to improved patient outcomes. Analysis of the components of the overall cost showed major differences in the stroke care costs between treatment arms. The life-time cost savings in terms of stroke care cost is estimated to be more than $8000 per patient for patients who had received mechanical thrombectomy. A small incremental cost for mechanical thrombectomy in the acute stroke care ($545) is due to the fact less patients die when compared with the usual care arm (thus incurring additional acute care costs).

Higher QALYs and life years were observed in the mechanical thrombectomy arm (a difference of 0.83 and 0.77 per patient, discounted incremental QALYs and life years, respectively), reflecting the higher mortality rate and lower quality of life in patients with more severe stroke outcomes in the usual care arm. A significantly larger proportion of patients had an mRS score of ≤2 (0.460 vs 0.265).

A break-down of these results can be found in Table 91.

Table 91 Break-down of base case results (per patient)

	MT + usual care	Usual care	Incremental
Costs			
Mechanical thrombectomy	$18,308	$-	$18,308
Acute stroke care	$21,193	$20,690	$503
Mid-term stroke care (to 365 days)	$14,034	$15,008	-$974
Long-term stroke care (>1 year)	$42,731	$50,447	-$7,716
Recurrent stroke costs	$5,711	$5,165	$545
Total costs	$101,977	$91,311	$10,666
Health outcomes			
Total life years	7.6331	6.8640	0.7691
Total QALYs	2.7183	1.8902	0.8281
% of independent patients at 90 days (mRS0-2)	0.4600	0.2650	0.1950

Note: See “Results - SUMMARY” worksheet of “MT MSAC June 2016 Section D.xlsx”.

The base case ICER is hence $12,880 per QALY gain, indicating a favourable cost-effectiveness of mechanical thrombectomy vs usual care. Other effectiveness measurements are also explored as shown in Table 92.

Table 92 ICERs of mechanical thrombectomy vs usual care

Effectiveness measure	Inc effectiveness	Inc cost	ICER
Total life years (discounted)	0.7691	$10,666	$13,868
Total QALYs (discounted)	0.8281		$12,880
% of independent patients at 90 days (mRS0-2)	0.1950		$54,699

Note: See "Results - SUMMARY" worksheet of "MT MSAC June 2016 Section D.xlsx".

The Applicant would like to ask the evaluators / MSAC that the interpretation of the presented cost-effectiveness evidence should be made with due considering about the significant clinical needs existing for an effective treatment option during the hyperacute stroke treatment phase. Mechanical thrombectomy considerably improves post-acute functional abilities (not to mention survival benefits) and reduces patient dependency, producing long-term and often permanent health / cost benefits. The proposed listing will thus be a much welcome funding to fill this gap.

D.5.2 Stepped economic evaluation

Table 93 below summarises the findings of stepped economic evaluation. Even with a short time horizon of 5 years, mechanical thrombectomy is suggested to have a reasonable cost-effectiveness. These findings provide greater confidence that availability of mechanical thrombectomy on the MBS delivers value for money – with clinical and cost benefits delivered over a relatively short time frame.

Table 93 Results of stepped economic evaluation

Analysis	Incremental effectiveness	Incremental costs	ICERs
Trial based			
in terms of additional independent person at 90 days (mRS0-2), MT cost only	0.1950	$18,308	$93,890
12-month analysis			
in terms of additional independent person at 90 days (mRS0-2), 12-month costs	0.1950	$17,837	$91,473
in terms of life years, 12-month costs	0.0492	$17,837	$362,403
in terms of QALYs years, 12-month costs	0.0937	$17,837	$190,361
5-year analysis			
in terms of life years, 5 year costs	0.2912	$15,255	$52,388
in terms of QALYs years, 5 year costs	0.3504	$15,255	$43,542
10-year analysis			

Analysis	Incremental effectiveness	Incremental costs	ICERs
in terms of life years, 10 year costs	0.5074	$13,048	$25,716
in terms of QALYs years, 10 year costs	0.5730	$13,048	$22,773
20-year analysis			
in terms of life years, 20 year costs	0.7247	$11,027	$15,216
in terms of QALYs years, 20 year costs	0.7870	$11,027	$14,012
Life-time analysis (base case)			
in terms of life years, life-time year costs	**0.7691**	**$10,666**	**$13,868**
in terms of QALYs years, life-time year costs	**0.8281**	**$10,666**	**$12,880**

D.5.3 Sensitivity analysis

Sensitivity analysis of the base case model

Model time horizon

It has been discussed that the model duration is expected to impact the ICER because all intervention costs are absorbed at baseline, while its cost / health benefits are accrued in the long run. The extrapolation is hence appropriate and necessary in performing a fair assessment of MT's cost-effectiveness.

Table 93 above suggested that mechanical thrombectomy was shown to have a favourable cost-effectiveness with an estimated ICER of $43,542 per QALY gain even with a very short time horizon of 5 years.

Selection of clinical inputs – 7 day and 90 day mRS distributions

The base case model was informed by the meta-analysed ITT data (Goyal et al 2016). Section B presented 5 individual RCTs, and these trials are considered individually in the following sensitivity analysis, as shown in Table 94.

Also, a subgroup analysis by the use of concurrent IV-tPA is reported by Goyal et al (2016; see Figure 16) and the ESCAPE trial. These data are also considered here, as also shown in Table 94.

