Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment of a national emergency endovascular service for mechanical thrombectomy in the management of acute ischaemic stroke

25 January 2017

Safer Better Care

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The Health Information and Quality Authority (HIQA) is an independent authority established to drive high quality and safe care for people using our health and social care services in Ireland. HIQA's role is to develop standards, inspect and review health and social care services and support informed decisions on how services are delivered.

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Foreword

Acute ischaemic stroke happens when there is a sudden loss of blood flow to an area of the brain due to obstruction of a blood supply vessel. This obstruction (usually due to a clot) impairs brain function. Symptoms and signs of stroke include:

- loss of vision in one or both eyes
- impaired speech
- muscular weakness or paralysis on one side of the body (including facial droop, arm drift or leg weakness.

Stroke can affect people physically, mentally, emotionally and or socially, with the consequences depending on the site and size of the brain area affected. Disability is so severe in 75% of stroke survivors that it decreases their ability to work. Diseases of the circulatory system, such as coronary heart disease and stroke, are the most common cause of death in Ireland, accounting for one in three of all deaths in 2014. An estimated 2,000 patients die in Ireland as a result of stroke each year. Approximately 4,300 people are admitted to hospital following an acute ischaemic stroke each year in Ireland.

There is evidence from randomised controlled trials that adding endovascular treatment with second-generation mechanical thrombectomy devices (to remove the clot) to standard medical care with intravenous thrombolysis (using medication to dissolve blood clots) significantly improves functional outcomes for eligible patients experiencing an acute ischaemic stroke.

This HTA examined the clinical effectiveness, cost-effectiveness, budget impact, organisational issues, and ethical and social issues associated with adding mechanical thrombectomy to standard medical care for eligible patients. It will inform policy decisions about potential improvements to stroke services.

The assessment was carried out by an Evaluation Team from the HTA Directorate in HIQA, while a multidisciplinary Expert Advisory Group was established to provide advice on the assessment. HIQA would like to thank its Evaluation Team, the members of the Expert Advisory Group, and all those who contributed to preparing this report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

Health Information and Quality Authority

Advice to the Minister for Health

This health technology assessment (HTA) examined the clinical effectiveness, cost-effectiveness, budget impact and the organisational and ethical implications of a national emergency endovascular service providing mechanical thrombectomy in addition to standard medical care for managing acute ischaemic stroke.

The key findings of this HTA, which inform and precede HIQA's advice, are:

- In Ireland, approximately 4,300 people are admitted to hospital following an acute ischaemic stroke each year. More than half of all strokes (55% to 57%) occur in men, with just under one in three strokes in men (around 30%) occurring in those under the age of 65. Based on demographic change alone, the total number of stroke cases in Ireland has been predicted to increase by between 4% and 5% each year from 2015 to 2020.

- Intravenous thrombolysis forms part of standard medical care for the management of acute ischaemic stroke. The narrow treatment window and strict exclusion criteria associated with this treatment has meant that, on average, approximately 12.3% of patients hospitalised with acute ischaemic stroke in Ireland receive thrombolysis. There is 24-seven access to thrombolysis in 82% of adult acute hospitals in Ireland, with patients in the remaining acute hospitals managed through a combination of limited local access and or arrangements for ambulance redirection to another hospital.

- Endovascular therapy using mechanical thrombectomy devices aims to retrieve thrombi (clots) and rapidly restore blood flow. Thrombectomy is indicated in addition to rather than a replacement for standard medical care in selected patients. Delivery of this procedure is confined to comprehensive stroke centres with access to neurosurgical care, advanced brain imaging and appropriate neuro-endovascular expertise.

- While there have been substantial improvements in acute stroke care in Ireland over the past eight years and a significant decline in stroke-related mortality, there continues to be significant variability in access to high-quality care. Stroke units and services — which vary in resources and level of service — are available in 78% of adult acute hospitals, although less than one third of patients are admitted directly to these units at initial presentation. Rates of thrombolysis have improved, although there is considerable regional variation. In the absence of a structured national service, mechanical thrombectomy is available on an ad hoc

basis in two centres nationally, with 85% of procedures (170 cases) provided in Beaumont Hospital in Dublin in 2016.

- Patient outcomes were evaluated using a meta-analysis of six randomised clinical trials published between 2015 and 2016. In selected patients, mechanical thrombectomy using second-generation (stent retriever) devices is a safe and effective procedure when provided in addition to standard medical care within six to 12 hours of stroke onset. It is significantly more likely to result in functional independence (RR: 1.56, 95% CI 1.37–1.78) based on the modified Rankin Scale. In terms of safety, it is not associated with an increased risk of symptomatic intra-cerebral haemorrhage or with an increased risk of all-cause mortality or recurrent ischaemic stroke at 90 days.

- A national endovascular treatment service would lead to an incremental cost and benefit of €2,626 and 0.19 quality-adjusted life years (QALYs) per eligible patient. The incremental cost-effectiveness ratio (ICER) was €14,016 per QALY at five years with a probability of being cost-effective of 70% and 99% at thresholds of €20,000 and €45,000 per QALY gained, respectively. There was a 9% chance of the intervention being cost-saving relative to standard medical care. The parameters with most influence on the ICER relate to the outcomes of functional independence and mortality at 90 days. An estimated 268 (95% CI: 210–322) thrombectomy procedures would be undertaken each year, of which 57 (95% CI: 38–78) additional patients (that is, increasing from 102 to 159) are predicted to regain functional independence at 90 days.

- The budget impact of moving from no service to a national emergency endovascular service for acute stroke was estimated to be €7.2 million over five years. The budget impact in the first year was estimated at €3.3 million based on the provision of one additional dedicated biplane angiography suite which would be required to ensure sufficient capacity for a national service without impacting on other endovascular services. Annual costs thereafter were estimated at between €0.8 million and €1.2 million based on treating 268 (95% CI: 210–322) patients each year. The five-year budget impact of moving from the current ad hoc service (200 patients per annum provided through the existing facilities) to a national service was estimated to be €2.8 million (of which €2.0 million would be incurred in the first year).

- Effective care is predicated on delivery of the intervention within the narrow treatment window available (between the onset of stroke symptoms and the time treatment must be initiated). To prevent delays in treatment, a series of pre-hospital, hospital and system-wide factors need to be addressed in any service

expansion to achieve timely, efficient delivery of safe and effective care. These factors include public awareness and timely presentation of patients at hospitals delivering acute stroke care, prompt access to diagnostic imaging and specialist stroke care at these units, and formalising arrangements for the efficient transfer to and management of eligible patients at comprehensive stroke centres resourced to provide this procedure.

- Providing a national service would have significant organisational and resource implications, in particular for the National Ambulance Service, in order to ensure timely transfer of patients to one of the two proposed treatment centres and to facilitate repatriation of patients post-intervention. An estimated 235 patients (95% CI: 180–286) would require ambulance transfer each year to and from the hospital in which thrombolysis is started, giving rise to an average of 491 (95% CI: 372–608) ambulance hours each way per annum.

- Geographic accessibility is the factor most likely to affect the equitable provision of mechanical thrombectomy. Existing documented regional variation in access to thrombolysis and stroke services in the hyperacute period (the first 6 to 12 hours after a stroke) and acute period (the first seven days after a stroke) will result in inequitable access to mechanical thrombectomy procedures unless the factors underpinning this variation are addressed.

- Development of key performance indicators and ongoing audit of outcomes against these criteria will be necessary to ensure that the benefits of mechanical thrombectomy observed in clinical trials are being replicated by a national service.

As economic models incorporate a number of assumptions and depend on the quality of data available, the results are subject to a degree of uncertainty. Bearing in mind the conservative estimates and assumptions that were used in this analysis and arising from the findings above, HIQA's advice to the Minister for Health and the Health Service Executive (HSE) is as follows:

- In selected patients, mechanical thrombectomy using stent retriever devices is a safe and effective procedure when provided as an adjunct to standard medical care within six to 12 hours of onset of an acute ischaemic stroke.

- Based on an estimated 268 (95% CI: 210–322) thrombectomy procedures undertaken each year, 57 (95% CI: 38–78) additional patients (that is, increasing from 102 to 159) are predicted to regain functional independence at 90 days after a stroke.

- Assuming one extra biplane angiography suite is provided, at €14,016 per QALY, a national emergency endovascular service providing mechanical thrombectomy would be cost-effective. The five-year budget impact of moving from no service to a national service is estimated at €7.2 million comprising €3.3 million in the first year and annual running costs thereafter estimated at €0.8 million to €1.2 million. The five-year budget impact of moving from the current ad hoc service (approximately 200 patients treated through existing facilities) to an organised national service is estimated to be €2.8 million (of which €2.0 million would be incurred in the first year).
- Ensuring equitable access to and benefit from mechanical thrombectomy will require the existing regional variability in access to thrombolysis and stroke services to be addressed. There are significant organisational and resource implications also for the National Ambulance Service to ensure timely transfer and repatriation of patients without compromising provision of ambulance services for other patients.
- In establishing a national service, it would be essential to develop quality key performance indicators and to put measures in place to audit and evaluate its effectiveness and safety.

Executive Summary

Background

Following a request from the HSE's National Clinical Programme for Stroke, the Health Information and Quality Authority (HIQA) agreed to carry out a health technology assessment (HTA) of endovascular treatment using mechanical thrombectomy for the management of acute ischaemic stroke. This work, with HIQA acting as lead author, was initially undertaken as a pilot rapid assessment for the European Network for Health Technology Assessment (EUnetHTA).

The pilot assessment, co-authored by HTA colleagues from Germany, was published by EUnetHTA in December 2015. The EUnetHTA report concluded that endovascular therapy using mechanical thrombectomy is a safe and effective adjunct to standard medical care for stroke in selected patients. It was subsequently updated and expanded in this HTA to include a review of the epidemiology of stroke in Ireland, an economic model and a review of the organisational and ethical implications in the context of the Irish healthcare system.

The purpose of this HTA was to examine the evidence for using mechanical thrombectomy in addition to standard medical care as a treatment strategy for acute ischaemic stroke in Ireland. This HTA considered seven domains, the findings for which are presented below.

Technology description

Acute ischaemic stroke occurs due to the obstruction of a blood vessel supplying blood to the brain. This obstruction, usually due to a thrombus (clot), results in disruption of the flow of blood to the brain, causing a focal or global neurological deficit (affecting bodily functions or mental processes) that lasts more than 24 hours, or causes death within 24 hours. Thrombolysis (administration of a drug to dissolve the thrombus) with intravenous (IV) tissue-plasminogen activator (t-PA) remains the standard medical care for acute stroke.

Thrombolysis, however, has been shown to have modest clinical efficacy in severely affected patients. In order for IV t-PA to be effective and provide maximum benefit, it must be administered within 4.5 hours of the onset of stroke symptoms. In addition, rates of recanalisation following treatment are dependent on the particular vessel affected and the location of the thrombus within that vessel. Thrombolysis has a limited impact on larger, more proximally situated thrombi and successful recanalisation of large vessel occlusions (blockages) with thrombolysis alone is

infrequent. The narrow time window and strict exclusion criteria associated with thrombolysis has meant that only a small portion of patients experiencing acute ischaemic stroke receive thrombolysis.

Endovascular therapy is a minimally invasive form of treatment for certain vascular diseases. During emergency endovascular therapy for acute ischaemic stroke, a catheter is sent to the site of the blockage (usually via the femoral artery in the groin) and the thrombus is removed mechanically or an attempt is made to dissolve it using intra-arterial thrombolysis. Mechanical thrombectomy devices aim to retrieve thrombi and rapidly restore blood flow in patients with acute ischaemic stroke due to occlusion of a proximal cerebral artery. Endovascular treatment with mechanical thrombectomy within 6–12 hours of stroke onset has been suggested as an effective and safe adjunct to standard medical care which includes thrombolysis with IV t-PA.

The mechanical thrombectomy devices may be subdivided by their mechanism of action: those that use an approach distal to the thrombus (retrievers) or proximal to the thrombus (aspiration devices). They may also be considered in terms of their time of development and approval for use, and may be separated into 'first-' and 'second-generation' retrieval devices and devices whose mechanism of action is based on suction/aspiration. As of August 2015, 15 mechanical thrombectomy devices had been CE-marked (that is, carry a mark indicating a manufacturer's declaration that the product complies with the essential requirements of the relevant European health, safety and environmental protection legislation). Consistent with the clinical trial evidence and international consensus guidelines, delivery of this procedure is confined to comprehensive stroke centres with access to neurosurgical care, advanced brain imaging and appropriate neuro-endovascular expertise.

Burden of disease

Diseases of the circulatory system, stroke and other circulatory diseases are the most common cause of death in Ireland, and accounted for 8,899 deaths or just over one in three deaths (34% of all mortality) in Ireland in 2014. An estimated 2,000 people die as a result of stroke each year in Ireland, giving an age-standardised death rate of 34.6 per 100,000 population. A 2014 HSE report predicted 20% increases in the prevalence of major chronic diseases by 2020 primarily due to population aging, with the number of people with stroke predicted to increase by between 4% and 5% each year from 2015 to 2020.

In Ireland, just over half (approximately 55% to 57%) of strokes occur in men. Ischaemic stroke accounts for approximately 85% of all acute strokes resulting in hospitalisation in Ireland, amounting to approximately 4,300 cases annually. The

average age for patients experiencing an acute stroke is approximately 75 years, with incidence increasing with age. However, stroke is not a condition confined to old age. In 2014, 27% of stroke cases occurred in those aged under 65 years.

Following major changes in the organisation and delivery of stroke care by the HSE, there have been substantial improvements in acute stroke care in Ireland over the past eight years, resulting in significant reductions in mortality. Thrombolysis rates have improved to a national average of 12.3%, although there is considerable variation between acute hospitals, not all of which have established 24-seven local access or protocols for patient transfer and redirection to an acute stroke unit.

Stroke units and services vary in their resourcing and level of service offered. Data from the Irish Heart Foundation/HSE National Stroke Audit indicate that in 2015, stroke units were available in 78% of adult acute hospitals, although less than one in three patients (29%) were admitted directly to these units at initial presentation.

Challenges remain many of which also have implications for the provision of mechanical thrombectomy. The precise time of stroke onset remains unknown in many cases, and a significant minority still arrive to hospital by means other than an ambulance. Almost two out of three hospitals that admit acute stroke patients now have dedicated stroke teams. However, noting that at least 55% of patients experiencing a stroke present outside of core hours (9am to 5pm, Monday to Friday), only one in three hospitals has 24-seven access to a dedicated stroke team.

At present in Ireland, endovascular procedures using mechanical thrombectomy is available on an ad hoc basis in two hospitals, with one hospital providing 85% of all such procedures (170 out of 200) in 2016.

Clinical effectiveness and safety

A systematic review was carried out to identify relevant clinical studies of the effectiveness and safety of mechanical thrombectomy in the treatment of acute ischaemic stroke. Patient outcomes were evaluated using a meta-analysis of randomised controlled trials.

Based on the available evidence from six randomised controlled trials published between 2015 and 2016, mechanical thrombectomy using second-generation (stent retriever) devices is a safe and effective procedure when provided as an adjunct to standard medical care within six to 12 hours of stroke onset. This evidence is conditional on its use in conjunction with non-invasive arterial imaging in selected patients with anterior circulation acute ischaemic stroke. Mechanical thrombectomy is significantly more likely to result in functional independence (RR: 1.56, 95% CI: 1.37–1.78) as measured by the modified Rankin Score (mRS) compared with

standard medical care alone. It is not associated with an increased risk of all-cause mortality at 90 days (RR: 0.85, 95% CI 0.67–1.07), or symptomatic intracerebral haemorrhage SICH (RR: 1.07, 95% CI 0.67–1.71). Pooled data from three trials does not suggest that the intervention is associated with a higher overall rate of recurrent ischaemic stroke within 90 days (RR: 3.09, 95% CI 0.86–11.11). While individual studies reported adverse events and or serious adverse events, a lack of clarity regarding what constitutes 'serious' events and inconsistencies in reporting makes comparative analysis across studies difficult.

The data obtained from the published randomised controlled trials represents the best available evidence and are likely to be broadly accurate for those currently receiving thrombectomy in Ireland. However, it is noted that most of the participating hospitals in the trials included in this analysis are high-volume stroke centres where the procedures were carried out in idealised circumstances. There is currently insufficient evidence to determine the applicability of this evidence to the larger, heterogeneous cohort of patients with acute ischaemic stroke who are treated in the real-world setting. Such patients may be ineligible for IV t-PA, arrive outside of the time window for treatment and or are managed in non-specialised settings.

This is particularly relevant in the Irish context where the 2015 Irish National Stroke Audit showed that many of those who currently experience an acute stroke in Ireland would be ineligible for mechanical thrombectomy as they could not receive it within an appropriate time frame from the onset of stroke symptoms. The evidence regarding mechanical thrombectomy continues to evolve, and it is likely that the patient population who are deemed eligible to benefit from this intervention will expand over time. Therefore, it is essential that as further evidence emerges and the technology becomes more widely available, that quality key performance indicators are developed and measures put in place to audit and evaluate the effectiveness and safety of a national service.

Review of cost-effectiveness

A systematic review was carried out to assess the available cost-effectiveness evidence for mechanical thrombectomy and to inform the economic analysis of a national endovascular programme in Ireland. Studies were included if they compared the costs and consequences of adding endovascular therapy using mechanical thrombectomy to standard medical care compared with standard medical care alone, for the management of acute ischaemic stroke. Eleven studies were identified that estimated the cost-utility or cost-benefit of mechanical thrombectomy relative to standard medical care. Studies could be divided into evaluations of first- and second-generation devices. The clinical effectiveness of second-generation devices is

supported by data from multiple randomised controlled trials, which is considered the best level of evidence. The cost of long-term stroke care used in the studies was found, on average, to be broadly consistent with estimates for Ireland. The applicability of the economic evaluations to the Irish healthcare setting was mixed, but was generally poor or moderate.

One high-applicability study was identified, a HTA by Health Quality Ontario in Canada. The Ontario HTA included a detailed and comprehensive economic evaluation, with healthcare costs broadly similar to those in Ireland. The Ontario study found mechanical thrombectomy to be cost-effective relative to IV t-PA alone. Detailed sensitivity analysis suggested that for time horizons greater than one year, mechanical thrombectomy was likely to be considered cost-effective relative to a willingness-to-pay threshold of CAN$20,000 per QALY. The findings of the Ontario study in terms of cost-effectiveness were similar to the other identified studies, providing reassurance about the consistency of cost-effectiveness evidence.

This review of the cost-effectiveness literature suggested that providing a service in Ireland can replicate the treatment times observed in the randomised controlled trials, and assuming availability of comprehensive stroke care, mechanical thrombectomy could be cost-effective in Ireland.

However, it was noted that the published evaluations assumed sufficient neuro-endovascular suite capacity — as capital investment in additional biplane angiography suites was not included. These evaluations also omitted costs associated with patient transfer and redirection by pre-hospital emergency care or other services to comprehensive stroke centres resourced to provide mechanical thrombectomy procedures. In light of how stroke services and population are distributed in Ireland, and the likely investment required to develop a national mechanical thrombectomy service, a cost-effectiveness analysis using Irish data was deemed necessary to support decision-making.

Economic evaluation

HIQA undertook an economic evaluation to determine the cost-effectiveness and budget impact of a national emergency endovascular service providing mechanical thrombectomy for treating acute ischaemic stroke in Ireland. The objective of this evaluation was to aid decision-making by estimating the incremental costs and benefits of adding this therapy to current standard medical care, which includes provision of IV and or IA (intra-arterial) thrombolysis, where appropriate. In the base-case analysis, it was assumed that one additional dedicated biplane angiography suite would be needed to provide sufficient capacity for a national

endovascular stroke service. It was assumed that existing national arrangements for thrombolysis would prevail and that eligible thrombectomy patients would be transferred from local acute stroke centres to one of two national endovascular treatment centres.

Based on this analysis, it was estimated that with a national thrombectomy service, 268 (95% CI: 210 to 322) thrombectomy procedures would take place each year. An estimated 57 (95% CI: 38 to 78) more patients would regain functional independence at three months after having a stroke. Using a five-year time horizon, the cost-utility of a national mechanical thrombectomy is estimated at €14,016 per quality-adjusted life year gained, and is therefore cost-effective given typical willingness-to-pay thresholds in Ireland. The calculated cost-utility is sensitive to the clinical effectiveness of mechanical thrombectomy in terms of achieving functional independence. Although the underlying trials demonstrate a treatment effect, there is uncertainty about the size of the effect due to heterogeneity in the trials informing the estimate. The estimate of cost-effectiveness presented here is conservative due to the short time-horizon and inclusion of a treatment effect on mortality. Based on the meta-analysis of the clinical trials, the effect on mortality was not statistically significant. If no effect is assumed, then the incremental cost-effectiveness ratio is €4,064 per quality-adjusted life year.

The budget impact of moving from no service to a national emergency endovascular service for acute stroke was estimated to be €7.2 million over five years. The budget impact in the first year was estimated at €3.3 million based on the provision of one additional dedicated biplane angiography suite which would be required to ensure sufficient capacity for a national service without impacting on other endovascular services. Annual costs thereafter were estimated at between €0.8 million and €1.2 million based on treating 268 (95% CI 210 to 322) patients each year. The five-year budget impact of moving from the current ad hoc service (200 patients per annum provided through the existing facilities) to a national service was estimated to be €2.8 million (of which €2.0 million would be incurred in the first year). The introduction of the service will have implications for 24-seven availability of appropriate staff at the two treatment centres.

The basecase analysis of cost-effectiveness and budget impact assumed the provision of one additional biplane angiography suite and a consistent volume of patients over time. In the event that the number of eligible patients increases over time, then it may become necessary to consider the provision of a second dedicated biplane suite to ensure timely access and to minimise disruption to other services.

It was estimated that 235 cases (95% CI: 180 to 286) would require ambulance transfer from the hospital in which IV thrombolysis was started to and from one of the two proposed tertiary referral centres carrying out mechanical thrombectomy in Ireland. The transfers are equivalent to 491 emergency ambulance hours (95% CI: 372 to 608) each year, and also 491 intermediate care vehicle hours (95% CI: 372 to 608) for the return journeys. This would have resource implications for the HSE's National Ambulance Service both in terms of the initial transfer of the patient and their subsequent repatriation to their local acute stroke unit once they were clinically stable post-procedure.

Organisational and social implications

To achieve comparable levels of efficacy and safety to those observed in randomised controlled trials, delivery of mechanical thrombectomy for treating acute ischaemic stroke must be confined to comprehensive stroke centres with access to neurosurgical, and neurocritical care. These centres must have appropriate neuro-endovascular expertise and access to advanced brain imaging. Two hospitals (Beaumont Hospital, Dublin and Cork University Hospital [CUH]) currently meet these criteria.

As a national emergency endovascular service for acute stroke has not been established, there are no formalised protocols for the inter-hospital transfer of patients to ensure safe and equitable access to mechanical thrombectomy. Mechanical thrombectomy is provided on an ad hoc basis in Beaumont Hospital and CUH, with a 24-seven service available in Beaumont Hospital only. This hospital provided 85% of all such procedures (approximately 170 cases out of 200) in 2016.

Ireland faces a number of challenges in ensuring appropriate access to mechanical thrombectomy for eligible patients. Many of these hurdles have been partially addressed through the development of the HSE's National Clinical Programme for Stroke and, in particular, the efforts which have gone into improving the identification and management of patients in the hyperacute period (the first six to 12 hours after stroke onset) as manifested by improved thrombolysis rates.

Effective care is predicated on the timely delivery of the intervention with only a narrow treatment window available between the onset of stroke symptoms and the time that treatment must be initiated. To prevent delays, a series of pre-hospital, hospital and system-wide factors need to be addressed in any service expansion to achieve timely, efficient delivery of safe and effective care. Pre-hospital factors include delays in the presentation of patients to hospitals providing acute stroke care. Data from the 2015 National Stroke Audit indicate that the median time from

onset of symptoms to presentation is approximately 2.5 hours (range 1.5 to 4.5 hours), with 22% of patients arriving more than six hours after symptom onset. Reasons for delays include poor public awareness of the symptoms and management of stroke, and transport or logistical issues. A new public awareness campaign may be required to improve recognition of stroke symptoms and the need for timely intervention. Auditing the bypass protocol implemented by the National Ambulance Service in 2014 that facilitates rapid transfer of suspected acute stroke patients to hospitals providing thrombolysis may help to identify areas for improvement. Within hospitals, there is a need for rapid diagnostic imaging and assessment by specialist stroke teams to ensure timely diagnosis, so that, where indicated, thrombolysis can be initiated within the available treatment window (three to 4.5 hours of stroke onset). Median 'door to scan time' in the 2015 National Stroke Audit was almost 9.5 hours which has implications for treatment options and patient outcomes. For eligible patients with large vessel occlusions, transfer protocols are required to ensure the efficient transfer of these patients to endovascular treatment centres. International guidelines suggest that the procedure should be offered in a small number of centres that are adequately resourced and sited to maximise patient access, workforce expertise and geographical coverage. Appropriate expertise in the management of the patient in the hyperacute period is also required.

Expanded access to mechanical thrombectomy has implications for both acute hospital- and community-based stroke services. Additional community-based rehabilitation may potentially be needed to ensure patients can achieve optimal outcomes in the post-acute phase.

Developing a national mechanical thrombectomy service has potentially significant organisational and resource implications for the National Ambulance Service. Adequate resources are required to ensure patients are transported quickly to the national emergency endovascular centres and to facilitate repatriation of clinically stable patients back to their local acute stroke unit after they have undergone the procedure. Use of existing ambulance capacity to transfer patients potentially long distance creates logistical issues as it may leave the referring area with reduced or no ambulance cover for extended periods. Resource implications therefore include adequate availability of both ambulances and trained emergency medical services staff. Given the existing national shortage of paramedic staff and the time to fully train new paramedics (up to two years), this may represent a capacity constraint in the short to medium term.

An organised national mechanical thrombectomy service will necessitate detailed service planning to ensure it adheres to requisite quality standards. This includes the

development of quality key performance indicators to measure performance against targets or expectations.

Ethical considerations

By their nature, public healthcare programmes raise a range of ethical issues which require consideration by policy makers. While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a way that is equitable, non-discriminatory, transparent and, as far as possible, non-coercive.

Mechanical thrombectomy is associated with improved functional outcomes, with an estimated 51% of eligible patients regaining functional independence at 90 days compared with 33% with standard medical care alone. Although mechanical thrombectomy may be associated with a higher rate of certain peri-procedural adverse events, these do not outweigh the benefits of improved functional outcomes.

While stroke is not a condition confined to old age, stroke patients tend to be elderly and may be experiencing confusion, partial paralysis and difficulty with speech. Obtaining informed consent from the patient may not be possible. However, this is also the case for standard medical care and other endovascular procedures that are used in the treatment of acute ischaemic stroke currently.

The factor most likely to affect the equitable provision of mechanical thrombectomy is geographic accessibility. While the treatment window for mechanical thrombectomy is longer than that for thrombolysis — and there is cohort of patients that may benefit from thrombectomy, but for whom thrombolysis is contraindicated — mechanical thrombectomy rates are largely predicated on the initial thrombolysis rates that are achieved. Poor access to specialist stroke teams or poor management of patients in the hyperacute period in hospitals receiving these patients will limit the number of otherwise eligible patients that could benefit from mechanical thrombectomy.

As noted, on average 12.3% of acute stroke patients receive thrombolysis, although there is considerable variability between hospitals, not all of which have established 24-seven local access or protocols for patient transfer and redirection. Similarly, while stroke units and services have been developed, their resources and services vary. Results from the economic evaluation undertaken in this HTA indicate that mechanical thrombectomy would be cost-effective given typical willingness-to-pay thresholds. Introduction of a national endovascular service for mechanical thrombectomy may have to be as part of a service reorganisation, which would likely benefit stroke patients generally.

In basing the HTA findings on a small number of randomised controlled trials, it is possible that the estimated benefits may overstate what might be achieved in practice. This could occur, for example, if the patient population in Ireland is systematically different from those included in the clinical trials or if the trial conditions cannot be mimicked in the Irish healthcare service. The assessment may therefore give rise to false expectations about the benefits that might be observed if mechanical thrombectomy is provided to eligible patients. Audit against key performance indicators will be necessary to ensure a national service is meeting requisite effectiveness and safety levels.

Conclusions

Health technology assessment (HTA) supports evidence-based decision-making in relation to making best use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given constrained healthcare budgets and increasing demands for services provided.

Bearing in mind the estimates and assumptions that were used in this HTA, the following conclusions may be drawn.

Evidence from a systematic review of randomised controlled trials carried out as part of this HTA suggests that mechanical thrombectomy is significantly more likely to result in functional independence.

The evidence is conditional on mechanical thrombectomy being used in conjunction with non-invasive arterial imaging, in selected patients within six to 12 hour onset of anterior circulation acute ischaemic stroke, and when using second-generation (stent retriever) devices.

An economic evaluation was undertaken in order to determine the cost-effectiveness and budget impact of a national emergency endovascular service providing mechanical thrombectomy for treating acute ischaemic stroke in Ireland. Taking into account the assumptions used in the economic model and the uncertainty of the parameter values, introducing a national mechanical thrombectomy service with one additional dedicated biplane angiography suite would be cost-effective under typical willingness-to-pay thresholds applied in Ireland.

Based on an estimated 268 (95% CI 210 to 322) thrombectomy procedures undertaken each year, 57 (95% CI 38 to 78) additional patients (that is, increasing from 102 to 159) are predicted to regain functional independence at 90 days after a stroke. The five-year budget impact is estimated at €7.2 million comprising €3.3

million in the first year and annual running costs afterwards estimated at €0.8 to €1.2 million. The five-year budget impact of moving from the current ad hoc service (200 patients per annum provided through the existing facilities) to a national service is estimated to be €2.8 million (of which €2.0 million would be incurred in the first year).

An organised national service would, however, necessitate detailed service planning to ensure it adheres to requisite quality standards. This includes the development of quality key performance indicators to measure performance against targets or expectations. An equitable, efficient and cost-effective national service is contingent on the procedure being offered in a small number of centres that are adequately resourced and sited to maximise patient access, workforce expertise and geographical coverage. Expanded access to mechanical thrombectomy has potential implications for the National Ambulance Service to ensure timely transfer of patients to these centres and repatriation of these patients to their acute local hospitals — while maintaining adequate ambulance services for other patients.

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- http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/WP5-SB16_Mechanical%20thrombectomy%20devices%20for%20acute%20ischaemic%20stroke.pdf .

The membership of the EAG was as follows:

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Organisations and individuals that assisted the Authority in providing information, in writing or through meetings, included:

Ms Mary Farrelly, Director of Finance and Procurement, Beaumont Hospital.
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Members of the Evaluation Team:

Members of the Authority's Evaluation Team were Dr Ronan Glynn, Dr Patricia Harrington, Dr Patrick Moran, Dr Máirín Ryan and Dr Conor Teljeur.

Conflicts of interest

None reported.

List of abbreviations used in this report

ADL	activities of daily living
AHA	American Heart Association
CE	Conformité Européen
CEA	cost-effectiveness analysis
CI	confidence interval
CT	computed tomography
CTA	computed tomography angiography
CUA	cost-utility analysis
DALY	disability-adjusted life year
EAG	expert advisory group
ECASS	European Cooperative Acute Stroke Study
EMA	European Medicines Association
ESMINT	European Society of Minimally Invasive Neurological Therapy
ESNR	European Society of Neuroradiology
ESO	European Stroke Organisation
EUnetHTA	European Network for Health Technology Assessment
FDA	US Food and Drug Administration
GBD	Global Burden of Disease Study
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIPE	Hospital Inpatient Enquiry
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
HTA	health technology assessment

IA	Intra-arterial
IAT	Intra-arterial thrombolysis
ICA	internal carotid artery
ICER	incremental cost-effectiveness ratio
ICH	intracerebral haemorrhage
INASC	Irish national audit of stroke care
IV	intravenous
IV t-PA	intravenous (IV) tissue-plasminogen activator (tPA)
KPI	key performance indicator
KSU	Karolinska Stroke Update
LVO	large vessel occlusion
MCA	middle cerebral artery
MRI	magnetic resonance imaging
MRA	magnetic resonance angiography
mRS	modified Rankin scale
NAS	National Ambulance Service
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
PRISMA	Preferred reporting items for systematic review and meta-analysis
QALY	quality-adjusted life year
RCT	randomised controlled trial
SICH	symptomatic intracerebral haemorrhage
TIA	transient ischaemic attack
TICI	thrombolysis in cerebral infarction

1. Introduction

1.1 Background to the request

The Health Information and Quality Authority (HIQA) received a request from Beaumont Hospital in Dublin to undertake a health technology assessment (HTA) to evaluate the use of endovascular therapy using mechanical thrombectomy devices for acute ischaemic stroke in Ireland. This followed international evidence from a number of clinical trials of its potential benefit. The hospital had participated in a multi-centre randomised controlled trial (RCT) which was halted early due to evidence of efficacy on interim analysis. The purpose of the HTA was to assess the clinical effectiveness, cost-effectiveness, budget impact and the organisational and ethical implications of this technology, so to inform decisions around a national emergency endovascular service for the management of acute ischaemic stroke.

HIQA is the national representative body for the European Network for Health Technology Assessment (EUnetHTA), work by which is funded by a grant from the European Commission. It is intended that work undertaken by, and output from, EUnetHTA will be applicable at local (regional and national) level across Europe and will therefore limit unnecessary duplication and improve efficiency in the assessment of new medical technologies. Work on the HTA of mechanical thrombectomy was initially undertaken as a pilot rapid assessment through HIQA's work with EUnetHTA. The rapid assessment, co-authored by HTA colleagues from Germany, was published by EUnetHTA in December 2015.[(1)]

The EUnetHTA report, which concluded that endovascular therapy using mechanical thrombectomy is a safe and effective adjunct to standard medical care for selected patients, was subsequently updated and adapted to include data on the burden of stroke in Ireland, a review of the cost-effectiveness literature, an economic model to estimate cost-effectiveness and budget impact, as well as a review of the organisational and ethical implications in the context of the Irish healthcare system.

1.2 Remit of the HTA

The specific remit of this HTA was to assess whether mechanical thrombectomy plus standard medical care (which may include intravenous and or intra-arterial thrombolysis, where appropriate) is more effective and, or safer than standard medical care alone in the management of acute ischaemic stroke, and in this context, whether it represents a cost-effective, affordable and implementable technology. The purpose of this report was to:

- describe the epidemiology of stroke in Ireland
- examine the current evidence of efficacy and safety for mechanical thrombectomy as a treatment in the management of acute ischaemic stroke
- review the international literature on cost-effectiveness of mechanical thrombectomy as a treatment in the management of acute ischaemic stroke
- assess the cost-effectiveness and budget impact of mechanical thrombectomy in the context of the Irish healthcare setting
- review potential implications for the organisation of acute stroke care
- consider any wider ethical or societal implications of mechanical thrombectomy as a treatment in the management of acute ischaemic stroke for patients, the general public or the healthcare system
- based on this assessment, to advise on the use of mechanical thrombectomy as an adjunct to standard medical care in the management of acute ischaemic stroke in Ireland.

1.3 Overall approach

This assessment represents an adaptation of the EUnetHTA report for which HIQA was the lead author. The adaption includes Irish-specific data relating to burden of disease and an assessment of relevant organisational issues. The systematic review of clinical effectiveness and safety was updated and a *de novo* systematic review of the cost-effectiveness literature undertaken. To evaluate the cost-effectiveness and budget impact of this technology in the Irish healthcare setting, an economic model developed to inform a HTA by Health Quality Ontario in Canada was adapted and populated with Irish relevant data.

HIQA convened an Expert Advisory Group comprising representation from relevant stakeholders including the HSE's clinical programmes for radiology and stroke, clinicians with specialist expertise, a representative from the National Ambulance Service, a representative of a patient organisation and international HTA experts. The role of the Expert Advisory Group was to inform and guide the process, provide expert advice and information and to provide access to data where appropriate. A full list of the membership of the Expert Advisory Group is available in the acknowledgements section of this report.

The Terms of Reference of the Expert Advisory Group were to:

- Contribute to the provision of high-quality and considered advice by the Authority to the Minister for Health.
- Contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate.
- Be prepared to provide expert advice on relevant issues outside of group meetings, as requested.
- Provide advice to the Authority regarding the scope of the analysis.
- Support the Evaluation Team led by the Authority during the assessment process by providing access to pertinent data, as appropriate.
- Review the project plan outline and advise on priorities, as required.
- Review the draft report from the Evaluation Team and recommend amendments, as appropriate.
- Contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

HIQA appointed an Evaluation Team to carry out the adaptation of the EUnetHTA assessment.

The draft assessment was submitted to the advisory group for review and discussion at a formal meeting of the group. Amendments were made, as appropriate, before the final draft was re-reviewed and subsequently submitted to the Board of HIQA for approval. The completed assessment was submitted to the HSE and Minister for Health as advice and was published on the HIQA website.

2. Description of the technology

The purpose of this chapter is to provide a brief description of mechanical thrombectomy as a treatment in the management of acute ischaemic stroke, and to provide an overview of the current Irish and international guidance for the treatment of acute ischaemic stroke.