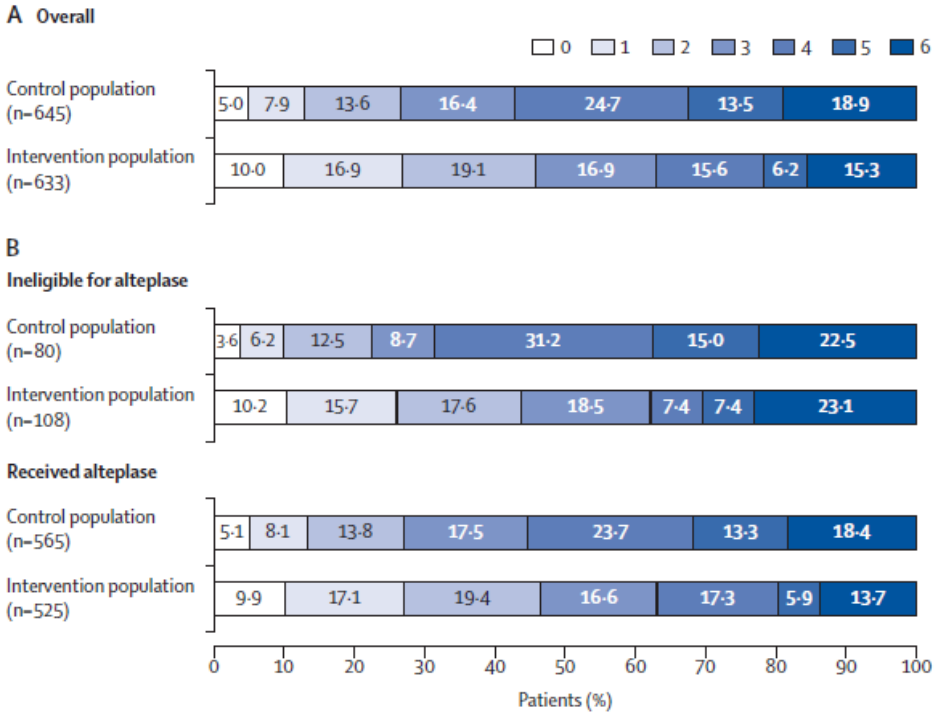


Figure 16 Scores on the mRS at 90 days based on IPD analysis

Abbreviations: IPD, individual patient data; mRS, modified Rankin Scale

Source: Goyal et al (2016); Figure 1

Table 94 Sensitivity analysis; selection of clinical data

Study	Inc. life year	Inc. QALY	Inc. cost	ICER per life year gain / QALY gain
Base case (Goyal; HERMES)	0.7691	0.8281	$10,666	$13,868 / $12880
SWIFT PRIME[1]	0.9470	1.0013	$10,986	$11,601 / $10,832
EXTEND-IA	1.9514	1.5935	$11,983	$6141 / $7520
ESCAPE	1.2495	1.1014	$13,358	$10,690 / $12,129
REVSACT	0.2378	0.5948	$6,768	$28,457 / $11,378
MR CLEAN	0.5384	0.5892	$11,680	$21,693 / $19,825
Meta-analysis (HERMES, IV-tPA eligible)	0.8822	0.8052	$13,363	$15,147 / $16,596
Meta-analysis (HERMES, IV-tPA ineligible)	0.3848	1.0531	-$2,649	Dominant / Dominant
ESCAPE IV-tPA eligible	1.8593	1.0697	$23,982	$12,899 / $22,420
ESCAPE IV-tPA ineligible	-0.4679	1.2451	-$19,037	Cheaper but less effective / Dominant

[1] Day 7 and Day 90 mRS distribution data available. The Day 90 data were used for Day 7 for this analysis (see below).

Table 94 confirms that mechanical thrombectomy is associated with a very favourable cost-effectiveness when compared with usual care alone.

The Applicant would like to note that mechanical thrombectomy was shown to be less costly,

but associated with a smaller expected number of life years vs usual care alone when the ESCAPE IV-tPA ineligible subgroup data were applied (see Table 95 below). This outcome was due to the fact 20% / 13% of patients were in mRS 6 at Day 90 for mechanical thrombectomy / usual care arms, respectively (Goyal et al 2015). These subgroup data were however based on a very small sample size; questioning the reliability of the Day 90 mRS distribution data. Indeed, the IV-tPA ineligible subgroup data from the HERMES meta-analysis (Goyal et al 2016; see Figure 16) were used by the model, mechanical thrombectomy was shown to have very favourable cost-effectiveness, as shown in Table 94.

Table 95 mRS at Day 90; ESCAPE, among subjects who did not receive IV-tPA

mRS	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	Dead
At Day 90							
Mechanical thrombectomy (n=45)	20.0%	20.0%	18.0%	13.0%	2.0%	7.0%	20.0%
Usual care (n=31)	6.0%	3.0%	19.0%	10.0%	39.0%	10.0%	13.0%

Source: Goyal et al 2015.

Section D.3.2 and D.4.1 discussed that no RCTs, except for SWIFT PRIME, reported Day 7 mRS data; thus the available Day 90 data were assumed to be applicable to Day 7 for each clinical data source considered above. A sensitivity analysis using the available SWIFT PRIME Day 7 data (see Table 82) returned an ICER of $10,972 (vs $10,832 when the Day 90 data were used for Day 7; see Table 94).

Selection of utility data

Sturm et al (2002) was selected as the base case source of utility values because it provided estimates elicited from Australian stroke survivors. As discussed above, some published studies reported a negative utility for mRS 5 (i.e., bedridden, incontinent, full time care), indicating that living with a score of mRS 5 is worse than death (Rivero-Arias et al 2010, Noto et al 2011 and Murphy et al 2001). When utility estimates reported by Rivero-Arias et al (2010) were applied, the ICER improves to $8,500 per QALY gain, as shown in Table 96 below.

A published systematic review and meta-analysis performed by Tengs and Lin (2003) suggested smaller utility decrements associated with progressively more severe disability levels (see Table 96). While considerably impacting the expected numbers of QALYs (in absolute terms; e.g., increase from 2.72 to 5.53 in the mechanical thrombectomy arm when Tengs and Lin 2003 is selected over Sturn et al 2003), the estimated number of incremental QALYs remained largely unaffected, leaving the ICER also largely unaffected.

The balance of evidence clearly suggests that the base case ICER is robust, but may be

reflect a conservative selection of utility inputs.

Table 96 Sensitivity analysis; selection of clinical data

Study	Utility values	Inc. QALY	Inc. cost	ICER per QALY gain
Base case (Sturn et al 2002)	mRS 0: 0.630 mRS 1: 0.630 mRS 2: 0.400 mRS 3: 0.1800 mRS 4: 0.060 mRS 5: 0.02	0.8281	$10,666	$12,880
Rivero-Arias et al 2010	mRS 0: 0.936 mRS 1: 0.817 mRS 2: 0.681 mRS 3: 0.558 mRS 4: 0.265 mRS 5: -0.054	1.2548	$10,666	$8500
Tengs and Lin 2003 (meta-analysis)[1]	mRS 0: 0.870 mRS 1: 0.807 mRS 2: 0.743 mRS 3: 0.680 mRS 4: 0.600 mRS 5: 0.520	0.8487	$10,666	$12,567

See Section C.4
[1] Linear interpolations applied.

Other model parameters

Other sensitivity analyses are also performed, as summarised in Table 97 below. These analyses supports the robustness of the base case results.

The ICER is relatively insensitive to changes in the cost inputs. When the procedural cost is increased by $5000, the ICER becomes $18,918; clearly suggesting the model's insensitivity to variations in the one-off procedural cost. As expected, the long-term patient costs have sizable impacts, although even an extremely conservative assumption (i.e., taking out the long-term costs altogether) returned an ICER of $22,198.