Acute ischaemic stroke occurs as a result of an obstruction within a blood vessel supplying blood to the brain, resulting in disruption of the flow of blood to the brain, causing a focal or global neurological deficit (affecting bodily functions or mental processes) lasting more than 24 hours, or causing death within 24 hours.[2]

2.1 The management of acute ischaemic stroke

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) study reported that patients with acute ischaemic stroke who received intravenous (IV) thrombolysis with tissue plasminogen activator (tPA) (alteplase) within three hours of onset of symptoms were at least 30% more likely to have minimal or no disability at three months than those who received placebo.[3] This finding, and meta-analyses of subsequent studies, showed a clear association between treatment efficacy and the interval between the onset of symptoms and administration of the thrombolytic agent. Regulatory approval for IV t-PA was given by the US Food and Drug Administration in 1996 and it was approved for use by the European Medicines Agency (EMA) in 2002. However, by 2007, it was reported that IV t-PA was still being used in less than 2% of patients across Europe, primarily because of delayed admission to hospital and apprehension about symptomatic intra-cerebral haemorrhage (SICH).[4, 5]

In 2002, as part of its approval process, the EMA requested that an observational safety study be initiated; subsequently, the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS–MOST) was undertaken. This study confirmed comparable safety and efficacy in routine clinical practice for IV t-PA to that seen in randomised controlled trials (RCTs).[6] The EMA also requested that an RCT be undertaken in which the therapeutic time window was extended beyond three hours. Consequently, between 2003 and 2007, the European Cooperative Acute Stroke Study (ECASS) III undertook a double-blind parallel-group trial which enrolled 821 patients from 130 centres across 19 European countries.[4] Patients were eligible for inclusion in the study if they were 18 to 80 years of age, had received a clinical diagnosis of acute ischaemic stroke, and were able to receive the IV t-PA within three to four hours after the onset of symptoms (this was amended to 4.5 hours in

2005). The primary efficacy end point was disability at day 90 (three-month visit), as assessed by means of the modified Rankin scale. This trial demonstrated significantly improved outcomes in those receiving IV t-PA up to 4.5 hours after onset of symptoms, when compared with placebo.[4]

In 2008, the European Stroke Organisation published guidelines for the management of acute ischaemic stroke.[7] These guidelines noted that 'patients admitted within three hours of onset of stroke may be candidates for intravenous (IV) thrombolysis' with tissue plasminogen activator (tPA), but require imaging with CT or MRI in the first instance to exclude haemorrhagic stroke (for which IV thrombolysis is contraindicated). These guidelines suggested that while IV t-PA may also hold benefit beyond the three-hour window, its use in routine clinical practice was not recommended.[7] However, the results of the European Cooperative Acute Stroke Study (ECASS) III prompted the American Heart Association (AHA) to publish an advisory statement in 2009 recommending the use of IV t-PA up to 4.5 hours after onset of symptoms, in the setting of ECASS III eligibility criteria. Similarly, in 2009, the European Stroke Organisation updated its guidelines to state that 'IV t-PA is recommended within 4.5 hours of onset of ischaemic stroke'.[8]

The past two decades has thus seen an increasing acceptance of IV t-PA as a key component in the treatment of acute ischaemic stroke and it is now the standard medical care against which other therapies must be compared.[9] However, despite this, the narrow time window and strict exclusion criteria associated with its use has meant that, internationally, IV t-PA is used in less than 5% of all patients experiencing an acute ischaemic stroke (although there is evidence of substantial international variation, with average current thrombolysis rates of 12.3% in Ireland).[10]

In addition, even for those who are eligible for IV t-PA, rates of recanalisation following treatment are dependent upon the particular vessel affected and the location of the thrombus within that vessel.[9] Reported recanalisation rates following IV t-PA range from 44% for the distal middle cerebral artery (MCA) to 26–40% for the proximal MCA and only 7–10% for occlusions of the intracranial internal carotid artery (ICA).[9] These limitations have led investigators to examine other possible mechanisms to achieve recanalisation of the occluded vessel in ischaemic stroke. One potential option is endovascular therapy, which includes two different modalities — intra-arterial administration of thrombolytic drugs (intra-arterial thrombolysis) and mechanical thrombectomy.

The efficacy of intra-arterial thrombolysis (IAT) was suggested by the results of a number of clinical trials, specifically the Prolyse in Acute Cerebral Thromboembolism (PROACT II) trial and the Interventional Management of Stroke (IMS) I and II trials.

PROACT II demonstrated that 66% of cases treated with intra-arterial recombinant pro-urokinase within six hours of symptom onset achieved partial or complete recanalisation; this compared with 18% in controls given IV t-PA alone.[11] To date, however, PROACT II remains the only randomised controlled trial of IAT versus IV t-PA which has demonstrated statistically significant clinical benefit in favour of IAT.[12]

The first Interventional Management of Stroke (IMS) Trial (IMS I) was published in 2004 and was the first study to suggest that a combined intravenous and intra-arterial thrombolysis approach to the management of acute ischaemic stroke could achieve superior outcomes compared with IV t-PA alone.[13] IMS II was published in 2007 — this built on IMS I by examining the use of the EKOS micro-infusion catheter for the provision of IA t-PA; this catheter employs ultrasound technology to help alter the structure of the thrombus and facilitate its removal.[14] IMS II compared the efficacy and safety of low dose IV t-PA (0.6 mg/kg) and IA t-PA (up to 22 mg) to historical results from the aforementioned NINDS study in which patients had received IV t-PA alone. The study reported that 46% of patients in IMS II achieved a good functional outcome (modified Rankin scale [mRS] of 0–2), compared with 39% in the NINDS t-PA arm, although IMS II also reported higher rates of symptomatic intracerebral haemorrhage (9.9% versus 6.6%). In addition, rates of complete recanalisation (TIMI 3) and partial recanalisation (TIMI 2/3) in IMS II were just 4% and 60%, respectively.

2.2 Endovascular therapy using mechanical thrombectomy

Endovascular therapy is a minimally invasive form of treatment for certain vascular diseases. During endovascular therapy for acute ischaemic stroke, a catheter is sent to the site of the blockage (usually via the femoral artery in the groin) and the thrombus removed mechanically or an attempt is made to dissolve the clot using intra-arterial thrombolysis as described in Section 2.1 above.

2.2.1 Mechanical thrombectomy devices

Mechanical thrombectomy devices aim to retrieve thrombi and rapidly restore blood flow in patients with acute ischaemic stroke. They may be used with aspiration and with the injection or infusion of contrast media and other fluids, and are subdivided by their mechanism of action: those that use an approach distal to the thrombus (retrievers) or proximal to the thrombi (aspiration devices). These devices can also be considered in terms of their time of development and approval for use, and may

be separated into 'first-' and 'second-generation' retrieval devices and devices whose mechanism of action is based on suction/aspiration (Table 2.1).

Table 2.1 Overview of mechanical thrombectomy devices[1]

Device type	Mechanism of action
Aspiration devices	Suction thrombectomy devices employ vacuum aspiration to remove occlusive clots. These are effectively like access catheters, but are developed to be flexible enough to navigate to the site of the clot while having a sufficiently large inner diameter to aspirate the clot within.
Stent retrievers (second-generation mechanical thrombectomy devices)	The stent retrievers are self-expanding stents that 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.
Coil retrievers (first-generation mechanical thrombectomy devices)	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 the delivery catheter, it immediately reassumes its native coil form. The neuro-interventionalist deploys the loops of the coil through the clot to engage the thrombus, and then pulls both coil and clot back into the catheter.

The Mechanical Embolus in Cerebral Ischaemia (MERCI) (Concentric Medical, California, USA) retrieval device was the first device approved for thrombectomy in patients experiencing acute ischaemic stroke. Approved by the US Food and Drug Administration (FDA) in 2004, it consists of a flexible corkscrew-shaped nitinol memory-wire which is extended past the thrombus and then pulled back, bringing the thrombus with it.

The Penumbra System (Penumbra Inc, California, USA) was approved by the FDA in 2007. The most commonly used 'aspiration' device, this system is predicated on the use of gentle aspiration of clot fragments via a suction device, with removal of residual thrombus achieved through direct engagement using a 'thrombus removal ring'.

The newer, second-generation devices are termed 'stent retrievers' and include the SOLITAIRE FR Revascularization Device (Covidien, Dublin, Ireland) and the TREVO device (Concentric Medical Inc.). These use a temporary stent which captures the thrombus and displaces it peripherally against the vessel wall thus restoring blood flow. The stent is then withdrawn and the thrombus is removed along with the stent.[15]

As of August 2015, fifteen mechanical thrombectomy devices had been CE-marked for use in acute ischaemic stroke (Table 2.2).

Table 2.2 CE-marked mechanical thrombectomy devices (as of August 2015)

Aspiration/suction devices
▪ Penumbra System®/ACE™ (Penumbra 3D Separator)
▪ SOFIA™ Distal Access Catheter
▪ Vasco+35ASPI
Stent retrievers
▪ Acandis Aperio® Thrombectomy Device
▪ BONnet
▪ Catch
▪ EmboTrap®
▪ ERIC®
▪ MindFrame Capture™ LP System
▪ REVIVE™ SE Thrombectomy Device
▪ Solitaire™ 2 and Solitaire™ FR Revascularization Devices
▪ Trevo® ProVue™ Retrieval System
▪ Trevo® XP ProVue™ Retrieval System
▪ pREset, pREset® LITE
Coil retrievers
▪ Merci Retrieval System

2.2.2 Treatment comparators

Standard of care for acute ischaemic stroke is defined by national and international clinical guidelines. As noted above, this includes the administration of intravenous

and, or intra-arterial thrombolysis where appropriate. Standard medical treatment including thrombolysis has been shown to have modest clinical efficacy in patients with severe stroke. Thrombolysis administered within 4.5 hours of symptom onset is associated with a recanalisation rate of approximately 46% and good functional recovery (as defined by a modified Rankin Score of 0 or 1) in approximately 35% of patients.[16, 17]

2.2.3 Potential benefits of mechanical thrombectomy devices relative to the treatment comparators

Mechanical thrombectomy is indicated as an adjunct to standard medical care. Potential benefits of mechanical thrombectomy include:

- Extension of the treatment window — the window of treatment for mechanical thrombectomy devices is potentially much longer than for treatment with IV t-PA, extending up to 12 hours after the onset of stroke symptoms.[18] In contrast, IV t-PA is only indicated for use in patients within 4.5 hours of symptom onset.[19]
- Efficacy against larger, more proximally situated thrombi — these thrombi may be relatively resistant to IV t-PA. Successful recanalisation of large vessel occlusion (LVO) with IV t-PA alone is infrequent, ranging from 10% in internal carotid artery (ICA) occlusions to 30% in middle cerebral artery occlusions.[20]
- Use in those for whom thrombolysis is contraindicated — IV t-PA is contra-indicated in cases where there is an elevated risk of cerebral and systemic haemorrhage.

2.2.4 The evidence for mechanical thrombectomy

The IMS III trial began enrolment in 2006 and compared combined IV t-PA and endovascular therapy with IV t-PA alone, with all eligible patients receiving IV t-PA within three hours of symptom onset. IMS III included the EKOS micro-infusion catheter along with the MERCI retriever in its protocol for what was to become the first published RCT of mechanical thrombectomy versus standard medical care alone.[21]

In 2012, the European Stroke Organisation (ESO), the European Society of Minimally Invasive Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR) issued a joint statement on mechanical thrombectomy.[22] This noted that, due to the lack of evidence from RCTs, the extent of clinical effectiveness and risks of mechanical thrombectomy remained unclear at that time. The first three RCTs to compare standard medical care with mechanical

thrombectomy were published in 2013.[21, 23, 24] Their results were disappointing for mechanical thrombectomy, and their publication was met with considerable controversy, with concerns raised in the medical community about the future of endovascular treatment for acute ischaemic stroke.[25] Some commentators surmised that the results signalled the end for mechanical thrombectomy as a treatment for acute ischaemic stroke. Others argued that the flaws inherent with the trials needed to be addressed in follow-up RCTs which more accurately reflected modern standards of care with regard to imaging and the types of device used.[25] [26] While waiting for these additional trials to be published, a further consensus statement was published in 2014.[27] This recommended that:

- Mechanical thrombectomy, in addition to intravenous thrombolysis within 4.5 hours when eligible, is recommended to treat acute stroke patients with large artery occlusions in the anterior circulation up to six hours after symptom onset (Grade A, Level 1a, KSU Grade A).
- Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis where this is indicated, and intravenous thrombolysis should not delay mechanical thrombectomy (Grade A, Level 1a, KSU Grade A).
- Mechanical thrombectomy should be performed as soon as possible after its indication (Grade A, Level 1a, KSU Grade A).
- 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 neuro-interventionists' discretion if rapid, complete and safe revascularisation of the target vessel can be achieved (Grade C, Level 2a, KSU Grade C).
- The decision to undertake mechanical thrombectomy should be made jointly by a multidisciplinary team comprising at least a stroke physician and a neuro-interventionalist and performed in experienced centres providing comprehensive stroke care and expertise in neuro-anesthesiology.
- If intravenous thrombolysis is contraindicated (e.g., warfarin-treated with therapeutic international normalised ratio [INR]), mechanical thrombectomy is recommended as first-line treatment in large-vessel occlusions (Grade A, Level 1a, KSU Grade A).
- Patients with acute basilar artery occlusion should be evaluated in centres with multimodal imaging and treated with mechanical thrombectomy in addition to intravenous thrombolysis when indicated (Grade B, Level 2a, KSU Grade C); alternatively they may be treated within an RCT for thrombectomy approved by the local ethical committee.

In 2015, the first RCT to demonstrate the superiority of endovascular intervention, including mechanical thrombectomy, over standard medical care was published.[28] Hailed as a landmark trial, MR CLEAN included 500 patients across 16 centres in the Netherlands who presented with clinical and radiological evidence of a proximal anterior circulation stroke within six hours of onset of symptoms. Second-generation stent retriever technology was used in 81.5% of the patients. The authors reported a significant difference in the rate of functional independence, as measured using the modified Rankin Score (mRS), in favour of mechanical thrombectomy. No differences in safety outcomes between those who did and did not receive the intervention were recorded.[28]

The publication of MR CLEAN was followed by the publication of five additional RCTs which also compared endovascular intervention against standard medical care.[18, 19, 29-31] All five of these trials individually reported in favour of mechanical thrombectomy, and their publication was met with a rapidly growing consensus that this technology may provide additional benefit to patients experiencing acute ischaemic stroke, when compared with standard medical care.[32, 33] The efficacy and safety of mechanical thrombectomy is assessed in detail in Chapter 4.

2.2.5 The provision of mechanical thrombectomy

The decision to undertake mechanical thrombectomy should be made jointly by a multidisciplinary team comprising — at a minimum — a stroke physician and a neuro-interventionalist. Endovascular therapy should be provided within comprehensive and some advanced stroke centres which, by definition, have advanced neuro-imaging capability, coordinated stroke care, specialised stroke teams, and a stroke unit to provide appropriate care and recovery after the hyperacute period.[34] An international, multi-society consensus document was published in 2016 which outlines many of the requirements for institutions performing mechanical thrombectomy, stating that they should have:

- angiography suites suitably equipped to handle these patients, as well as equipment and capability to handle the complications
- dedicated stroke and intensive care units (preferably dedicated neuro-intensive care unit), staffed by physicians with specific training in those fields
- vascular neurology and neurocritical care expertise
- neurosurgery expertise, including vascular neurosurgery
- all relevant neuro-imaging modalities (computed tomography [CT]/computed tomography angiography [CTA], magnetic resonance imaging [MRI]/magnetic

resonance angiography [MRA], trans-cranial Doppler [TCD]), including 24-seven access to CT and MRI.[35]

The document also stated that 'physicians providing intra-arterial treatment for acute stroke are required to have appropriate training and experience for the performance of neuro-angiography and interventional neuroradiology.'[35]

2.3 Summary

Acute ischaemic stroke occurs as a result of an obstruction within a blood vessel supplying blood to the brain, resulting in disruption of the flow of blood to the brain, causing a focal or global neurological deficit (affecting bodily functions or mental processes) lasting more than 24 hours, or causing death within 24 hours.

In the 1990s, intravenous thrombolysis as delivered in the form of IV t-PA was demonstrated to be effective at improving disability outcomes in patients with acute ischaemic stroke. Regulatory approval for IV t-PA was given in the US in 1996 and in Europe in 2002. Intravenous thrombolysis is now regarded as the standard of care for acute ischaemic stroke, against which other therapies must be compared.

Until 2009, European guidelines did not recommend use of IV t-PA more than three hours after symptom onset. Coupled with a requirement for CT or MRI diagnosis to exclude haemorrhagic stroke (for which IV thrombolysis in contraindicated), only a small percentage of patients were eligible for IV t-PA therapy. In 2009, guidelines were revised and IV t-PA is now recommended up to 4.5 hours after symptom onset. However, despite the demonstrated efficacy and effectiveness of IV t-PA, the narrow time window and strict exclusion criteria associated with thrombolysis has meant that in Ireland, on average, approximately 12.3% of patients experiencing acute ischaemic stroke receive thrombolysis, although there is considerable regional variation.[36-39] The 2015 Irish Heart Foundation/HSE National Stroke Audit reported 24-seven access to thrombolysis in 82% (21 out of 27) acute hospitals with ambulance redirection procedures in place in a further 15% (4 out of 27) sites. The experience in Ireland has been similar to that observed internationally.[39]

Successful recanalisation is dependent on the vessel affected and the location of the thrombus within the vessel. Endovascular therapies, such as intra-arterial administering of thrombolytic drugs and mechanical thrombectomy, were developed in an attempt to improve recanalisation rates.

Since the early 2000s, a range of mechanical thrombectomy devices have been developed. Mechanical thrombectomy devices aim to retrieve thrombi and rapidly restore blood flow in patients with acute ischaemic stroke. Devices can be classified

as retrievers and aspiration devices. The first-generation of devices were coil retrievers, in which a wire coil is deployed through a catheter and used to engage the clot and used to pull it back into the catheter. Second-generation retrievers are stent retrievers. Rather than a wire coil, these use a self-expanding stent to entangle the clot and remove it through the catheter. Aspiration devices use suction to draw the clot into a catheter. As of August 2015, fifteen mechanical thrombectomy devices had been CE-marked.

The first trials to examine the effectiveness and safety of mechanical thrombectomy in the management of acute ischaemic stroke commenced in 2004. The first three RCTs comparing mechanical thrombectomy with standard medical care (including IV t-PA) were published in 2013. The results of a further six RCTs were published in 2015 and 2016. Mechanical thrombectomy is indicated as an adjunct to rather than a replacement for standard medical care. The safety and efficacy of mechanical thrombectomy is reviewed in detail in Chapter 4.

The decision to undertake mechanical thrombectomy should be made jointly by a multidisciplinary team that, at a minimum, includes a stroke physician and a neuro-interventionalist. Endovascular therapy should be provided within centres that have advanced neuro-imaging capability, coordinated stroke care, specialised stroke teams, and a stroke unit to provide appropriate care and recovery after the hyperacute period.