Also expectedly, the long-term mRS transition assumptions have sizable impact. The base case analysis was informed by the 3-year observational data reported by Gensicke et al (2013). As discussed above, all reported mRS transitions are assumed to be absorbed by 12 months. Under this same assumption, when the 7-year follow-up data reported by Magalhaes et al (2014) are applied, the ICER increases to $33,101. As discussed in Section C.7, this data set is based on a cohort of patients diagnosed with stroke in 1998 to 2000; likely reflecting outdated stroke care. Also, a very high proportion of patients died by the end

of 7 years in this study (e.g., approximately 80% for mRS 4-5 at 3 months; see Section C.7). To this end, assuming all possible mRS transitions (including to mRS 6) to occur within 12 months would lead to a gross underestimation of survival / functional outcome benefits offered by mechanical thrombectomy over usual care. Risk of stroke recurrent also appears to have some impacts; however, not altering the base case conclusion. *See findings from Alternative Model 1 and 2 below for further examination of extrapolation-related uncertainties.*

The balance of evidence clearly suggests that the current analysis robustly demonstrates mechanical thrombectomy to be cost-effective under the proposed MBS listing when added to the current usual care.

Table 97 Sensitivity analysis; other parameters

Variable (base case)	Assumptions tested	Inc. QALY	Inc. cost	ICER per QALY gain
Base case	**-**	**0.8281**	**$10,666**	**$12,880**
Cost inputs				
Procedural cost ($18,308.49)	Plus $1000	0.8281	$11,666	$14,088
	Plus $2500	0.8281	$13,166	$15,899
	Plus $5000	0.8281	$15,666	$18,918
	Carotid stenting in 8.6% during the procedure (EXTEND-IA) at $2921 per procedure[1]	0.8281	$10,918	$13,183
Management of adverse event (not considered)	Risk of access site hematoma in REVASCAT (10.7% at $1828 per episode; see Section C.5)	0.8281	$10,862	$13,116
Acute-/mid-term stroke management cost (by mRS; $14,647 to $23,695)	Halved	0.8281	$10,412	$12,573
	Doubled	0.8281	$11,175	$13,494
	No cost for mRS 6 (deaths)	0.8281	$10,637	$12,844
Long-term costs (by mRS; $1431 to $17943)	Halved	0.8281	$14,525	$17,539
	Doubled	0.8281	$2,950	$3,562
	Taken out	0.8281	$18,383	$22,198
Extrapolation (also see Alternative models 1 and 2 below)				
Long-term mRS transitions (Gensicke et al 2013; see Section C.7)	Aoki 2016 (5 year data; all changes occur by 12 months)	0.7613	$16,778	$22,039
	Magalhães 2014 (7 year data; all changes occur by 12 months)	0.5389	$17,838	$33,101
	No transition after Day 90 („trial based)	1.0688	-$3,290	-$3,078
Recurrent stroke (6.49% to Day 365, 2.01% annually thereafter; Mohan 2011)	Half	0.8857	$9,541	$10,771
	Double	0.7238	$12,702	$17,550
	Taken out (also see Table 98)	0.9473	$8,337	$8,801
	Use mechanical thrombectomy for	0.8928	$13,671	$15,312

Variable (base case)	Assumptions tested	Inc. QALY	Inc. cost	ICER per QALY gain
	recurrent strokes (for the mechanical thrombectomy arm)			
Others				
Other cause death (as per Aus life table)	Elevated post-stroke mortality (based on Slot 2009)	0.8285	$12,959	$15,642
Discounting (5% per annum)	Taken out	1.2381	$6,803	$5,495

[1] MBS item 35307 ($1121.15) + $1800 for a stent.

Alternative models to explore key extrapolation issues

As discussed above, the modelling of stroke recurrence added considerable complexity to the otherwise very simple model. It has been also discussed that the model may have a potential double counting of mRS changes because while the modelling of stroke recurrence is explicitly incorporated in the base case model, the mRS transition data from Gensicke et al (2013) might have already accounted for recurrence-related mRS changes.

Alternative Model 1 omits the explicit modelling of stroke recurrence. This alternative model will hence address the considerable model complexities necessary to capture the mRS transitions caused by stroke recurrence. This model assumes no further mRS transitions post 3 years[17], as reported by Gensicke et al (2013), and these transitions are assumed to be absorbed by 12 months in the model.

Table 98 suggests the base case results may have underestimated the true cost-effectiveness of mechanical thrombectomy.

Table 98 ICERs of mechanical thrombectomy vs usual care – Alternative Model 1

Effectiveness measure	Inc effectiveness	Inc cost	ICER
Total life years (discounted)	0.8303	$8,337	$10,041
Total QALYs (discounted)	0.9473		$8,801

Note: See "Results - SUMMARY" worksheet of "MT MSAC June 2016 Section D.xlsx".

As also discussed in Section C.7.3, the Applicant acknowledges that the assumption of having all mRS changes absorbed by 12 months affects the way discounting is performed by the model, in particular, the calculation of life years over the model time horizon.

To this end, Alternative Model 2 applies annualised mortality rates based on the reported 3-year rates throughout the long-term phase (instead of assuming these deaths to occur by 12

[17] Other cause deaths can still occur, represented by a mRS 6 transition.

months); 5.11% and 32.14% per annum for mRS 0-4 and mRS 6, respectively (see Section C.7.3; Gensicke et al 2013). Transitions across mRS 0 to 5 are still assumed to be absorbed by 12 months in this alternative model.

This model again ascertains a favourable cost-effectiveness of mechanical thrombectomy vs usual care with an estimated ICER of $22,601 per QALY gain, as shown in Table 99.

Table 99 ICERs of mechanical thrombectomy vs usual care – Alternative Model 2

Effectiveness measure	Inc effectiveness	Inc cost	ICER
Total life years (discounted)	1.1177	$14,683	$13,136
Total QALYs (discounted)	0.9203		$15,953

Note: See "Results - SUMMARY" worksheet of "MT MSAC June 2016 Section D.xlsx".

Of note, this model applies higher post-stroke mortality risks than other two models presented previously. Figure 17 suggest a modelled overall survival rate of approximately 40% at 10 years, with an additional survival in the mechanical thrombectomy arm by roughly 10%. Survival data reported in the Perth Community Stroke Study (Hardie et al 2003; see Section C.6) largely confirm the modelled survival curves, as shown in Figure 18.

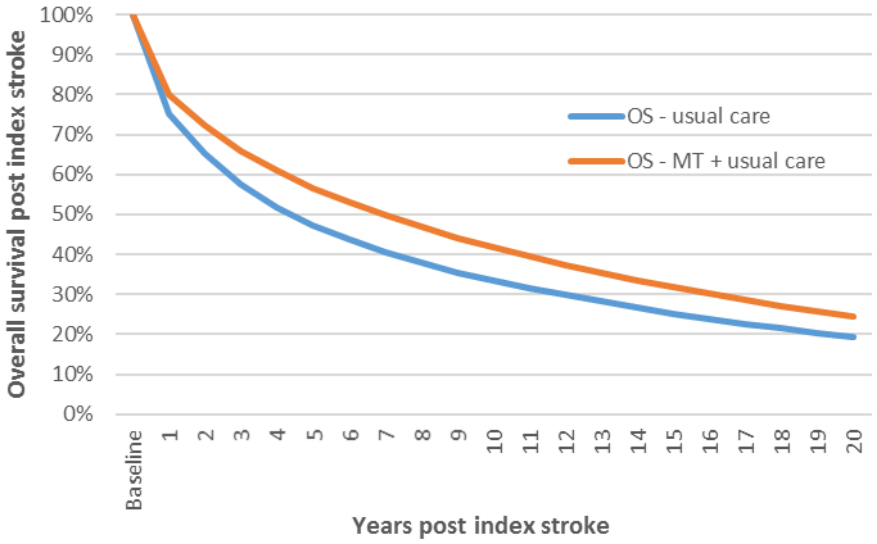


Figure 17 Post-stroke survival as modelled in Alternative Model 2

Note: See "Trace_MT Ob data based" and "Trace_Control Ob data based" worksheets of "MT MSAC June 2016 Section D.xlsx".

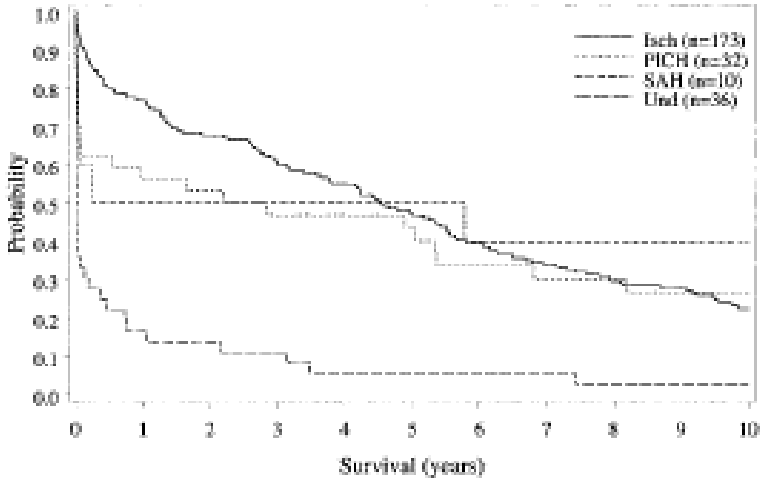


Figure 18 Kaplan-Meier curves showing probability of survival over 10 years of follow-up stratified by the pathology of first-ever stroke

Note: Taken from Hardie et al 2003. Isch indicates cerebral infarction; PICH, primary intracerebral haemorrhage; SAH, subarachnoid haemorrhage; and Und, undetermined.

Conclusion from the sensitivity analysis

A range of sensitivity analysis and the presentation of alternative models (primarily to address extrapolation-related uncertainties) have been presented to demonstrate the robustness of the base case results. These analyses, as a whole, are believed to provide a sufficient evidence base in favour of the acceptable cost-effectiveness of mechanical thrombectomy under the proposed listing on the MBS. Of note, the presented model does not account for indirect costs (productivity loss) or carers' burden, which may hence represent a significantly conservative analysis; likely underestimating the true cost-effectiveness of mechanical thrombectomy.

E. ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

Summary

- The available epidemiological data suggests an estimated total of 18,320 ischaemic stroke cases associated with large vessel occlusion in 2016. The eligibility for mechanical thrombectomy is estimated to be met by up to 2,700 cases if a full uptake is achieved (i.e., the procedure is given to all potentially eligible patients; private and public combined).
- The infrastructure to provide adequate "hyperacute" care during the first critical hours of symptom onset is suboptimal in Australia (National Stroke Foundation 2015). For example, IV-tPA was given in only 7% of all ischaemic cases (or 24% of those arriving within 4.5 hours of onset). The number of mechanical thrombectomy procedures will be hence limited by the case load capacity available in Australia; currently there are six private centres offering the service, each performing on average 10 procedures each year.
- The case load capacity analysis estimates that up to 10 private centres would be offering the service by the fifth year of listing; each centre performing on average 15 procedures each year. This equates to $393,750 in Year 5 for the proposed service. The total MBS costs for that year (including other services such as anaesthetics and imaging tests) would be $578,687.
- The availability of mechanical thrombectomy on the MBS is estimated to provide cost savings to the wider Australian healthcare system: from $884,244 in Year 1, rising to $2,456,232 in year 5.
- Broader societal benefits and indirect cost savings from avoided impact on productivity costs and reduced carer burden are also anticipated as result of improved access to mechanical thrombectomy.

As also acknowledged in the Protocol, the current submission proposes clearly defined eligibility criteria, restricting the requested MBS funding to a specific patient population for which the efficacy and safety of the procedure has been demonstrated (see Section C.2 and C.3).

For individuals who are experiencing an AIS, the key to favourable prognosis is early reperfusion of ischaemic brain. Importantly, a speedy intervention with an effective treatment during the first critical hours provides mortality benefits as well as long-term (often life-long) functional benefits among survivors. To achieve reperfusion, intravenous tissue plasminogen activator (IV-tPA) is recommended in treatment guidelines; however, many patients fail to respond to, or are ineligible to receive thrombolytic therapy. MT has become an important complementary or alternative treatment option for these patients. Section B has presented comprehensive clinical data to support its effectiveness and safety. Also, the favourable cost-effectiveness of MT has been adequately demonstrated in this patient population by the current submission (see Section C and Section D).

Estimated financial implications of adding MT for the treatment of AIS due to a LVO are determined in this section. A review of epidemiological data is presented to examine the

annual incidence of AISs associated with LVO in Australia. The patient subpopulation for which MT is considered as a viable treatment option will be however smaller than the overall ischaemic stroke incidence because of patient eligibility criteria.