2.4 Key messages

- Acute ischaemic stroke occurs as a result of an obstruction within a blood vessel supplying blood to the brain, resulting in disruption of the flow of blood to the brain, causing a focal or global neurological deficit (affecting bodily functions or mental processes) lasting more than 24 hours, or causing death within 24 hours.
- Intravenous thrombolysis is now regarded as the standard of care for acute ischaemic stroke, against which other therapies must be compared.
- The narrow time window and strict exclusion criteria associated with thrombolysis has meant that, in Ireland, only a small portion — approximately 12.3% on average — of patients experiencing acute ischaemic stroke receive thrombolysis; this is consistent with international trends.
- Mechanical thrombectomy devices aim to retrieve thrombi and rapidly restore blood flow in patients with acute ischaemic stroke.
- The first trials to examine the effectiveness and safety of mechanical thrombectomy in the management of acute ischaemic stroke commenced in

2004.

- As of August 2015, fifteen mechanical thrombectomy devices had been CE-marked. They can be broadly subdivided by their mechanism of action; those that use an approach distal to the thrombus (retrievers) or proximal to the thrombi (aspiration devices).
- Mechanical thrombectomy is indicated as an adjunct to rather than a replacement for standard medical care.
- Delivery of this procedure is confined to comprehensive stroke centres with access to neurosurgical care, advanced brain imaging and appropriate neuro-endovascular expertise.

3. Burden of disease

This chapter describes the epidemiology of acute ischaemic stroke and its current management in Ireland.

3.1 Pathophysiology of stroke

Acute ischaemic stroke occurs as a result of an obstruction within a blood vessel supplying blood to the brain. This can occur because of large-artery atherosclerotic infarction, which may be extracranial or intracranial; embolism from a cardiac source; small-vessel disease; other determined cause such as dissection; hypercoagulable states or sickle cell disease; and infarcts of undetermined cause.[2]

Some of the common signs of stroke include:

- asymmetry in the face or a droop on one side of the face
- weakness on one side of the body (such as an arm, leg, or both)
- numbness or unusual sensations on one side of the body
- trouble speaking (speech is slurred; cannot repeat a simple phrase).[40]

A large case-control study of stroke has identified 10 risk factors that explain approximately 90% of the population-attributable risk, with hypertension being the most important risk factor.[41] Other significant risk factors which contribute to the risk of stroke include lipid levels, physical inactivity, smoking and diet. In addition, larger waist-to-hip ratios, a history of diabetes, increased alcohol intake, psychosocial stress and or depression, and cardiac morbidity all contribute to stroke.[42]

Stroke can affect people physically, mentally, emotionally and or socially. The consequences of stroke vary widely depending on the size and location of the lesion.[43] Dysfunction corresponds to the areas in the brain that have been damaged. Disability affects 75% of stroke survivors enough to decrease their employability.[44]

3.2 The burden of stroke

3.2.1 The international burden of stroke

In 2010, estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD 2010) ranked stroke as the second most common cause of death and the third most common cause of disability-adjusted life-years (DALYs) worldwide.[45] Although mortality rates and mortality-to-incidence ratios have decreased in the past two decades, the global burden of stroke in terms of the absolute number of people affected every year, stroke survivors, related deaths, and DALYs lost are increasing, with most of the burden in low-income and middle-income countries. It has been suggested that if current trends continue there will be almost 12 million stroke deaths, 70 million stroke survivors, and more than 200 million DALYs lost globally by 2030.[45]

In 2013, acute ischaemic stroke accounted for approximately 67% (6.8 million) of new strokes globally.[46] This was also responsible for approximately 3.3 million deaths, representing 51% of all mortality due to stroke, and 47.4 million DALYs lost — representing 42% of all DALYs lost due to stroke.[46]

3.2.2 The burden of stroke in Ireland

Diseases of the circulatory system (cardiovascular diseases, CVD) — including coronary heart disease (CHD), stroke and other circulatory diseases — are the most common cause of death in Ireland, and accounted for 8,899 deaths (an annual rate of 1.9 per 1,000 population) or 34% of all mortality in 2014.[47]

In 2010, the Irish Heart Foundation estimated that approximately 7,735 individuals experience a stroke annually in Ireland.[48] An estimated 2,000 people die as a result of stroke each year in Ireland, giving an age-standardised death rate of 34.6 per 100,000 population.[49, 50] A 2014 HSE report predicted 20% increases in the prevalence of major chronic diseases by 2020 primarily due to population aging, with the number of people with stroke predicted to increase by between 4% and 5% per annum between 2015 and 2020.

Importantly from a heath systems perspective, the total direct expenditure on stroke is estimated to account for between 2% and 4% of total health expenditure. Adjusting for demographic change alone, it is predicted that the total annual cost of stroke in Ireland will be €723–€1,247 million in 2021, representing a 52–57% per cent increase compared with 2007 (range €489-€805 million).[50]

3.2.3 Incidence by age and sex in Ireland

The third Annual Report (2014) of the National Stroke Register was published in December 2015.[51] This Register was developed as part of the National Clinical Programme for Stroke and has been implemented as an 'add-on screen' to the existing Hospital In-Patient Enquiry (HIPE) system to facilitate stroke teams to enter a stroke-specific dataset. The Annual Report for 2014 confined its analysis to those hospitals that submitted data on at least 80% of the patients they had treated for stroke; as a result, just 13 of the 27 hospitals which receive patients experiencing a stroke in Ireland were included in the analysis. A total of 1,848 cases of cerebral infarction or intracerebral haemorrhage were discharged from this subset of 13 hospitals during 2014 according to HIPE. Of these, 1,744 were entered into the National Stroke Register, of which 98.1% (n=1,711) were emergency admissions; the remaining 33 cases were admitted electively (n=24), as an emergency readmission (n=8) or as an elective readmission (n=1).

In order to assess the representativeness of their data, the authors of the third Annual Report (2014) of the National Stroke Register compared their data with that from the 27 hospitals as a whole, as reported for those cases recorded on HIPE with a principal diagnosis of cerebral infarction or intracerebral haemorrhage. In 2014, there were 5,090 such cases admitted to these 27 hospitals. The comparison between the Register and the HIPE data, performed by the authors of the National Stroke Register Annual Report, along with the figures reported by the National Stroke Audit, 2015, are outlined in Table 3.1 below.

All three datasets suggest that, in Ireland, more than half (55–57%) of acute strokes occur in men and that cerebral infarction (acute ischaemic stroke) accounts for approximately 85% of all strokes resulting in hospitalisation annually.

The average age across datasets for patients experiencing an acute stroke was 73–75 years, with incidence increasing with age. Stroke is not a condition confined to old age, however. The National Stroke Register reported that 27% of cases of acute stroke in 2014 occurred in those aged less than 65 years, with a similar finding (24%) reported by the National Stroke Audit in 2015. The 2015 audit noted that this figure had increased from 19% in the previous audit in 2008. A key finding noted by the authors of the 2015 audit — and replicated across all three datasets above — is that nearly one in three strokes in males (30%) occurred in the under-65 age group.

Table 3.1 Comparison of data on stroke-related admissions for 2014 from the National Stroke Register , National HIPE file and National Stroke Audit [39, 51]

	National Stroke Register, 2014* (n=1,744)[51]	HIPE, 2014 (n=5,090)*	National Stroke Audit, 2015 (n=874) **
Males (%)	57	55	57¥
Females (%)	44	45	41¥
Males mean age (yrs)	69	69	71
Males <65 yrs (%)	34	32	30
Females mean age (yrs)	75	75	77
Females <65 yrs (%)	17	18	15
Length of stay (days)			
Mean	19.8	19.7	22.4
Median	9	9	11
In-hospital mortality (%)	13	14	14
ICH:IC^	1:5.5	1:5.5	1:5.5

* Cases relate to admission with a principal diagnosis of cerebral infarction or intracerebral haemorrhage.
**Cases relate to admission with a principal diagnosis of cerebral infarction or intracerebral haemorrhage or stroke, not specified as haemorrhage or infarction, and excludes cases related to readmission of a previous event or complications of a previous stroke.
¥ Gender-related data was missing in 1% of cases.
^Ratio of intracerebral haemorrhage to cerebral infarction. A ratio of 1:5.5 equates to 84.6% of stroke-related admissions being due to cerebral infarction.

3.3 The management of acute ischaemic stroke in Ireland

- The first Irish National Audit of Stroke Care (INASC) in 2006–2007 reported that stroke services in Ireland required substantial development.[52] The findings from that audit informed the development of the National Cardiovascular Health Policy, *Changing Cardiovascular Health 2010–2019*, which was published in 2010.[53] This policy acknowledged that stroke services at the time were much less developed than cardiac services. It made a number of recommendations in

relation to the development and provision of stroke units and emergency care for patients experiencing a stroke, and the organisation of stroke services, including: All hospitals admitting patients with acute stroke should have a stroke unit, as defined by the European Stroke Organisation.*

- Stroke units should have adequate and appropriate staffing.
- Emergency stroke treatment by a consultant stroke physician should be available on a 24-hour, seven-day basis to all acute stroke patients within each stroke network.
- Each stroke network should agree a model of service delivery to meet the need for a 24-hour, seven-day thrombolysis service.
- Specialist stroke services should be organised into population-based stroke networks, with network hospitals designated as:
  - (i) general stroke centres or
  - (ii) comprehensive stroke centres.

Publication of the national policy was followed by the launch of the HSE's National Clinical Programme for Stroke in 2010, which was established with three specific aims, which were to:

- provide national rapid access to best-quality stroke services
- prevent one stroke every day
- avoid death or dependence in one patient every day.[54]

The evidence suggests that the provision of, and outcomes from stroke care have improved in Ireland in the interim. The aforementioned caveats around the National Stroke Register data notwithstanding, the 2014 National Stroke Register annual report noted that 69.4% of patients admitted with acute ischaemic stroke and intracerebral haemorrhage had been admitted to a stroke unit for at least some of their hospital stay — the national key performance indicator (KPI) is for 50% of stroke patients to be admitted to a stroke unit.[51] Thrombolytic therapy was administered to 10.5% (166/1,583) of those presenting with acute ischaemic stroke — the national target is 9% — and almost 97% of stroke patients presenting with acute stroke received a CT or MRI scan.[51] In 2014, the median length of stay in hospital for patients experiencing an acute stroke was nine days with a mean length of stay of 19.8 days (Table 3.1). This compared with median and mean length of stays of 11 and 24 days, respectively, in 2012.

* The European Stroke Organisation (ESO) defines a stroke unit as follows: 'A stroke unit consists of a discrete area of a hospital ward that exclusively or nearly exclusively takes care of stroke patients and is staffed by a specialist multidisciplinary team. The core disciplines of the team are medicine, nursing, physiotherapy, occupational therapy (OT), speech and language therapy (SLT) and social work. The multidisciplinary team should work in a coordinated way through regular meetings to plan patient care. Programmes of regular staff education and training should be provided.'

The second Irish National Stroke Audit (2015), also noted substantial improvements in stroke care and outcomes when compared with the previous audit in 2006–2007, with a reduction in inpatient mortality of more than one quarter and a reduction in discharges direct to nursing homes of one third.[39] Consistent with the results from the Stroke Register data, the 2015 audit reported that 11% (81/874) of patients with acute ischaemic stroke received thrombolysis, representing a tenfold increase since the 2007–2008 audit. Thrombolysis rates varied substantially by hospital group and by individual hospital, although it was noted that direct comparison between sites was not appropriate as the audit was limited to a small sample size and only captured data at a point in time. Stroke units are now available in 78% of receiving hospitals (21 out of 27), although these vary in their resourcing and level of service offered. Less than one in three patients (29%) is admitted to these units at presentation, with only 54% of patients experiencing an acute stroke admitted to a stroke unit during the course of their hospital stay.[39]

A number of issues have been also been highlighted by the 2014 Register's report and the 2015 National Stroke Audit. Information on the time from stroke symptom onset to hospital arrival was only available for 42% of cases. For those in whom this information was available, 68.6% arrived within four hours of symptom onset.[51] Similarly, the audit — in highlighting the challenges which are faced by those tasked with improving rates of thrombolysis and thrombectomy — noted that information on the time from onset of stroke to presentation to the emergency department was available in 65% of cases. In the remaining cases, the time of onset was either unknown or the patient had a stroke during sleep. While almost two out of three people presented to hospital by ambulance, this was substantially less than the (82%) reported in a similar audit in the UK in 2014 [55]. Furthermore, the 2015 audit reported that, nationally, the median time from onset of symptoms to presentation varies appreciably by hospital (national median 2 hours 26 minutes, interquartile range 1 hour 21 minutes to 6 hours 6 minutes), with 22% of patients arriving at hospital more than six hours after symptom onset.[39] The 2015 National Stroke Audit also noted that 55% of people presented to the emergency department outside of office hours and that, while almost two thirds (17/27) of hospitals now have stroke teams on call to provide acute care, almost half of these are only able to provide cover Monday to Friday, 9am–5pm.[39]

In 2016, approximately 85% (170/200) of endovascular procedures using mechanical thrombectomy were performed in just one hospital (Beaumont Hospital, Dublin).[39] A 2015 publication describing the hospital's experience as a regional stroke centre noted that 93 consecutive cases of acute ischaemic stroke were treated with endovascular treatment over a 42-month period from January 2010 to June 2013.[56] Of this patient cohort, 67% (n=64) received IV t-PA, with stent

retriever mechanical thrombectomy employed in 89% (n=83) of cases; 15% (n=14) received IA t-PA.[56]

Beaumont Hospital participated in the ESCAPE trial and treated 280 patients between 2010 and 2015 inclusive (with half of these receiving the treatment in 2015).[57] A smaller number of cases have been undertaken in Cork University Hospital, which provided 30 procedures in 2016. The technology has not yet been employed elsewhere. The safety and efficacy of endovascular therapy using mechanical thrombectomy is assessed in detail in Chapter 4.

3.4 Key messages

- In Ireland, approximately 4,300 individuals are admitted to hospital following an acute ischaemic stroke each year.
- The total number of stroke cases in Ireland, based on demographic change alone, has been predicted to increase by 4% to 5% annually between 2015 and 2020.
- An estimated 2,000 people die as a result of stroke each year in Ireland, giving an age-standardised death rate of 34.6 per 100,000 population.
- The total direct expenditure on stroke is estimated to account for between 2% and 4% of total health expenditure.
- In Ireland, more than half of strokes (55%-57%) occur in men, with approximately 30% of strokes in men occurring in those aged less than 65 years.
- While there have been improvements in acute stroke care in Ireland over the past eight years, resulting in significant reductions in mortality, substantial service deficiencies still remain. Rates of thrombolysis have improved to an average of 12.3%, although there is considerable regional variation. Stroke units and services have been developed, although these vary in their resourcing and the level of service offered. In 2015, 29% of people with an acute stroke were admitted to a stroke unit on presentation, with only 54% being admitted to a stroke unit during the course of their hospitalisation.
- Challenges to the provision of optimal acute stroke care remain, and many of these have implications for the provision of mechanical thrombectomy. The time of onset remains unknown in many cases, a significant minority still arrive to hospital by means other than an ambulance and while the majority of hospitals now have stroke teams, many of these are not available outside of core hours (Monday to Friday, 9am to 5pm) — which is when the majority of patients

experiencing a stroke present to hospital services.

- At present in Ireland, endovascular procedures using mechanical thrombectomy is available in two hospitals with one hospital providing 85% of all such procedures (170 out of 200 procedures in 2016).

4. Clinical effectiveness and safety

This chapter examines the current evidence of efficacy and safety for endovascular therapy using mechanical thrombectomy for the management of acute ischaemic stroke.

4.1 Methods

4.1.1 Search strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[58]

A systematic literature search was used to identify randomised controlled trials (RCTs) published between 1 January 2005 and August 2015; this search was subsequently updated to March 2016. Studies were identified via electronic searches in databases (PubMed [Medline], Embase, Cochrane Register of Controlled Trials, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), and the Stroke Trials Registry). Studies of any language were considered. References from the included studies and review articles were scanned. The full search strategies are outlined in Appendix 1. In addition, one further RCT which met the inclusion criteria, THRACE, was published in October 2016, and the results of this study have also been included in our analyses.

Inclusion and exclusion of studies was based on the Population, Intervention, Control, Outcomes, and Study Design (PICOS) protocol (Table 4.1). Comparators were chosen based on CE-mark-specific indications, information published in clinical guidelines for treatment of acute ischaemic stroke and in assessment guidelines published by the European Network of Health Technology Assessment (EUnetHTA).[22, 59, 60]

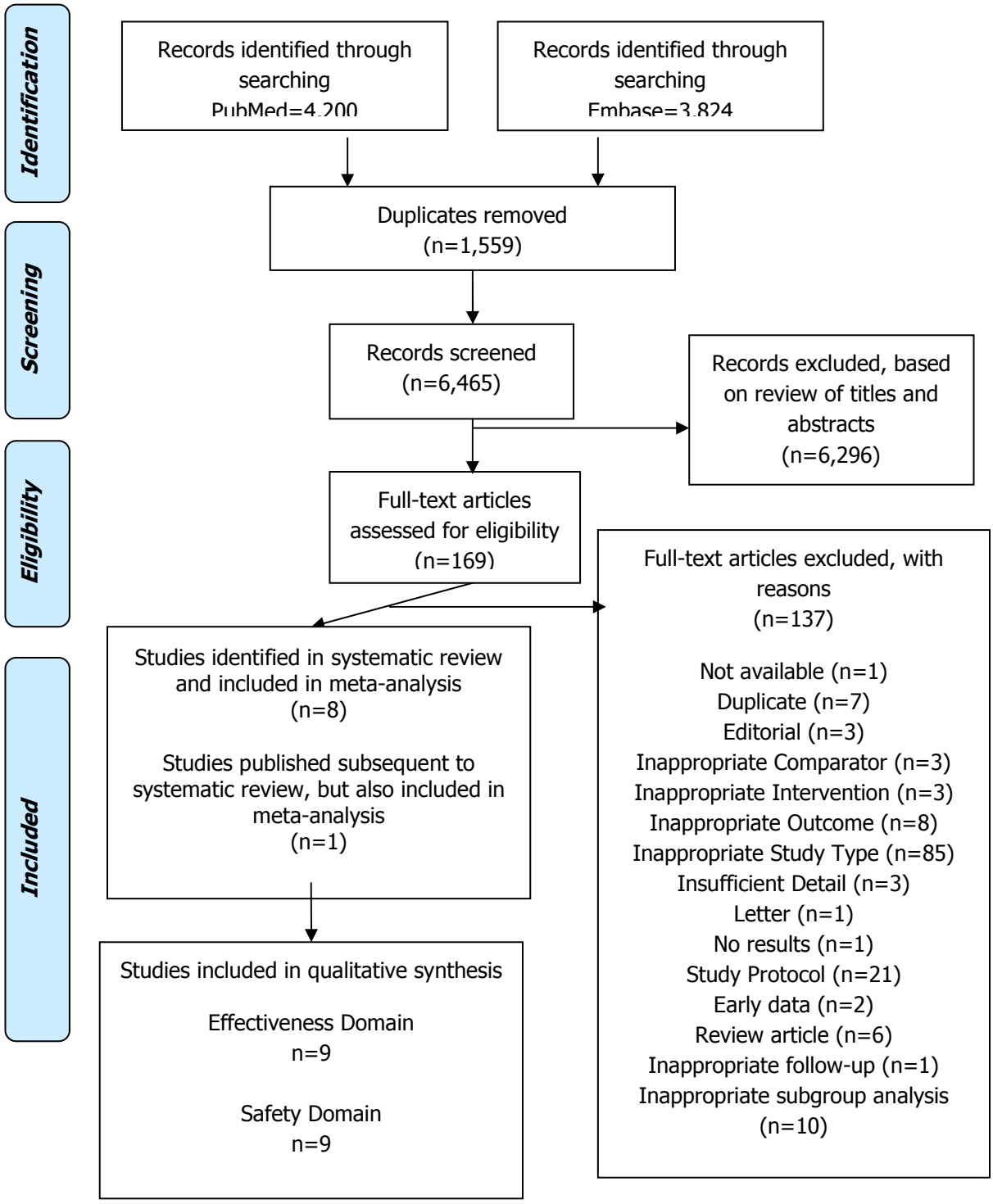
The articles were reviewed and selected by the authors and an independent investigator according to predefined selection criteria. Subsequently, these investigators then met and discussed areas of agreement and completeness, and disagreements were resolved by consensus. Figure 4.1 shows the PRISMA flow chart of study selection. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the quality of the evidence. The risk of bias was assessed using the Cochrane risk-of-bias tool for RCTs. Assessment was based on the presence or absence of evidence of random sequence generation, allocation concealment, blinding of participants and personnel, blinding

of outcome assessment, incomplete outcome data, and selective reporting. Other potential biases were also considered on a study-by-study basis.