Here, the Applicant would like to note that, while a relatively large patient pool potentially eligible for MT may exist in the community (i.e., up to 3,400 cases, see Section E.2), the actual MT usage will be limited by the caseload capacity available in Australia to perform the procedure. There are currently 6 private centres equipped to perform MT in Australia, each providing on average 10 procedures each year (Medtronic, data on file). An analysis of likely local capacity to perform the procedure is presented to provide more realistic budget estimates to the MBS. For completeness, the submission also presents an estimate of the size of the population that would be eligible of MT if it were funded, based on the available epidemiological data. This of course assumes no capacity or infrastructure constraints on providing MT – with access available to all potentially eligible AIS patients.

E.1 Justification of the selection of sources of data

As noted above, while the epidemiological evidence suggests a sizable potentially eligible patient population for MT, the actual MT usage will be limited by the capacity to perform the procedure. For completeness, estimates of the eligible population size based on epidemiological data are presented in Section E.1.1. However, an analysis of likely local caseload capacity is performed to inform more realistic budget estimates to the MBS. This is presented in Section E.1.2 below.

E.1.1 Epidemiology of acute ischaemic stroke due to large vessel occlusion

There exists good data capture for stroke incidence in Australia. It is estimated that 18,320 AIS are caused by LVO in Australia every year, as presented in Table 100 below. This estimate slightly differs from 13,578 as presented in the Protocol; primarily because a local and more recent proportion of ischaemic strokes in the overall stroke incidence is being applied (79%; compares to 88% based on D'Anna et al 2015) and a more locally-relevant estimate for the proportion of LVO is also employed here (68%; compares to 46% in the Protocol based on Wade et al 2009).

Table 100 Estimated incidence of acute ischaemic stroke due to large vessel occlusion in Australia, 2016

Parameter	Reported rate	Estimated incidence	Source
Population of Australia	-	24,359,761	Australian Bureau of Statistics, Population Projection 3220.0, Series B
All-cause stroke	0.14%	34,104	AIHW "Stroke and its management in Australia: an update", 2013
% of stroke that is ischaemic	79%	26,942	National Stroke Foundation. National Stroke Audit – Acute Services Report 2015. Melbourne, Australia
% of ischaemic stroke that is LVO	68%	18,320	Perth Community Stroke Study (Hankey et al 1998)

Note: See full calculation details in the attached Section E spreadsheet. See Table 4 of the Protocol.

Abbreviations: AIHW = Australian Institute of Health and Welfare; AIS = acute ischaemic stroke; LVO = large vessel occlusion.

There is a paucity of incidence data by stroke subtypes. While slightly dated (data collection between February 1989 and August 1990), a large, population-based study performed in Australia, the Perth Community Stroke Study, suggested that 68% of all ischaemic cases were due to large artery occlusion (Hankey et al 1998), as shown in Table 101. This study also suggested that 73% of all recorded stroke cases were ischaemic (n=250/343), demonstrating a good consistency with the national and more recent data reported by the National Stroke Foundation (2015; see Table 100)

Table 101 Ischaemic stroke by stroke subtypes, the Perth Community Stroke Study

Stroke types / subtypes	N	%
Cerebral infarction	250	100%
Large artery occlusion	170	68%
Lacunar	25	10%
Cardioembolic	43	17%
Boundary zone	12	5%

Source: Hankey et al 1998 (see Section C.6).

E.1.2 Estimated number of patients potentially eligible for mechanical thrombectomy under the proposed indication

Use of IV-tPA and admission within 4.5 hours of symptom onset

A significant proportion of patients receiving MT are expected to be given a concomitant IV-tPA. The National Stroke Audit Acute Services Report 2015 reported that only 7% of all ischaemic stroke patients received IV-tPA in 2015, and this rate has been stable since 2013 (National Stroke Foundation 2015). These data are based on a clinical audit targeting all

public and private centres admitting more than 50 stroke patients a year in Australia (National Stroke Foundation 2015).[18]

Of note, the Audit also suggested that IV-tPA was administered in only 24% of all ischaemic stroke patients who arrive within 4.5 hours of symptom onset (National Stroke Foundation 2015). Indicating that many patients may have been contraindicated for IV-tPA for reasons other than time since stroke onset. While the Audit suggests the IV-tPA therapy is also used in some patients after 4.5 hours of symptom onset, these numbers roughly mean that approximately 30% of all ischaemic patients arrive within 4.5 hours of symptom onset (see Table 102).

Based on the rate of treatment reported in the NSF Audit, it can be estimated that approximately 1300 patients with AIS due to LVO could be treated with IV-tPA, as shown in Table 102. Furthermore, approximately 5500 patients are admitted to hospital within 4.5 hours of symptom onset. Of note, this approach assumes that the reported data are directly applicable to the LVO subgroup.

Table 102 Estimated incidence of acute ischaemic stroke due to large vessel occlusion – IV-tPA treated and admission by 4.5 hours of symptom onset

Parameter	Reported / derived rate	Estimated incidence	Source
Patients treated with IV-tPA	7%	1,282	National Stroke Foundation 2015 Relevant to all ischaemic cases; assumed to be applicable to the LVO subgroup.
Patients arriving within 4.5 hrs of symptom onset	30%	5,496	Approximation. Only 24% of patients arriving within 4.5 hrs receive IV-tPA and the overall IV-tPA use is 7%. Derived based on National Stroke Foundation (2015). Relevant to all ischaemic cases; assumed to be applicable to the LVO subgroup.

Note: See full calculation details in the attached Section E spreadsheet.

Abbreviations: LVO = large vessel occlusion; IV-tPA, intravenous tissue plasminogen activator.

Consideration for patient eligibility selection for mechanical thrombectomy

A range of factors are considered in determining a patient's eligibility for MT. Recommendations made in the published treatment guidelines have been discussed in Section A and again summarised in Table 103 below. In addition to the confirmed diagnosis of AIS due to LVO, such factors as time since onset, location of occlusion (imaging tests), and pre-stroke functional ability are considered in selecting eligible candidates. It is nonetheless expected that the final eligibility selection in practice would be based on clinical

[18] There are 119 public and eight private centres in total. The Audit achieved a 89% participation rate or 106 public and six private participated.

judgement made on the individual patient basis.

The above analysis estimated that roughly 5500 patients are admitted to hospital within 4.5 hours of symptom onset (see Table 102). While no evidence is available to assist this estimation, it could be reasonably speculated that less than 8,000-10,000 patients would meet a time based eligibility criterion alone (i.e., 43-54% arriving within ~6 hours of symptom onset; see Table 103). Of note, an analysis from the US suggests 61% would arrive within the 6-hour window, and this rate would be lower given the greater geographical spread of the Australian population (Lacey et al, 2001).

It is important to note that criteria (see Table 103) other than the aforementioned time based criterion are also considered in practice in assessing the patient eligibility. which would likely further reduce the patient pool

Table 103 Summary of guideline recommendations relevant to proposed populations most suitable for mechanical thrombectomy

Relevant recommendations from guidelines	
US guidelines (Powers, 2015)	Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatments are being considered (Class I; Level of Evidence A). Patients should receive 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. 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. 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). 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, haemorrhagic coagulopathy, or receiving anticoagulant medications).
European guidance (ESO, 2014)	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). Mechanical thrombectomy should be performed as soon as possible after its indication (Grade A, Level IA, KSU Grade A). 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 IA, KSU Grade A).
European assessment (EUnetHTA, 2015)	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.

Abbreviations: 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

No specific information is available to inform the proportion of AIS cases (due to LVO) that would meet all the eligibility criteria and present as a suitable candidate for the procedure. The Ontario HTA evaluation for mechanical thrombectomy however suggested that 10% of all AIS cases would be potentially considered for the procedure (2016), which would translate to 2,694 based on the AIHW data above (26,942; see Table 100).

All calculations and supporting evidence / assumptions are summarised in Table 104 below.

Table 104 Estimated number of patients potentially becoming eligible for mechanical thrombectomy under the proposed listing in 2016 (not considering the capacity issues)

Parameter	%	Estimated incidence	Source
Incidence of AIS with LVO (see Table 100)			
Population of Australia	-	24,359,761	Australian Bureau of Statistics, Population Projection 3220.0, Series B.
All-cause stroke	0.14%	34,104	AIHW "Stroke and its management in Australia: an update", 2013
% of stroke that is ischaemic	79%	26,942	National Stroke Foundation. National Stroke Audit – Acute Services Report 2015. Melbourne, Australia.
% of ischaemic stroke that is LVO	68%	18,320	Perth Community Stroke Study (Hankey et al 1998)
Estimation of % meeting the "time based" eligibility alone, i.e., 6 hours from onset (Table 102)			
Patients treated with IV-tPA	7%	1,282	National Stroke Foundation 2015 Relevant to all ischaemic cases; assumed to be also applicable to the LVO subgroup.
Patients arriving within 4.5 hrs of symptom onset	30%	5,496	Derived based on National Stroke Foundation (2015); see Table 102 Relevant to all ischaemic cases; assumed to be also applicable to the LVO subgroup.
Patients arriving within 6 hrs of symptom onset	43-54%	8,000-10,000	Estimate and assumption. Supported by the US data (61%, Lacy et al 2001); expected to be lower in Australia (because of, e.g., the greater geographical spread of the Australian population)
Estimation of % meeting other eligibility			
Patients meeting the eligibility criteria for mechanical thrombectomy in Australia	10% of all AIS	2,694	Informed by the Ontario HTA group, suggesting 10% of all AIS would be considered for the procedure (2016).

Note: See full calculation details in the attached Section E spreadsheet. See Table 100,

Abbreviations: AIHW = Australian Institute of Health and Welfare; AIS = acute ischaemic stroke; LVO = large vessel occlusion.

The balance of evidence hence suggests that each year roughly 2,700 patients may become

eligible for MT in Australia if MT is fully accessible to these patients (i.e., 100% uptake rate, private and public combined). The available evidence presented in the following section will highlight that there exists a paucity of adequate infrastructure to offer hyperacute care such as MT in Australia. The actual usage will be hence limited by the local capacity to deliver the MT services. This is examined in the following section.

E.1.3 Caseload capacity to perform mechanical thrombectomy in Australia

While the available epidemiological evidence may suggest that up to 2,700 patients may satisfy the eligibility criteria for MT, the actual usage will be limited by the capacity available to perform the procedure in Australia. Also, stroke care is predominantly provided in the public sector in Australia. The aforementioned National Stroke Foundation report suggests there are only eight private centres admitting more than 50 stroke patients a year in Australia; further reducing potential cost implications to the MBS.

Current caseload capacity in Australia – the 2015 National Stroke Audit

The infrastructure to provide adequate "hyperacute" care during the first critical hours of symptom onset is less than satisfactory in Australia. The National Stroke Audit Acute Services Report 2015 notes that "*acute stroke care and services in this country have stagnated. Despite significant advancements in the treatment and care guidelines for acute stroke and the best efforts of health professionals and hospitals, many patients are missing out on best practice care. Patients are continuing to suffer poorer outcomes and even death as a result. Just one hospital in the survey was found to meet all the elements of a comprehensive stroke service including, but not limited to, the provision of hyperacute treatments (endovascular [clot retrieval] therapy and intravenous thrombolysis [clot busting] services) and stroke unit care 24 hours a day, seven days a week*" (pg. 4; National Stroke Foundation 2015).

Relevant findings from the Audit are summarised in Table 105 below. The findings were not reported by private and public centres in the publication (National Stroke Foundation 2015). While this Audit only targeted those centres that treat ≥50 patients per year (with 89% participation rate), it is expected that MT services will be primarily performed at these mid/large centres.

Onsite neurosurgical procedures are delivered at 28 centres (26%) in Australia, while 19 (18%) centres were capable of providing endovascular clot retrieval procedures like mechanical thrombectomy. Only 11 centres are equipped to offer the service 24/7 (10%; see Table 105). Of relevance, the number of patients treated with IV-tPA is relatively small per centre; 14 patients on average. The Audit found that only 48 patients in total received IV-tPA

at the six private centres participated in the Audit, i.e., 8 patients per centre.

The balance of evidence hence clearly indicates that the actual number of patients treated with MT on the MBS would be small, limited by the capacity to deliver MT services in the private sector in Australia. This is considered in the following section.