Table 4.1 PICOS analysis for identification of relevant studies

Population	**Adults aged 18 years or older with acute ischaemic stroke in the anterior and or posterior region**
Intervention	Mechanical thrombectomy which could be used in combination with IV and or IA thrombolysis, or as an alternative to it in patients experiencing an acute ischaemic stroke who are not candidates for thrombolysis, or in patients in whom thrombolysis appears to have failed, plus standard of care.
Comparator	Standard of care alone, which could include IV and/or IA thrombolysis where appropriate
Outcomes	Measures taken as surrogate markers of clinical effectiveness were: ▪ mortality at 90 days ▪ disability at 90 days (modified Rankin Score [mRS], see below) ▪ neurologic deficit (National Institutes of Health Stroke Scale [NIHSS score], see below) ▪ ability to perform activities of daily living (ADLs) at 90 days (Barthel Index, see below) ▪ reperfusion (pre- versus post-treatment perfusion lesion volume, a modified Thrombolysis in Cerebral Infarction [mTICI] score or a Thrombolysis in Cerebral Infarction Score [TICI] score, see below) ▪ quality of life at 90 days (EuroQol Group – 5 Dimension Self-Report Questionnaire [EQ-5D] [EQ-5D-3L], see below). Measures taken as surrogate markers of safety were: ▪ mortality at 90 days ▪ symptomatic intra-cerebral haemorrhage (SICH) ▪ any cerebral haemorrhage at 90 days ▪ recurrent ischaemic stroke at 90 days ▪ device- and or procedure-related adverse events.
Study design	Randomised controlled trials

Figure 4.1 Flowchart of study selection[†]



[†] PubMed (Medline) and Embase — no additional studies found through other databases.

The following information was extracted from the included RCTs and their published supplementary materials:

- background characteristics (trial, first author, trial period, location, number of centres, number of patients, devices used)
- study characteristics (objective, comparator, inclusion and exclusion criteria)
- patient characteristics (number of patients, mean age, gender, baseline National Institutes of Health Stroke Scale [NIHSS] score, pre-stroke modified Rankin Score [mRS])
- timing characteristics (median time in minutes from stroke onset to thrombolysis, randomisation, groin puncture, and the duration of the procedure)
- proportion of patients in intervention groups who received IV t-PA, IA t-PA and proportion who underwent mechanical thrombectomy and general anaesthetic.
- outcomes (see below)
- funding sources, potential sources of bias.

4.1.2 Outcome measures

The mRS is a global measure of disability. The scale ranges from 0 to 6, with 0 indicating no symptoms and 6 indicating death; persons with a score of 0, 1 or 2 are considered to be independent in daily function.

0	No symptoms.
1	No clinically significant disability (able to carry out all usual activities, despite no symptoms).
2	Slight disability (able to look after own affairs without assistance but unable to carry out all previous activities).
3	Moderate disability (requires some help but able to walk unassisted).
4	Moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted).
5	Severe disability (requires constant nursing care and attention, bedridden, and incontinent).
6	Death.

Although inter-rater reliability has been demonstrated to vary with the use of the mRS, it remains the most prevalent functional outcome measure in contemporary stroke research.[61]

Neurological deficit was measured using the NIHSS. This scale ranges from 0 to 42, and quantifies neurological deficits into 11 categories, with higher scores indicating more severe neurological deficit. The NIHSS is the most widely used scale for the assessment of neurological impairment in persons who have experienced a stroke, and has shown excellent reproducibility and inter-rater reliability.[62]

The Barthel Index is used to measure the ability to perform activities of daily living. This index ranges from 0 to 100 with higher values indicating good performance of activities of daily living. A score between 95 and 100 indicates no disability that interferes with daily activities. The Barthel Index has demonstrated excellent intra-observer reliability as a measure of outcome after stroke, although this has not been adequately tested in large multi-centre trials.[63]

The extent of reperfusion was assessed in three studies based on comparison of pre- and post-treatment perfusion-lesion volume as measured using perfusion imaging (CT or MRI).

The EuroQol Group — 5 Dimension Self-Report Questionnaire (EQ-5D, EQ-5D-3L) — examines five dimensions of health status, namely mobility, self-care, usual activities, pain and or discomfort, and anxiety and or depression. Each dimension has three levels: no problems, slight or moderate problems; and extreme problems. More recently, the EQ-5D-5L has been developed, which contains five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The modified Treatment in Cerebral Ischaemia (also termed the modified Thrombolysis in Cerebral Infarction [mTICI]) classification is a measure of reperfusion based on CT angiography (CTA) or magnetic resonance angiography (MRA). Scores range from 0 (no flow) to 3 (normal flow):

Grade 0	No perfusion.
Grade 1	Antegrade perfusion beyond the occlusion, but limited distal branch filling with slow distal perfusion.
Grade 2a	Antegrade perfusion of less than half of the occluded artery ischaemic territory.
Grade 2b	Antegrade perfusion of more than half of the target artery ischaemic territory.
Grade 3	Complete antegrade perfusion of the occluded artery ischaemic territory.

The Treatment in Cerebral Ischaemia (also termed the Thrombolysis in Cerebral Infarction [TICI]) classification is also a measure of reperfusion based on CT

angiography (CTA) or magnetic resonance angiography (MRA).[64] Scores in this also range from 0 (no perfusion) to 3 (complete perfusion), as follows:

0	No perfusion.
1	Penetration with minimal perfusion. The contrast material fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.
2a	Only partial filling (less than two thirds) of the entire vascular territory is visualised.
2b	Complete filling of all of the expected vascular territory is visualised, but the filling is slower than normal.
3	Complete perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction *and* clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

It is noted that the description of the outcome which the mTICI and TICI scores are taken to represent varied across the included studies. They were variably described as being measures of reperfusion (ESCAPE, MR CLEAN) or revascularisation (MR RESCUE, REVASCAT) or recanalisation (EXTEND-IA), with the terms often used interchangeably.

4.1.3 Data analysis

All meta-analyses were conducted using R statistical software, version 3.2.2, and the metafor 1.9-8 package within R.[65, 66] Due to the expected heterogeneity across studies in terms of devices used and time to procedure, random effects meta-analysis was used. Binary outcomes were pooled as risk ratios. Heterogeneity was assessed on the basis of I^2 values. Values in excess of 75% were interpreted as considerable heterogeneity, and values between 75% and 90% were interpreted as potentially substantial heterogeneity.

Meta-analysis was performed for six outcomes: mortality at 90 days; mRS at 90 days; Barthel Index at 90 days; SICH; any cerebral haemorrhage; and recurrent ischaemic stroke at 90 days. A meta-analysis was not performed for mTICI at final angiography as results for this outcome were provided for the intervention group only; consequently this and the other remaining outcomes of interest are presented in narrative format only.

As a number of important methodological differences were identified between the trials, a subgroup analysis was performed for trials in which the majority, or all, of the devices used were stent retrievers, and in which non-invasive arterial imaging was used to guide patient selection. Meta-analysis was carried out for five outcomes: mortality at 90 days; mRS at 90 days; SICH; any cerebral haemorrhage; and recurrent ischaemic stroke at 90 days.

4.2 Results

4.2.1 Included studies

Nine RCTs with a total of 2,835 patients were included for assessment of effectiveness; a total of 1,318 patients were randomised to the control groups and 1,517 were randomised to the intervention groups (endovascular treatment) (Table 4.2). Please also see additional tables in Appendix 2.

4.2.1.1 Study characteristics

All nine trials followed up their cohorts for a minimum of 90 days. The median number of participating centres was 22 (range 4–58). The median duration of the included trials was 40 months (range 20–80 months). The MR RESCUE trial began enrolment in June 2004 and finished enrolling in 2011, but the exact month is not clear. The duration of 80 months is based on the trial having completed enrolment in January 2011. The earliest trial began enrolling in 2004 and the latest in 2013, with all publishing their main results between 2013 and 2016.

Seven of the nine trials used non-invasive arterial imaging to guide patient selection; MR RESCUE and SYNTHESIS Expansion did not. One additional study (IMS III) altered its protocol after 284 participants had undergone randomisation; this change permitted the use of computed tomography angiography (CTA) in determining trial eligibility for patients with an NIHSS score of 8 or 9. MR RESCUE substratified their cohort by penumbral pattern, such that those assigned to undergo mechanical thrombectomy and those assigned to receive standard care were further subcategorised into those with favourable (substantial salvageable tissue and small infarct core) and unfavourable (large core or small or absent penumbra) penumbral patterns, as assessed using pre-treatment CT or MRI.

All trials compared endovascular therapy (mechanical thrombectomy with or without IA t-PA) as an adjunct to standard medical care, with standard medical care alone, including IV t-PA where appropriate. A median of 87.1% (range 0–100%) of patients in the intervention group received IV t-PA. A median of 81.5% (range 30.9–100%) of those assigned to the intervention group underwent mechanical thrombectomy.

Table 4.2 Details of randomised controlled trials included for assessment of effectiveness

Author and year published	Trial name	Country	Number of centres	Products used	Study duration
Kidwell 2013 [23]	MR RESCUE	North America	22	Merci Retriever; Penumbra System®;	2004–2011*
Broderick 2013 [21]	IMS III	USA, Canada, Australia, Europe	58	Merci Retriever; Penumbra System®; Solitaire™ FR	2006–2012
Ciccone 2013 [67]	SYNTHESIS Expansion	Italy	24	Including: Solitaire™, Penumbra System® Trevo®, Merci	2008–2012
Berkhemer 2015 [68]	MR CLEAN	Netherlands	16	Retrievable stents used in 81.5% cases	2010–2014
Campbell 2015 [69]	EXTEND IA	Australia, New Zealand	10	Solitaire™ FR	2012–2014
Jovin 2015 [70]	REVASCAT	Spain	4	Solitaire™ FR	2012–2014
Saver 2015 [19]	SWIFT PRIME	USA, Europe	39	Solitaire™ FR; Solitaire™ 2	2012–2014
Goyal 2015 [18]	ESCAPE	Canada, USA, UK, South Korea, Ireland	22	Solitaire™ FR + unspecified others	2013–2014
Bracard 2016 [31]	THRACE	France	26	Retrievable stents used in 83% cases; aspiration systems used in 16%	2010–2015

* The MR RESCUE trial began enrolment in June 2004. It finished enrolling in 2011 but the exact month is not clear. The duration of 80 months is based on the trial having completed enrolment in January 2011.

Six trials were stopped early. IMS III was stopped early because of futility after 656 participants had undergone randomisation. The release of data from MR CLEAN led to interim analyses being performed in SWIFT PRIME, ESCAPE, EXTEND IA, and THRACE and all were stopped early. REVASCAT was stopped early because of a claimed loss of equipoise as a result of the release of data from MR CLEAN, EXTEND IA and ESCAPE. The remaining three trials, MR CLEAN, SYNTHESIS Expansion and MR RESCUE, were completed as per their protocols.

4.2.1.2 Patient characteristics

All studies specified that patients had to be aged 18 years and over to be eligible for inclusion. Six studies had an upper age limit for inclusion — four excluded patients aged greater than 80 years (SYNTHESIS Expansion, REVASCAT, SWIFT PRIME, THRACE); one excluded those aged greater than 82 years (IMS III); and one excluded those aged greater than 85 years (MR RESCUE). Five studies reported mean ages for their intervention and control groups, while the other four reported median ages; two trials reported a difference in ages between groups of greater than one year (MR RESCUE, intervention group mean age 64 years; control group mean age 67 years; THRACE intervention group median age 66 years; control group 68 years). All trials reported mean or median ages for their control and intervention groups between 64 and 71 years.

The location of the stroke was confined to the anterior circulation (intracranial ICA, MCA [M1 and/or M2] and/or anterior cerebral artery [A1 and/or A2]) in six of the eight trials; IMS III (4/434), SYNTHESIS Expansion (25/362) and THRACE (2/208) included patients with occlusions in the posterior circulation.

Six of the eight trials specified a pre-stroke functional ability as part of their inclusion criteria; two trials required patients to have had a pre-stroke mRS of ≤1 (REVASCAT, SWIFT PRIME); three trials required a pre-stroke mRS of ≤2 (IMS III, MR RESCUE, EXTEND IA); and one trial required a pre-stroke score on the Barthel Index of ≥90 (ESCAPE).

Four trials (IMS III, MR CLEAN, REVASCAT, SWIFT PRIME) reported pre-stroke mRS scores for their intervention and control arms; the proportion of patients with mRS scores of 0 (intervention group range 81.5–87.3%; control group range 80.1–88.7%) or ≤1 (SWIFT PRIME, intervention group 99%, control group 98%) were similar in both arms of each of these trials (see Appendix 2, Table App2.1).

Six trials required a minimum baseline level of clinical severity for inclusion, as measured using the NIHSS. One trial required a baseline NIHSS of ≥2 (MR CLEAN), two required a baseline NIHSS ≥6 (MR RESCUE, REVASCAT) and one a baseline

NIHSS of ≥8 (SWIFT PRIME). One trial specified that in order to be eligible for inclusion, patients had to have a baseline NIHSS of ≥10 at the time that IV t-PA was begun or an NIHSS of >7 and <10 with an occlusion seen in M1, ICA or basilar artery on CTA (IMS III). The sixth trial, THRACE, required that patients have a baseline NIHSS score ≥10 and ≤25.

The median baseline NIHSS scores in the control and intervention arms of MR RESCUE were both 16 for those with favourable penumbral patterns, and 20.5 and 19 for those with non-favourable patterns, respectively. The median baseline NIHSS scores in the control arms of the other trials ranged from 13 to 18. The median baseline NIHSS scores in the intervention arms of these trials ranged from 13 to 18. Just one trial had a difference of greater than one point in the median baseline NIHSS scores of control and intervention arms (EXTEND IA; control median baseline NIHSS, 13; intervention, 17).

Four trials noted that included patients must have been eligible for, or have commenced infusion of IV t-PA within 4.5 hours of symptom onset (see Appendix 2, Table App 2.1). IMS III required that IV t-PA had commenced in all patients within three hours of symptom onset. Similarly, THRACE required that IV t-PA had commenced in all patients within three hours of symptom onset; after enrolment of 80 patients, however, this time limit was extended to four hours.

The maximum time allowed between onset of symptoms and commencement of endovascular intervention ranged from 5 to 12 hours (ESCAPE) across the trials (see Appendix 2, Table App2.1).

Three trials specified an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) as part of their inclusion and exclusion criteria. ASPECTS aims to assess early ischaemic changes (<3 hours from symptom onset) on pretreatment CT studies in patients with acute ischaemic stroke of the anterior circulation and identifies stroke patients unlikely to make an independent recovery despite thrombolytic treatment.[71] REVASCAT excluded patients who had an ASPECTS score of less than seven on non-contrast CT or less than six on diffusion-weighted imaging-MRI (DWI-MRI). SWIFT PRIME excluded patients with an ASPECTS score of less than six on non-contrast CT or DWI-MRI. ESCAPE, meanwhile, excluded patients with an ASPECTS score of less than six on non-contrast CT or CTA.

The proportion of men in the control and intervention groups was similar, and ranged between 47% and 59% in both groups (See Appendix 2, Table App2.2).

4.2.1.3 Timing characteristics

Six trials provided data on median time from onset of symptoms to commencement of thrombolysis with IV t-PA for both their control and intervention arms. The median time from onset of symptoms to thrombolysis in the control groups in these trials ranged from 87 to 153 minutes; it ranged from 85 to 150 minutes in the intervention arms. In five of these trials (MR CLEAN, EXTEND IA, SWIFT PRIME, ESCAPE and THRACE), the median time to thrombolysis was shorter in the intervention group than in the control group. In the other trial (REVASCAT), the median time to thrombolysis was longer in the intervention group (Appendix 2, Table App 2.3). The difference in the median time from symptom onset to thrombolysis between these arms ranged from two minutes (MR CLEAN) to 18 minutes (EXTEND IA). In the SYNTHESIS Expansion trial, only those in the control arm received IV t-PA; the median time from onset of symptoms to thrombolysis in this group was 165 minutes.

Six trials provided information on the median time from onset of symptoms to randomisation for both their control and intervention arms (Appendix 2, Table App 2.3). The median time from onset of symptoms to randomisation in the control groups in these trials ranged from 145 to 226 minutes; it ranged from 148 to 223 minutes in the intervention arms. The difference in the median time from symptom onset to randomisation between these arms ranged from two minutes (SWIFT PRIME) to eight minutes (MR CLEAN).

The MR RESCUE trial reported a mean time from onset of symptoms to randomisation of 315 (standard deviation [SD] 90) and 346 (SD 70) minutes for their control and intervention arms, respectively (these are estimates of the mean and standard deviation for the control and intervention arms, derived from pooling mean times for those with favourable and non-favourable penumbral patterns in each of these arms). The IMS III trial authors noted that all patients were randomised within 40 minutes of thrombolysis while the EXTEND IA authors reported that the median time from thrombolysis to randomisation in the control and intervention arms was 29 and 36 minutes, respectively.