Table 105 Capacity to provide selected hyperacute services within hospitals (N=108) by hospital volume

	All hospitals (+50 stroke patients per year) (N=108)	Hospitals admitting 50-74 strokes (N=16)	Hospitals admitting 75-199 strokes (N=38)	Hospitals admitting 200-349 strokes (N=29)	Hospitals admitting 350-499 strokes (N=8)	Hospitals admitting 500+ strokes (N=17)
Element of service – hyperacute phase	**n (%)**	n (%)	n (%)	n (%)	n (%)	n (%)
Onsite mechanical thrombectomy service	**19 (18)**	NR	NR	NR	NR	NR
Onsite endovascular (clot retrieval) stroke service – 24/7	**11 (10)**	0 (0)	0 (0)	2 (7)	3 (38)	10 (59)
Onsite neurosurgical services (e.g. for hemicraniectomy due to large middle cerebral artery infarcts)	**28 (26)**	0 (0)	0 (0)	12 (41)	4 (50)	12 (71)
Delivery of IV-tPA	**82 (76)**	8 (50)	25 (66)	24 (83)	8 (100)	17 (100)
Median number of patients receiving thrombolysis in the last year from 82 hospitals offering thrombolysis n, (IQR)	**14 patients (8–32)**	3 patients (1–6)	8 patients (4–12)	14 patients (10–20)	43 patients (31–50)	52 patients (33–73)

Source: National Stroke Foundation 2015

Private centres currently equipped to provide mechanical thrombectomy and expected future uptake

The Applicant is aware of six private centres currently equipped and able to provide MT services in Australia.

Each centre is understood to be performing on average 10 procedures each year. A successful listing of MT service on the MBS would likely increase the caseload capacity but the uptake is expected to be very gradual given the infrastructure / technical / staffing requirements associated with the procedure.

The following analysis will assume that 10 private centres will be offering the service by Year 5. Each centre is assumed to provide an average of 15 procedures each year. An alternative "high uptake" scenario is also presented, where there are 15 centres, each performing 20 procedures each year by Year 5.

E.2 Estimation of use and costs of the proposed medical service

E.2.1 Caseload capacity to perform MT procedures in Australia

Section E.1.3 discussed that there are currently six private centres performing MT in Australia, with each centre treating roughly 10 patients each year. This means that 60 procedures are currently provided at these private centres in total.

Table 106 presents the current and anticipated caseload capacity for MT in Australia. As a base case analysis, the Applicant expects that up to 10 private centres would be equipped to deliver MT services over time, and with the MBS funding each centre would be providing 15 procedures each year.

Table 106 Number of MT procedures performed at private centres in Australia

Caseload scenarios	Current	Base case scenario, by Year 5	High uptake scenario, by Year 5
Facilities equipped with MT capacity	6	10	15
Number of procedures per facility	10	15	20
Total procedures per year	60	150	300

Note: See full calculation details in the attached spreadsheet ("MT MSAC June 2016 Section E.xlsx")

An alternative 'uptake' scenarios are also considered, as shown in Table 106. This scenario should be considered as conservative from the perspective of the MSAC (i.e.,

overestimation) The Applicant notes that if MT is added on the MBS, the uptake will be gradual because all centres are required to have adequate infrastructure to perform MT. The high uptake scenarios would be informative for the purpose of this submission, but will most likely be overestimation of MT uptake in practice.

By assuming a linear growth in the MT caseload capacity from the current level, the total number of MT procedures performed at private centres in Year 1 – Year 5 of listing under the three alternative caseload scenarios can be determined, as shown in Table 107 below.

Table 107 Number of MT procedures performed at private centres in Australia, Year 1 to Year 5 based on the linear growth assumption from the current caseload

Caseload scenarios	Current	Year 1 (2017)	Year 2	Year 3	Year 4	Year 5 (see Table 106 above)
Current (or no MBS listing)						
Total procedures per year	60	60	60	60	60	60
Base case scenario						
Total procedures per year	60	78	96	114	132	150
High uptake scenario						
Total procedures per year	60	108	156	204	252	300

Note: See full calculation details in the attached spreadsheet ("MT MSAC June 2016 Section E.xlsx")

E.2.2 Estimated costs of MT to the MBS

Section C.4 has discussed and justified that the proposed MBS fee for MT is $3,500 at full benefit or $2,625 at 75% benefit amount.

It is estimated that the MBS costs of the proposed item would be $204,750 in Year 1, increasing to approximately $393,750 in Year 5 under the base case caseload scenario (at 75% benefit amount). Cost estimates under the alternative caseload scenario under consideration are summarised in Table 108.

Table 108 Estimated MBS costs of mT, Year 1 to Year 5 of listing

Caseload scenarios	Year 1	Year 2	Year 3	Year 4	Year 5
Base case scenario					
Total procedures per year	78	96	114	132	150
Total MBS costs					
- at full benefit	$273,000	$336,000	$399,000	$462,000	$525,000
- at 75% benefit	$204,750	$252,000	$299,250	$346,500	$393,750
High uptake scenario					
Total procedures per year	108	156	204	252	300
Total MBS costs					
- at full benefit	$378,000	$546,000	$714,000	$882,000	$1,050,000
- at 75% benefit	$283,500	$409,500	$535,500	$661,500	$787,500

Note: See full calculation details in the attached spreadsheet ("MT MSAC June 2016 Section E.xlsx")

E.3 Estimation of changes in use and cost of other MBS items

As discussed in Section C.5 above, the cost of general anaesthesia is assumed to be incurred in 36% of patients undergoing MT, while regional sedation is provided in the remaining 64%; generating additional costs to the MBS (see Table 109). Also, it is assumed that patients will require two additional imaging tests post procedure; whole head digital subtraction angiography (DSA) to assess for embolisation to new brain territory or other complications (MBS item 60009) and leg angiography and management of groin arteriotomy (MBS item 60072); these services are also costed accordingly in Table 109 below.

Table 109 Estimated MBS costs of specialist consultations, Year 1 to Year 5 of listing

Caseload scenarios	Year 1	Year 2	Year 3	Year 4	Year 5
Base case scenario					
Total procedures per year	78	96	114	132	150
Anaesthesia					
General anaesthesia *(only relevant to 36% of patients)*					
Initiation of management (MBS item 20210)	$8,340	$10,264	$12,189	$14,113	$16,038
Intra-arterial cannulation (MBS item 22025)	$2,224	$2,737	$3,250	$3,764	$4,277
Management of anaesthesia (MBS items 23403)	$2,224	$2,737	$3,250	$3,764	$4,277
Blood pressure monitoring (MBS item 22012 or 22014)	$1,668	$2,053	$2,438	$2,823	$3,208
Assistence (MBS item 25015)	$556	$684	$813	$941	$1,069
Regional anaesthetics for the rest (MBS item 18225)	$2,498	$3,075	$3,652	$4,228	$4,805
Post-operative imaging					
Digital subtraction angiography (MBS item 60009)	$107,351	$132,125	$156,898	$181,672	$206,445
Leg angiography (MBS item 60072)[a]	$3,362	$4,138	$4,913	$5,689	$6,465
Total MBS costs					
- at full benefit	$128,223	$157,813	$187,403	$216,993	$246,583
- at 75% benefit	$96,167	$118,360	$140,552	$162,745	$184,937
High uptake scenario					
Total procedures per year	108	156	204	252	300
See the attached spreadsheet for individual costing					
Total MBS costs					
- at full benefit	$177,540	$256,447	$335,353	$414,260	$493,166
- at 75% benefit	$133,155	$192,335	$251,515	$310,695	$369,875

Note: See full calculation details in the attached spreadsheet ("MT MSAC June 2016 Section E.xlsx").