All trials provided information regarding the time from onset of symptoms to the start of the procedure for those randomised to the intervention arms (Appendix 2, Table App 2.3). Six provided median times; these ranged from 210 (EXTEND IA) to 269 minutes (REVASCAT). MR RESCUE reported a mean time from onset of symptoms to the start of the procedure for those randomised to the intervention arm of 381 (SD 74) minutes, while IMS III reported a mean time of 208 (SD 46.7) minutes. The ESCAPE trial authors did not report this information directly; they did,

however, note that the median time from stroke onset to study CT was 134 minutes, while the median time from study CT to groin puncture was 51 minutes.

Three trials reported the median duration of the procedure: EXTEND IA (43 [interquartile range (IQR) 24–53] minutes), REVASCAT (75 [IQR 50–114] minutes) and THRACE. Median values for the THRACE trial were reported separately for those undergoing general anaesthetic (45 [28-70] minutes) and those who underwent the procedure with local anaesthetic or conscious sedation (56 [24-86] minutes). See Appendix 2, Table App 2.3.

4.2.1.4 Quality assessment

While the risk of bias overall for each of the RCTs was rated as low (see Appendix 3), a number of issues which could potentially have affected the outcome data were identified. The quality of the evidence was rated as low for mRS (moderate when confined to studies commenced from 2010 onwards) and moderate for other outcomes of effectiveness (see Appendix 3).

One of the nine trials (MR RESCUE) carried out a per-protocol analysis, while the other eight were analysed on an intention-to-treat basis. In MR RESCUE, 9 of the 127 subjects were excluded from the final analysis and this may have affected the effectiveness outcomes under review.

While the majority of the studies reported all or the majority of primary and secondary outcomes, IMS III had planned, but did not report, outcomes for EQ-5D, the trail-making test and the Barthel Index.

With the exception of mortality at 90 days and SICH, there was inconsistency in how these nine trials reported their safety outcomes, making comparability and interpretation difficult.

A further concern is the number of trials (six) which were stopped early (see Section 4.2.1.1 above). Early stopping rules are integral to RCT design, both to allow for loss of equipoise, and to prevent harm and unacceptable adverse events. However, it must also be acknowledged that trials that stop early for benefit may under- or over-estimate the treatment effect of the intervention; truncated RCTs have previously been demonstrated to be associated with greater effect sizes than RCTs not stopped early.[72]

4.2.2 Clinical Effectiveness

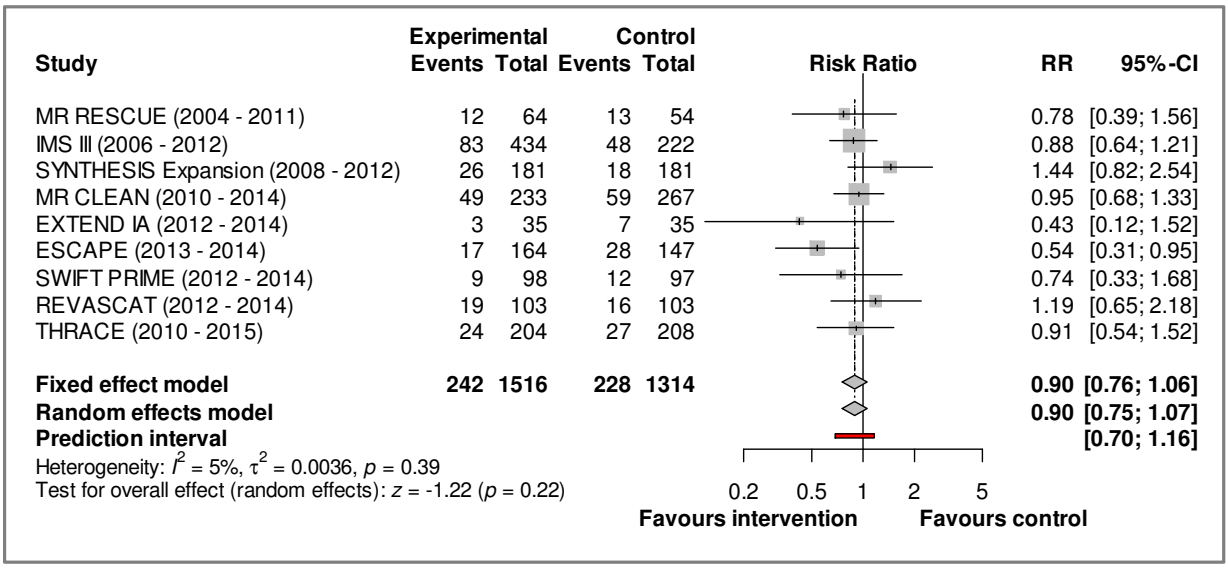
4.2.2.1 Mortality from ischaemic stroke

Data on mortality from ischaemic stroke were not reported by the studies.

4.2.2.2 All-cause mortality at 90 days

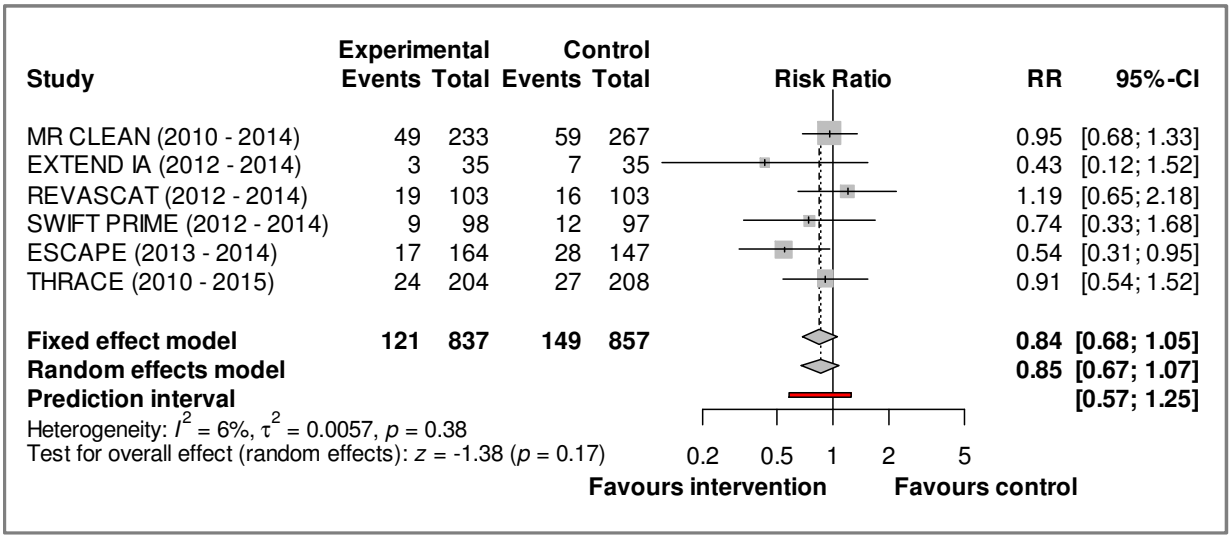
All nine trials reported all-cause mortality at 90 days, with data reported on 2,830 patients in total. There were 242 deaths out of 1,516 patients in the intervention arm (15.9%), with 228 deaths in 1,314 patients in the control arm (17.4%). One study found a statistically significant reduction in mortality associated with the intervention (ESCAPE). The pooled risk ratio for mortality was 0.90 (95% CI: 0.75 to 1.07; p = 0.22) (see Figure 4.1). There was no evidence of a difference in mortality rates at 90 days between patients randomised to intervention and control arms.

Figure 4.1 Meta-analysis of all-cause mortality at 90 days (all trials)



A subgroup analysis was performed using data from the six trials commenced from 2010 onwards (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE, THRACE). In these trials, there were 121 deaths out of 837 patients in the intervention arm (14.5%) and 149 deaths out of 857 patients in the control arm (17.4%). The pooled risk ratio for mortality was 0.85 (95% CI: 0.67 to 1.07; p = 0.17) (Figure 4.2). There was no evidence of a difference in mortality rates at 90 days between patients randomised to intervention and control arms.

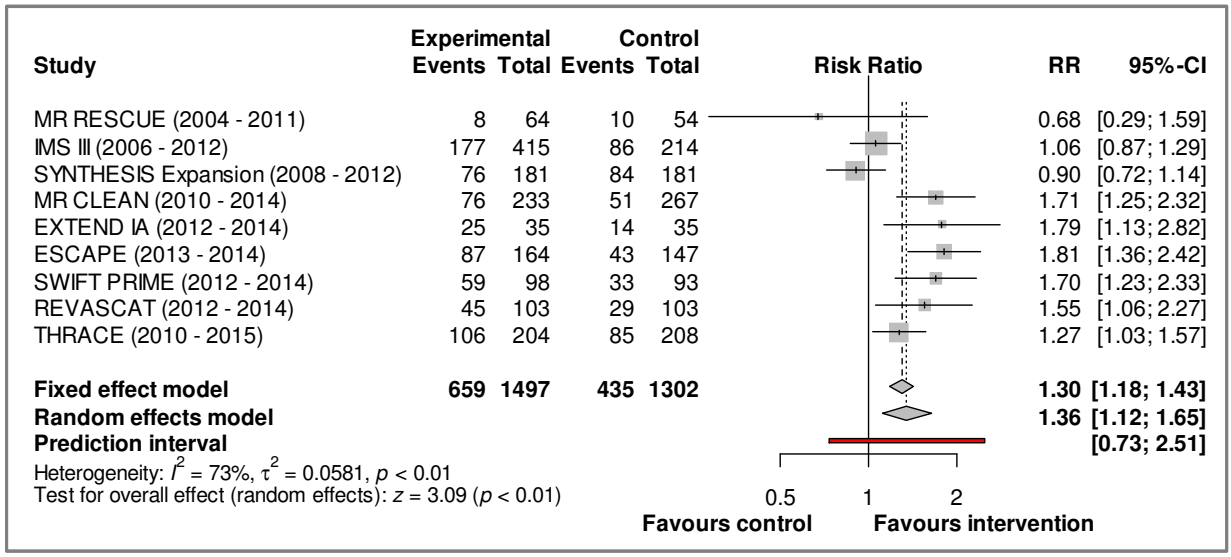
Figure 4.2 Meta-analysis of all-cause mortality at 90 days (trials commenced from 2010 onwards)



4.2.2.3 mRS at 90 days

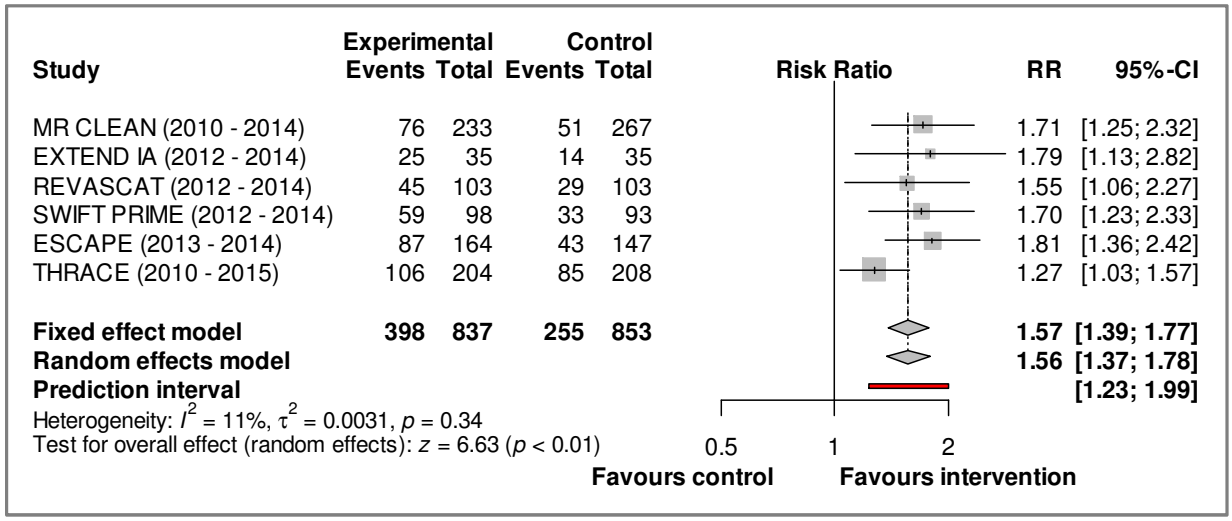
All nine trials reported data for mRS at 90 days, with data available on 2,830 patients. In total, 44.0% (659/1,497) of patients in the intervention arm were reported to have achieved an mRS of 0–2 at 90 days; compared with 33.4% (435/1,302) of patients who were assigned to the control arms of the studies. The risk ratio for achieving an mRS of 0–2 at 90 days was 1.35 (95% CI: 1.12 to 1.64; p=0.002) in favour of the intervention. The evidence presented suggests that the intervention is associated with higher likelihood of being independent, as assessed using the mRS, at 90 days post-acute ischaemic stroke (Figure 4.3).

Figure 4.3 Meta-analysis of modified Rankin Scale at 90 days (all trials)



While the studies exhibit a high degree of statistical heterogeneity overall (I^2 = 72.6%; p=0.0003), this heterogeneity is completely eliminated by only including the six studies which began enrolling from 2010 onwards (Figure 4.4).

Figure 4.4 Meta-analysis modified Rankin Scale at 90 days (trials commenced from 2010 onwards)



When limiting the analysis to these six studies, 47.5% (398/837) of patients in the intervention arm were reported to have achieved an mRS of 0–2 at 90 days; compared with 29.9% (255/853) of patients who were assigned to the control arms of these studies. The absolute benefit of the intervention on mRS at 90 days across these latter six trials ranged from 11.1% in THRACE to 31.4% in EXTEND IA. In a

subgroup analysis of these six trials, the risk ratio for achieving an mRS of 0–2 at 90 days was 1.56 (95% CI: 1.37 to 1.78; p<0.0001) in favour of the intervention (Figure 4.4).

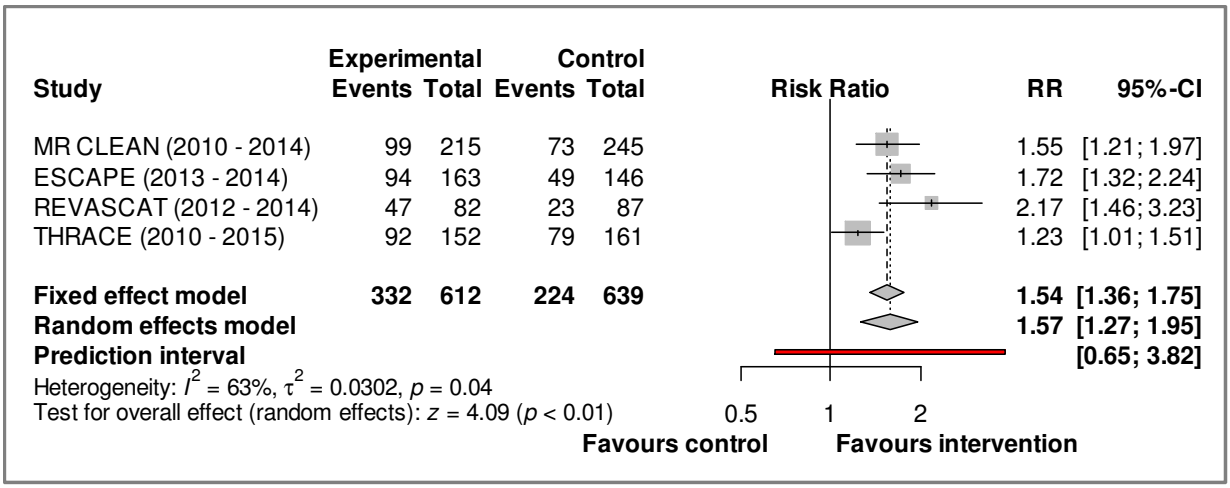
4.2.2.4 Barthel Index at 90 days

Four trials (MR CLEAN, REVASCAT, ESCAPE, and THRACE) provided data which were amenable to comparison in relation to the Barthel Index. All four reported the proportion of patients in the control and intervention groups (total = 1,251 patients) who achieved a score of 95 or more at 90 days; 54.2% (332/612) of patients achieved this score in the intervention groups with 35.1% (224/639) achieving it in the control arms.

The risk ratio for achieving a Barthel Index of 95 or higher at 90 days was 1.57 (95% CI: 1.27 to 1.95; p<0.0001) in favour of the intervention. This evidence suggests that the intervention is associated with better outcomes in relation to activities of daily living (ADL), as measured using the Barthel Index, at 90 days, with all four studies individually demonstrating a statistically significant benefit from the intervention (Figure 4.5).

A fifth trial, SWIFT PRIME, reported median Barthel Index scores at 90 days for those in the intervention (n = 88/98) and control groups (n = 77/98) for whom the information was available; the median scores at 90 days were 100 (IQR 10–100) and 90 (IQR 0–110) for the intervention and control groups, respectively.

Figure 4.5 Meta-analysis of Barthel Index at 90 days (all trials)



4.2.2.5 NIHSS

The NIHSS ranges from 0 to 42, and quantifies neurological deficits into 11 categories, with higher scores indicating more severe neurological deficit. Seven studies provided data on NIHSS scores post-stroke (Appendix 2) This data varied in how it was reported, however, and thus a meta-analysis is not possible. In addition, while the project plan for this assessment specified that NIHSS score change at 24 hours would be evaluated, again this was not possible because of inadequate reporting of this outcome by the studies under consideration.

Two trials (MR CLEAN and ESCAPE) reported the median NIHSS at 24 hours in the control and intervention groups. Both reported better median NIHSS scores in the intervention versus the control groups. The intervention group in ESCAPE had a median NIHSS of six (IQR 3–14), while the control group had a median NIHSS of 13 (IQR 6–18). The MR CLEAN trial reported a median NIHSS of 13 (IQR 6–20) in the intervention group, and a median NIHSS of 16 (IQR 12–21) in the control group.

Two further studies (SWIFT PRIME and REVASCAT) reported different measures of NIHSS at 24–27 hours and another (EXTEND IA) reported at three days only. THRACE reported NIHSS score at 24 hours, at discharge or at seven days and at three months. Regardless of the reporting method, all studies reported better scores in the intervention versus the control groups.

SWIFT PRIME reported mean change at 27 hours (intervention group –8.5 [±7.1]; control group –3.9 [±6.2]), while REVASCAT reported the proportion of patients who achieved either a reduction of eight or more NIHSS points or a score of two or less at 24 hours (intervention group 59/100; control group 20/100). EXTEND IA reported the proportion of patients who achieved a reduction of at least eight NIHSS points or a score of either zero or one at three days (intervention group 28/35; control group 13/35).