[a] Adjusted for multiple service rule (Rule A)

E.4 Estimated financial implications for the MBS

Table 110 below hence summarises the total costs to MBS under the alternative caseload scenarios.

Table 110 Estimated MBS costs in total, Year 1 to Year 5 of listing

Caseload scenarios	Year 1	Year 2	Year 3	Year 4	Year 5
Base case scenario					
Total MBS costs					
- at full benefit	$401,223	$493,813	$586,403	$678,993	$771,583
- at 75% benefit	$300,917	$370,360	$439,802	$509,245	$578,687
High uptake scenario					
Total MBS costs					
- at full benefit	$555,540	$802,447	$1,049,353	$1,296,260	$1,543,166
- at 75% benefit	$416,655	$601,835	$787,015	$972,195	$1,157,375

Note: See full calculation details in the attached spreadsheet ("MT MSAC June 2016 Section E.xlsx"). See Table 109 and Table 108 above.

E.5 Estimated financial implications for government health budgets

As demonstrated in the Section D model, the functional benefits offered by MT over usual care are expected to generate cost savings in terms of patient care cost in the long run. The model estimated that for each patient undergone MT a total saving of $8187 can be made over the modelled life-time period when compared with usual care alone (discounted; see Section D.5).

Based on this per patient estimate, the likely cost savings to the wider Australian healthcare system can be derived, as summarised in Table 111; highlighting that the proposed listing would provide overall cost savings when the long-term cost savings to the wider Australian healthcare system is taken into account. This analysis only considers direct healthcare costs – the financial impact of stroke extends far beyong the impact on healthcare budgets – hence, significant indirect cost savings from avoided impact on productivity costs and reduced carer burden are also anticipated as result of improved access to mechanical thrombectomy.

Table 111 Estimated cost savings from improved functional outcome, Year 1 to Year 5 of listing; based on the discounted life-time cost from the Section D model

Caseload scenarios	Year 1	Year 2	Year 3	Year 4	Year 5
Base case scenario					
Total procedures per year	78	96	114	132	150
Total cost savings (discounted life-time cost)	-$638,620	-$785,994	-$933,368	-$1,080,742	-$1,228,116
High uptake scenario					
Total procedures per year	108	156	204	252	300
Total cost savings (discounted life-time cost)	-$884,244	-$1,277,241	-$1,670,238	-$2,063,235	-$2,456,232

Note: See full calculation details in the attached spreadsheet ("MT MSAC June 2016 Section E.xlsx").

F. ADDITIONAL RELEVANT INFORMATION

Lack of definitive funding arrangements for non-implantable medical technology used to deliver MBS services is a barrier to effective adoption of new services implemented following MSAC evaluation.

The Applicant raises this as a relevant factor - worth emphasising for the proposed service and not already requested elsewhere for inclusion in the assessment report

In the Applicant's submission[19] to the MBS Taskforce Review consultation, we noted the following general points:

Development of new medical services utilising innovative non-implantable technology to deliver the service require MSAC evaluations to inform decisions relating to public funding of the new service. MSAC may find these new services are cost-effective, with positive MSAC advice leading to the creation of new MBS items. However, this may not lead to optimal adoption of new therapies or diagnostic procedures: current Commonwealth (i.e. Prostheses List) arrangements for assessing devices for private health insurer reimbursement are limited to permanently implanted medical devices.

Unlike Prostheses List arrangements for implanted technology, there is no clear funding pathway for non-implanted technologies. In the absence of clear funding arrangements access to new services involving non-implanted technology is limited. This potentially creates a perverse incentive to use existing services (which may be less effective), especially where there is certainty of funding of technologies used to deliver the service. This is inconsistent with achieving the best possible patient outcomes for healthcare spending, particularly if a new service, using a non-implanted technology is found to be more clinically and cost-effective than existing services.

This 'disconnect' between positive MSAC advice and the absence of definitive funding arrangements for non-implantable technology is inconsistent with optimising the full potential of new MBS services to deliver benefits to patients and the healthcare system. In addition this 'disconnect' represents an inefficient use of MSAC resources, i.e. it creates a situation where considerable time and resources are spent informing the development of a new MBS item, that cannot be optimally implemented due to the absence of definitive funding of the technology used to deliver the service. It also limits clinicians' ability to choose the most suitable technologies to best align MBS services with individual patient needs.

[19] Medtronic Submission to the MBS Review Consultation – November 2015

Examples of technologies where there is a 'disconnect' between development of a new MBS service and absence of definitive funding arrangements include services using cardiac ablation catheters (MBS 38287; 38290; 38293) and coronary pressure measuring systems (MBS 38241) to assess the extent of cardiac ischaemia (measurement of fractional flow reserve – FFR).

With regards to the current Application:

PASC[20] noted that stent retrieval devices do not meet the criteria for inclusion on the Prostheses List as they are not a permanent surgical implant and were concerned about who would potentially pay for the device, particularly if it is not reimbursable through private health insurers. The Applicant proposed to address this issue through the MBS review process.

Applicant comment

To further clarify – during the PASC teleconference we discussed the disconnect between positive advice for listing from MSAC and new MBS services using non-implanted technology – arising due to the absence of a definitive funding pathway for non-implanted technology (i.e. do not meet Prostheses List criteria). We commented that this issue had been raised in feedback provided during the MBS Taskforce Review consultation process – noting that adoption of new items/use of existing items may be suboptimal where there is no definitive funding pathway for the technology necessary to deliver the medical service.

Furthermore, due to the emergency nature of MT, case-by-case, pre-intervention, device funding requests cannot be considered by private health insurers.

For the current Application - should positive advice from MSAC lead to the implementation of a mechanical thrombectomy MBS item – we propose that MSAC and the Department of Health (DOH) consult to determine how stent retrieval/mechanical thrombectomy devices could be funded under Part C of the existing PL arrangements (e.g. Health Minister consideration for inclusion on Part C of the PL - as was the step taken for Cardiac Remote Monitoring Systems; Application 1197.1) or through the *selective* expansion of the PL criteria to include non-implantable devices associated with *new* MBS services.

[20] Application 1428: PASC Meeting April 2016, Application Outcome

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