In THRACE, the median NIHSS score was significantly better in the intervention (IC) than in the control group (CG) when measured at 24 hours (IG: 9; CG: 12, p=0.04), at discharge or at seven days (IG:4; CG:8, p=0.001) and at three months (IG:2; CG:4, p=0.01).

4.2.2.6 Reperfusion at 24 hours and/or revascularization at final angiography

Three studies (EXTEND IA, MR RESCUE, SWIFT PRIME) reported on reperfusion, but only one of these was at 24 hours; EXTEND IA reported that the median percentage reduction in the reperfusion–lesion volume between initial and 24-hour imaging was

100% (IQR 100–100) in the intervention group and 37% (IQR -0.50–0.96) in the control group. EXTEND IA also reported the proportion of patients in the control and intervention groups who achieved >90% reperfusion at 24 hours without SICH; the proportions were 31/35 (89%) and 12/35 (34%) for the intervention and control groups, respectively.

SWIFT PRIME reported on reperfusion, but at 27 hours rather than at 24 hours; 83% (53/64) and 40% (21/52) of the intervention and control groups achieved ≥90% reperfusion at 27 hours, respectively.

MR RESCUE assessed reperfusion (defined as a reduction of ≥90% in the volume of the perfusion lesion from baseline) at Day 7; of those for whom information was available, 48.9% (23/47) and 51.3% (20/39) of the intervention and control groups achieved this degree of reduction, respectively.

Seven studies reported the proportion of patients in their intervention group who demonstrated a TICI (MR RESCUE) or an mTICI (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE, THRACE) score of 2a-3 or 2b-3. These latter six studies reported proportions of mTICI 2b-3 which ranged from 58.7% (115/196) (MR CLEAN) to 88% (73/83) (SWIFT PRIME) while MR RESCUE reported that 40/56 (71.4%) had a TICI score of 2a-3 at Day 7.

An eighth study, IMS III, reported final mTICI scores based on the location of the vessel occlusion which had caused the stroke; the percentage of the intervention group who achieved an mTICI score of 2b-3 ranged from 23% (multiple M2 occlusions) to 44% (M1 occlusion or single M2 occlusion).

4.2.2.7 Health-related quality of life (EQ-5D)

Not all trials included health-related quality of life as a primary or secondary endpoint.

Four trials reported on health-related quality of life using the EQ-5D, a generic measure, with higher scores reflecting better quality of life. It was not clear whether the studies used the '3L' or '5L' version of this measure. The scales used were either from 0 to 100 (ESCAPE) or from –0.33 to 1 (REVASCAT, MR CLEAN, THRACE).

ESCAPE reported median scores at 90 days in the intervention group of 80 (IQR 60–90) and control group of 65 (IQR 50–80), along a scale from 0 to 100.

REVASCAT, MR CLEAN and THRACE also reported median scores at 90 days, but reported these along a different scale (–0.33 to 1). REVASCAT reported median

scores in the intervention and control groups of 0.65 (IQR 0.21–0.79) and 0.32 (IQR 0.13–0.70), respectively. MR CLEAN reported median scores in the intervention and control groups of 0.69 (IQR 0.33–0.85) and 0.66 (IQR 0.30–0.81), respectively. Finally, THRACE reported median scores in the intervention and control groups of 0.64 (IQR 0.3–0.8) and 0.62 (IQR 0.3–0.8) respectively.

No data were available on disease-specific quality of life.

4.2.3 Safety

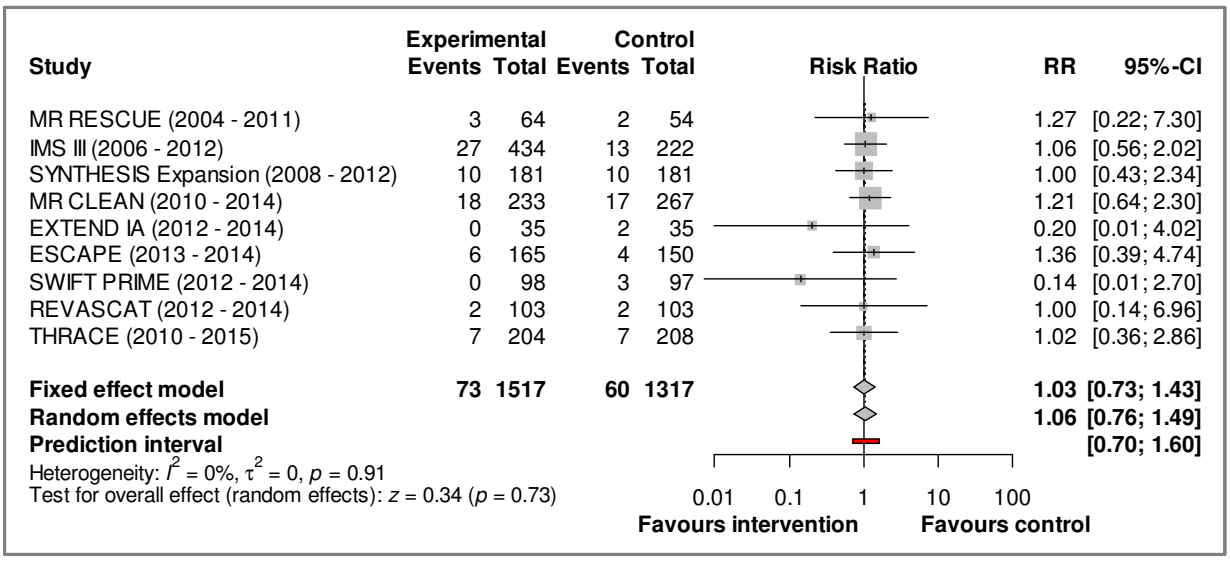
4.2.3.1 All-cause mortality at 90 days

Please see Section 4.2.2.2 for further information on this outcome.

4.2.3.2 Symptomatic intracerebral haemorrhage

All nine trials reported data on SICH across a total cohort of 2,834 patients. In total, 4.8% (73/1,517) of patients in the intervention arm and 4.6% (60/1,317) of patients in the control arm experienced an SICH. This evidence suggests no difference between intervention and control with respect to the rate of SICH (risk ratio = 1.06; 95% CI: 0.76 to 1.49; p = 0.73, see Figure 4.6).

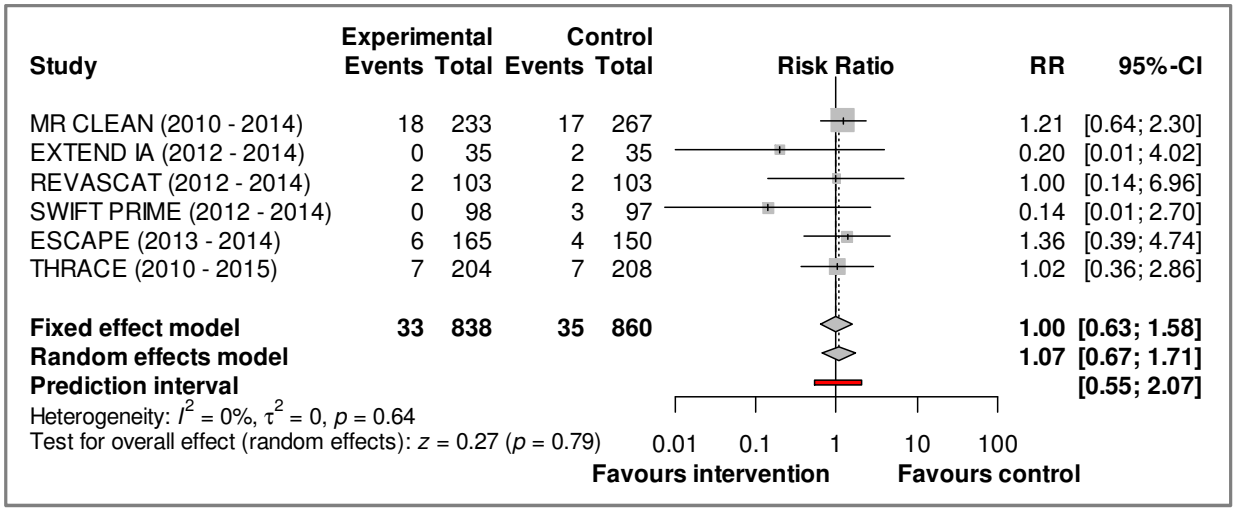
Figure 4.6 Meta-analysis of symptomatic intracerebral haemorrhage (all trials)



A subgroup analysis was performed using data from the six trials commenced from 2010 onwards (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE, THRACE, see Figure 4.7). In these trials, there were 33 events in 838 patients in the intervention arm (3.94%) and 35 events in 860 patients in the control arm (4.07%).

The pooled risk ratio for SICH was 1.07 (95% CI: 0.67 to 1.71; p = 0.79, see Figure 4.7). There was no evidence to suggest a difference between intervention and control in terms of the rate of SICH.

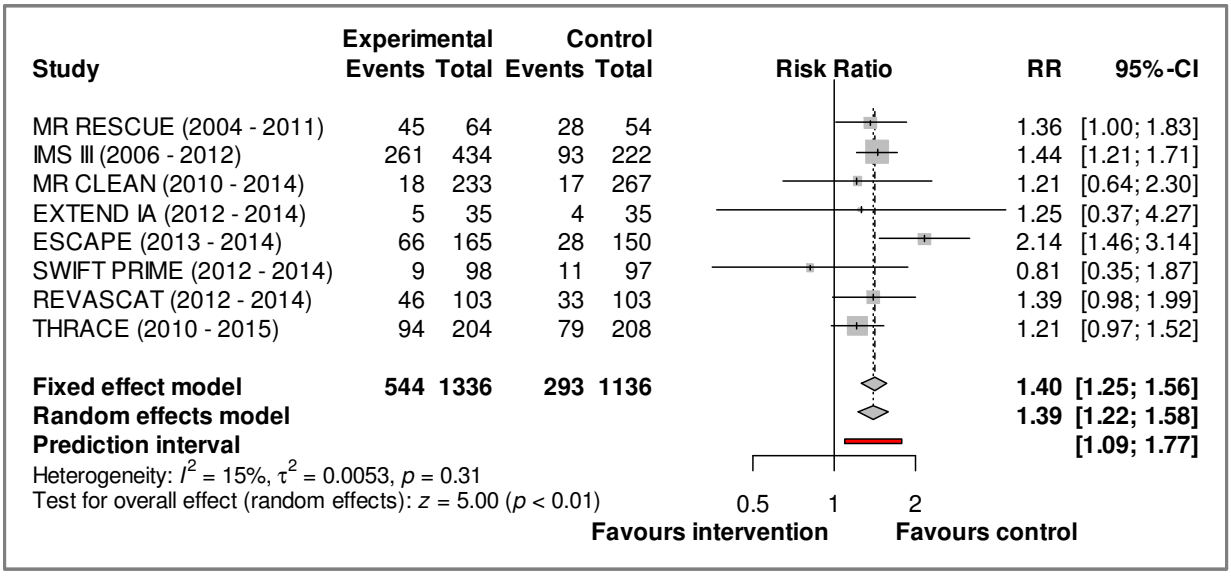
Figure 4.7 Meta-analysis of symptomatic intracerebral haemorrhage (trials commenced from 2010 onwards)



4.2.3.3 Any cerebral haemorrhage

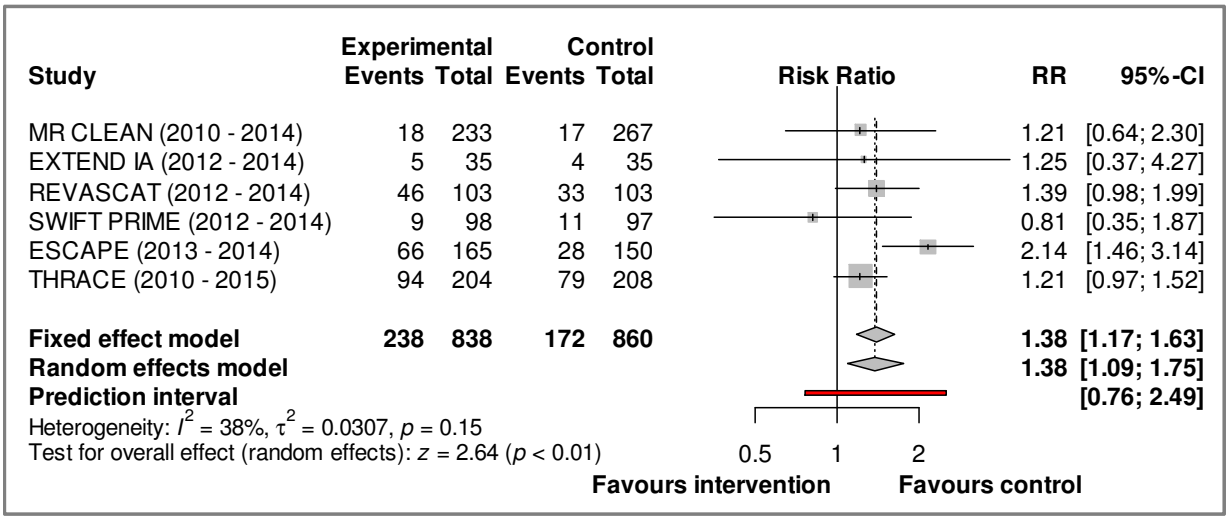
Eight of the nine studies reported comparable data on any cerebral haemorrhage at between 24 and 30 hours (it was unclear which events qualified in SYNTHESIS Expansion and hence this was not included). A total of 40.7% (544/1,336) patients in the intervention arm and 25.8% (293/1,136) patients in the control arm experienced a cerebral haemorrhage (Figure 4.8). The risk ratio for any cerebral haemorrhage was 1.39 (95% CI: 1.22 to 1.58; p<0.0001). The evidence suggests that the intervention is associated with a higher overall rate of cerebral haemorrhage when compared with the control.

Figure 4.8 Meta-analysis of any cerebral haemorrhage (all trials)



A subgroup analysis of any cerebral haemorrhage was performed using data from the six trials commenced from 2010 onwards (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE, THRACE) (Figure 4.9). In these trials, there were 238 events in 838 patients in the intervention arm (28.4%) and 172 events in 860 patients in the control arm (20.0%). The pooled risk ratio for any cerebral haemorrhage at 90 days was 1.38 (95% CI: 1.09 to 1.75; p = 0.01). This evidence suggests that the intervention is associated with a higher overall rate of any cerebral haemorrhage at 90 days when compared with the control.

Figure 4.9 Meta-analysis of any cerebral haemorrhage (trials commenced from 2010 onwards)



4.2.3.4 Recurrent ischaemic stroke within 90 days

Four trials (IMS III, MR CLEAN, ESCAPE, and REVASCAT) provided data on the number of patients who suffered a recurrent ischaemic stroke within 90 days; the proportion of the intervention group suffering this adverse event ranged from 3.9% (in REVASCAT) to 5.6% (in MR CLEAN). The proportion of patients with recurrent ischaemic stroke in the control group ranged from 0.4% (in MR CLEAN) to 6.3% (in IMS III). The pooled data from these four trials do not suggest that the intervention is associated with a higher overall rate of recurrent ischaemic stroke within 90 days, when compared with the control (risk ratio = 1.97; 95% CI: 0.64 to 6.03; p = 0.24, see Figure 4.10).

While substantial statistical heterogeneity is noted between the four included studies (I^2 = 67.8%; p = 0.03), this is reduced by exclusion of the earliest trial (IMS III) with all three later trials indicating that the intervention is not associated with a higher rate of recurrent ischaemic stroke. Subgroup analysis, including only these latter three trials, again suggests that the intervention is not associated with a higher overall rate of recurrent ischaemic stroke within 90 days, when compared with the control (risk ratio = 3.09; 95% CI: 0.86 to 11.11; p = 0.08, see Figure 4.11).

One additional trial, SYNTHESIS Expansion, reported that 2.2% (4/181) of patients in the intervention group had experienced a new stroke at seven days.

Figure 4.10 Meta-analysis of recurrent ischaemic stroke within 90 days (all trials)

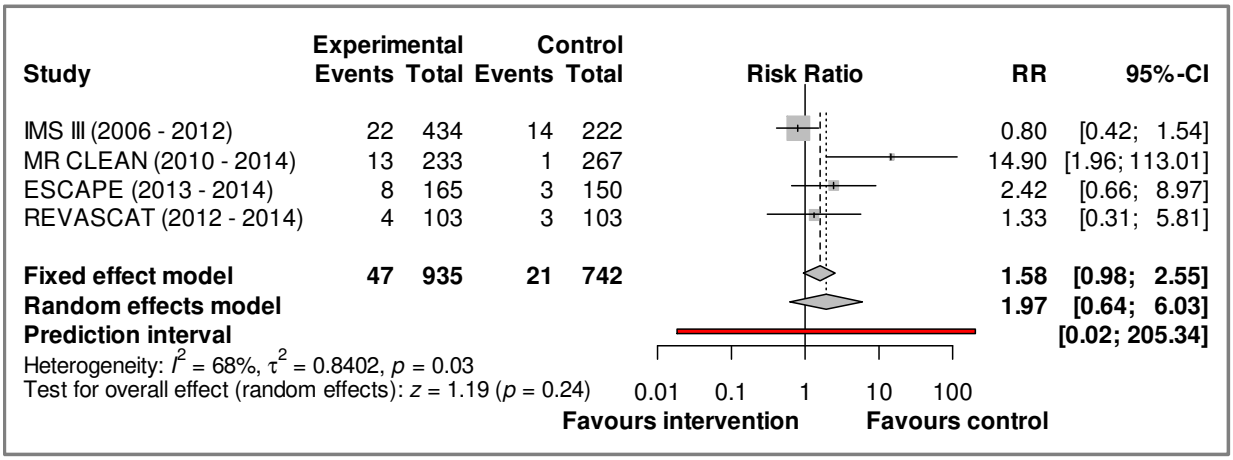
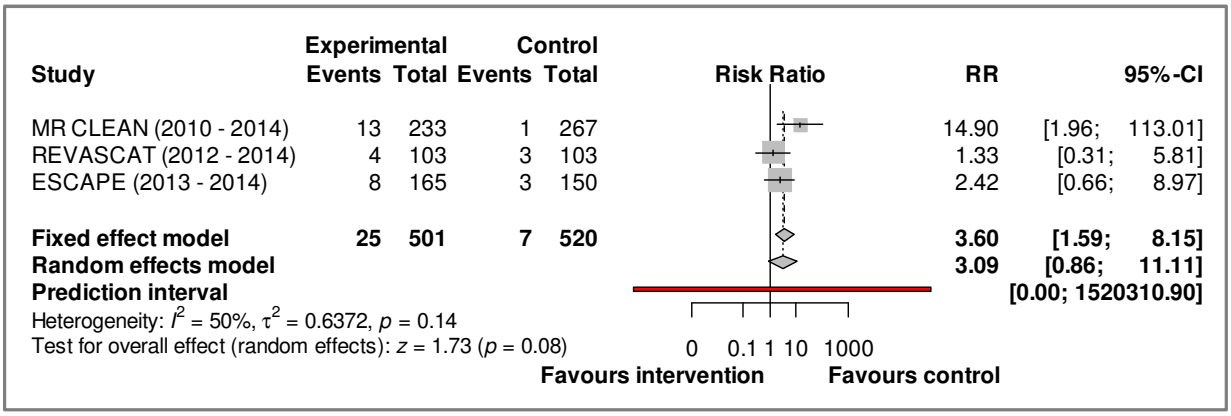


Figure 4.11 Meta-analysis of recurrent ischaemic stroke within 90 days (trials commenced from 2010 onwards)



4.2.3.5 Device- and or procedure-related adverse events

While individual studies report adverse events and or serious adverse events, a lack of clarity regarding what constitutes 'serious' and inconsistencies in reporting made comparative analysis across studies difficult. Eight of the nine trials provided data on device- and or procedure-related adverse events (SYNTHESIS Expansion did not) (Appendix 2). These were reported differently across the seven trials, however, making comparability difficult. Five trials did not differentiate between device-related and procedure-related adverse events — MR RESCUE, IMS III, EXTEND IA, REVASCAT and ESCAPE.

The earliest trial to have begun enrolment, MR RESCUE, reported that there were 10 such events among the intervention group cohort of 64 patients; it was not clear whether these events were in 10 individual patients. The adverse events comprised one device fracture, seven vessel perforations, one vessel dissection and one embolus to a previously uninvolved territory.

IMS III reported that 16.1% (70/434) of patients in the intervention group experienced a device- or procedure-related adverse event, including groin haematoma, vessel dissection or perforation and emboli to previously uninvolved territories.

EXTEND IA reported that 11.4% (4/35) of patients experienced an adverse event which could be classified as device- or procedure-related, specifically, wire perforation (n = 1), groin haematoma (n = 1) and emboli to previously uninvolved territories (n = 2).

REVASCAT reported that there were 30 complications in their intervention cohort of 103 patients which could be classified as device- or procedure-related, specifically,

arterial dissection or perforation (n = 9), emboli to previously uninvolved territories (n=5), groin haematoma (n = 11) or pseudoaneurysm (n = 1) and vasospasm requiring treatment (n = 4). It was not clear whether these events were experienced by 30 different patients or if some patients experienced more than one of these complications.

The ESCAPE trial reported that 10.9% (18/165) of patients experienced a total of 19 adverse events which could be classified as device- or procedure-related – these included four serious adverse events (haematoma at access site: n = 3; perforation of middle cerebral artery: n = 1) and 15 'non-serious' adverse events (access site femoral haematoma: n = 12; carotid dissection: n = 1; cranial nerve palsy (cavernous sinus syndrome): n = 1; and subarachnoid haemorrhage: n = 1).

SWIFT PRIME reported that there were seven device-related adverse events in five patients (5.1%, 5/98), all of which were classified as 'non-serious', specifically, cerebral vasospasm (n = 4), intraventricular haemorrhage (n = 1), subarachnoid haemorrhage (n = 1) and subarachnoid contrast extravasation (n = 1). Procedure-related adverse events were not reported.

MR CLEAN reported that 11.2% (26/233) of patients in the intervention group experienced a procedure-related adverse event. These included emboli to previously uninvolved territories in 20 patients (8.6%), procedure-related vessel dissections in four patients (1.7%) and vessel perforations in two patients (0.9%). Device-related adverse events were not reported separately.

THRACE reported that there were 51 procedure-related adverse events in 145 patients who underwent thrombectomy. These events included vasospasm (23%), embolisation in a new territory (6%), dissection (3%), groin haematoma (2%) and arterial perforation (1%). Device-related adverse events were not reported separately.

Table 4.3 Adverse events reported in the eight included randomised controlled trials

Study Year published Name	Device and/or Procedure Related	Serious	Non-Serious
Kidwell 2013 MR RESCUE	10/64[¥]	79/127[±]	Not reported
Broderick 2013 IMS III	70/434	I: 256/434 C: 126/222	Not reported
Ciccone 2012 Synthesis Expansion	Not reported	I: 10 (11 events) /181^ C: 5 (6 events) / 181^	^
Berkhemer 2015 MR CLEAN	26/233[¥¥¥]	110/233 113/267	Not reported
Campbell 2015 EXTEND IA	4/35[¥]	I: 7/35* C: 10/35*	*
Jovin 2015 REVASCAT	30/103[¥]	Unable to interpret	Unable to interpret
Saver 2015 SWIFT PRIME	7/98[¥]	I: 30/97 C: 35/98	Not reported
Goyal 2015 ESCAPE	18/165	I: 35/165 C: 27/150	I: 156/165 C:114/150
Bracard 2016 THRACE	51/145[¥]	I: 17/204 C: 15/208	I: 51/204[†] C: 58/208[†]

[¥] Not clear if these were unique patients.
[±] Not characterised according to whether intervention or control group.
[¥¥¥] Not clear that this was the total number. All classified as 'procedure-related'.
*Not characterised as serious or non-serious. Included death, SICH, wire perforation, angio-oedema, groin haematoma and embolisation into another vessel territory.
^These events were characterised as non-cerebral events and were subdivided into fatal (I:3/181, C: 1/181) and non-fatal (I: 7/181, C: 4/181) rather than severe and non-severe adverse events. They included severe extracranial bleeding, pulmonary embolism, myocardial infarction, sepsis, deep vein thrombosis and pulmonary oedema.
† Not clear if these were both serious and non-serious adverse events, or non-serious adverse events only.

4.2.3.6 Perforation/dissection

There were insufficient data to address this question. Please see section 4.2.3.5 above for information in relation to device and, or procedure-related adverse events.

4.2.3.7 Other haemorrhage

There were insufficient data to address this question. Please see section 4.2.3.5 above for information in relation to device- and or procedure-related adverse events.

4.7 Caveats to the interpretation of this evidence

Neither MR RESCUE nor SYNTHESIS Expansion used non-invasive arterial imaging to identify patients for enrolment. IMS III, which began enrolment in 2006, did not begin using CT angiography (CTA) to identify the site of occlusion until after 284 participants had undergone randomisation; from then on, CTA was used to determine trial eligibility for patients with an NIHSS score of 8 or 9. The other six trials used either CTA and or MRA to guide patient selection.

In addition to the use of imaging for patient selection, there are a number of additional caveats to the interpretation of the evidence presented in this assessment. The quality of the pooled data for the outcomes under review was rated as low or moderate and the individual trials span a time frame in which both the technology itself and the process of identifying patients who could potentially benefit from the technology have changed significantly.

The effectiveness outcome for which this analysis is most consistent is mRS ≤2 at 90 days, with the pooled data suggesting that mechanical thrombectomy is significantly more likely to result in functional independence when compared with standard medical care. It has been argued that the methodology and devices (predominantly stent retrievers) employed in the later six trials are those which are more relevant to current clinical practice. It is therefore pertinent to note that subgroup analysis of these six trials demonstrated an improved effect of the intervention on mRS at 90 days, when compared with its overall effect as analysed across all nine trials.

Similarly to mRS, the Barthel Index can also be used to measure disability or dependence in activities of daily living (ADL) following a stroke. While concerns have been raised in general that there is a lack of consensus across these two measures,[73] this does not appear to be the case here; in keeping with the positive association between thrombectomy and mRS as discussed above, the pooled data from the four trials which provided information on median Barthel Index score at 90 days further suggest that mechanical thrombectomy has a significant positive effect on morbidity and function. All four trials were performed with newer generation devices with all commenced in 2010 or later.

While seven trials reported on NIHSS in different ways and at different time points, all indicated better outcomes in the intervention groups — the significance of this is difficult to assess, however, given the aforementioned heterogeneity in reporting. Similarly, while just two trials reported on reperfusion at 24 hours, and again did so in different ways, both reported markedly improved rates of reperfusion in the intervention versus the control groups (it should be noted, however, that MR RESCUE, which reported on reperfusion at seven days, suggested no difference at this time point).

Restoration of cerebral blood flow on final angiography, as assessed using the TICI or mTICI score, varied markedly across the eight trials for which data were presented and, while there are reasons for this variability (that is to say, the absence of appropriate imaging in some patients in MR CLEAN), it is difficult to arrive at any firm conclusions in relation to this outcome measure.

Four trials reported health-related quality of life, as measured using the EQ-5D; the results from all four are consistent in suggesting that mechanical thrombectomy may have a positive effect on this outcome measure.

While eight of the nine RCTs reported on device- and or procedure-related events, differences in reporting make comparability difficult. Five of the trials did not differentiate between device- and procedure-related adverse events and the range of these events across the five trials varied widely; from 10.9% to 29.1% of the intervention cohort. Just one of the nine RCTs specifically reported device-related events (SWIFT PRIME, 5.1% of intervention group).

4.8 Discussion

The assessment of the clinical effectiveness and safety of mechanical thrombectomy for acute ischaemic stroke is based on nine RCTs, with a total of 2,835 patients. As noted above, while the risk of bias was generally rated as low, the quality of the pooled data for the outcomes under review was rated as low or moderate. In addition, a number of important points about the trials need to be reiterated.

While mechanical thrombectomy is the subject of this analysis, the RCTs examined 'endovascular intervention' which includes both mechanical thrombectomy and intra-arterial thrombolysis, in which tPA is infused directly into the artery close to the occlusion. Two of the studies, in particular, had markedly lower proportions of their intervention groups undergoing mechanical thrombectomy (IMS III: 39.2%, SYNTHESIS Expansion: 30.9%); this compared with the other seven trials where the

proportion of the intervention group undergoing mechanical thrombectomy ranged between 71.1% and 100%.

There were a number of reasons for the different rates across the trials, including the use or non-use of imaging in patient selection, clinical deterioration or improvement, and system or process issues (that is, the availability of an interventionist). That said, all of the trials randomised patients on the basis that they were eligible for mechanical thrombectomy, and analysis in eight trials was performed on an intention-to-treat basis, with the ninth based on a per-protocol analysis (MR RESCUE).

The type of devices used has changed over time; this is significant because the year of commencement of enrolment across the nine trials ranged from 2004 (MR RESCUE) to 2013 (ESCAPE). The first three trials to begin enrolment used first-generation devices alone (MR RESCUE) or in the majority of cases (IMS III, SYNTHESIS Expansion). In contrast, the later trials used newer generation 'stent retrievers' in all (EXTEND IA, REVASCAT, SWIFT PRIME) or the majority of cases (MR CLEAN, ESCAPE, THRACE).

Six of the nine trials focused exclusively on patients with anterior acute ischaemic stroke. IMS III included those with occlusion in the basilar artery, but this consisted of just four patients, while SYNTHESIS Expansion included 30 patients (8%) with posterior circulation stroke as assessed on day seven; THRACE included four patients (1%) with posterior circulation stroke. The results presented here should therefore be taken to be indicative of the effectiveness or otherwise of mechanical thrombectomy in the management of anterior circulation acute ischaemic stroke. Further studies are required before a determination on the efficacy of mechanical thrombectomy in the posterior circulation can be made.

Relative to the number of trials completed, a large number of systematic reviews of mechanical thrombectomy have been published. Of the more recent reviews, those publishing based on the first eight RCTs (excluding THRACE) estimated effect sizes in line with those presented in this report (which includes THRACE).

Of note, at least three individual patient data meta-analyses were also published in 2016 [74-76]. Campbell et al. focused on trials in which the Solitaire device had been the only or predominant device used (SWIFT PRIME, ESCAPE, EXTEND IA and REVASCAT). They concluded that this device, when used in the management of large vessel occlusion ischemic stroke, selected by imaging and within six hours of stroke onset is associated with a relative risk of achieving an mRS of 0-2 (functional independence) at 90 days of 2.60 (95% CI 1.9-3.5).

The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration published two further individual patient meta-analyses in 2016, both of which were based on data from the 1,287 patients from five of the nine trials included in HIQA's analysis above (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE). The first of these, published by Goyal et al., concluded that mechanical thrombectomy, when used in conjunction with standard medical care, holds significant additional benefit over standard medical care alone in terms of functional outcomes. They also concluded that there was no evidence of heterogeneity of treatment effect across any of the prespecified variables: age, sex, NIHSS, site of intracranial occlusion, IV t-PA received or ineligible, ASPECTS, time from onset to randomisation, and presence of tandem cervical carotid occlusion. The authors did acknowledge, however, that because some of the trials had been stopped early, the possibility existed of over-estimation of treatment effect. They further acknowledged that the trials had been conducted in highly specialised centres and that in order to establish broad applicability of this technology, there will need be careful systematic collection of registry data. The second analysis from the HERMES collaboration, published by Saver et al., suggested that mechanical thrombectomy may be beneficial in patients who receive it up to seven hours following symptom onset — although they also noted that the effects became non-significant after 7.3 hours from onset.[76]

Notwithstanding the limitations identified, the evidence presented suggests that mechanical thrombectomy is not associated with an increased risk of all-cause mortality at 90 days, SICH or with recurrent ischaemic stroke at 90 days, when compared with standard medical care — although it should be noted that the evidence for recurrent ischaemic stroke at 90 days is based on four trials only. Pooled data from eight trials suggest that the intervention may be associated with a higher rate of any cerebral haemorrhage when compared with standard medical care; the significance of this is difficult to quantify, however, because it includes all reported cases of cerebral haemorrhage, some of which would have been clinically insignificant.

In conclusion, while there are a number of caveats as discussed, the evidence suggests that mechanical thrombectomy, when used in conjunction with non-invasive arterial imaging, in selected patients with anterior circulation acute ischaemic stroke, and when using second-generation (stent retriever) devices, has a beneficial effect on morbidity and function, and health-related quality of life at 90 days, and is not associated with an increased risk of all-cause mortality at 90 days, SICH or with recurrent ischaemic stroke at 90 days. The applicability of the evidence from these clinical trials will, however, depend on the extent to which trial

conditions, particularly in relation to patient selection and timely treatment, are replicated in routine practice.

4.9 Key messages

- A systematic review was carried out to identify relevant studies of the effectiveness and safety of mechanical thrombectomy in the management of acute ischaemic stroke
- Nine randomised controlled trials were included in this meta-analysis. These were published between 2013 and 2015 and include 2,835 patients.
- While the risk of bias was generally rated as low, the quality of the pooled data for the outcomes under review was rated as low or moderate
- The individual trials span a time frame in which both the technology itself and the process of identifying patients who could potentially benefit from the technology have changed significantly.
- While individual studies reported adverse events and or serious adverse events, a lack of clarity regarding what constitutes 'serious' and inconsistencies in reporting makes comparative analysis across studies difficult
- The evidence suggests that, compared with standard medical care alone, mechanical thrombectomy, when used in conjunction with non-invasive arterial imaging, in selected patients with anterior circulation acute ischaemic stroke, and when using second-generation (stent retriever) devices within six to 12 hours of stroke onset:
  - is significantly more likely to result in functional independence (mRS) (RR: 1.56, 95% CI: 1.37–1.78)
  - is not associated with an increased risk of all-cause mortality at 90 days (RR: 0.85, 95% CI 0.67–1.07), SICH (RR: 1.07, 95% CI 0.67–1.71) or with recurrent ischaemic stroke at 90 days (RR: 3.09, 95% CI 0.86–11.11).

5. Review of cost-effectiveness

This chapter reviews the existing international evidence on the cost-effectiveness of mechanical thrombectomy and considers the applicability of the results to the Irish setting.

5.1 Search strategy

A systematic review was carried out to assess the available evidence on the cost-effectiveness of mechanical thrombectomy. Studies were included if they compared the costs and consequences of mechanical thrombectomy with or without intravenous tissue plasminogen activator (IV t-PA) to routine care (which may include intravenous and/or intra-arterial thrombolysis where appropriate). The review was carried out in accordance with national guidelines on the retrieval and interpretation of economic evaluations of health technologies.[90]

The search for economic evaluations was carried out in MEDLINE, EMBASE, EBSCOhost (including Academic Search, CINAHL, and EconLit), the Cochrane Library, and Google. The search was restricted to studies published between January 2005 and 6 April 2016. In addition, systematic reviews of the clinical effectiveness of mechanical thrombectomy were also hand-searched for primary studies that included cost or economic outcomes.

Studies were eligible if they compared the costs and consequences of mechanical thrombectomy added to routine care compared with routine care alone for people with acute ischaemic stroke in the anterior and/or posterior region. It was not necessary for all patients receiving the intervention to receive mechanical thrombectomy, as successful recanalisation may be achieved by IV t-PA alone. The intervention had to be compared with either IV -tPA alone or an alternative definition of best medical care.

The studies had to report the cost-effectiveness of the intervention as cost-effectiveness, cost-utility, or cost-benefit. Eligible study types were randomised controlled trials (RCTs), observational studies, and economic modelling studies.

The Consensus on Health Economic Criteria (CHEC)-list was used to assess the applicability of the studies.[77] An assessment of the relevance of the economic models and their credibility was considered using a questionnaire from the International Society of Pharmacoeconomic Outcomes Research (ISPOR).[78] Study applicability was graded as high (results likely to be accurate), moderate (results

subject to bias, but likely to be broadly accurate), and low (results at high risk of bias and unlikely to be accurate).

In the following sections, costs reflect those quoted in the original studies with 2015 Irish Euro equivalent prices reported in parentheses.

5.2 Results

Of 1,645 articles identified, a total of 11 relevant studies were identified (see Table 5.1). The studies included ten cost-utility analyses and one cost-benefit analysis. Six of the studies were based in North America and the remaining five were based in European countries.

Table 5.1 Economic evaluations of mechanical thrombectomy

Author (year)	Country	Technology	Comparator	Evaluation type
Patil (2009) [79]	US	Merci retriever	Standard medical therapy with no thrombolytics	Cost-utility
Nguyen-Huynh (2011) [80]	US	Merci retriever	Best medical therapy outside the three hour IV t-PA window	Cost-utility
Kim (2011) [81]	US	Merci retriever	IV t-PA alone within three hour IV t-PA window	Cost-utility
Bouvy (2013) [82]	Netherlands	Stent retrievers	IV t-PA alone and conservative medical therapy	Cost-utility
Leppert (2015)[83]	US	CE-marked devices	IV t-PA alone	Cost-utility
Ganesalingam (2015) [84]	UK	Stent retrievers	IV t-PA alone	Cost-utility
Thurman (2015) [85]	Sweden	New-generation devices	IV t-PA alone	Cost-utility
Mangla (2016) [86]	US	CE-marked devices	IV t-PA alone	Cost-benefit
Ontario (2016) [87]	Canada	New-generation devices	IV t-PA alone	Cost-utility
Aronsson (2016) [88]	Sweden	Stent retrievers	IV t-PA alone	Cost-utility

Lobotesis (2016) (89)	UK	CE-marked devices	IV t-PA alone	Cost-utility

Abbreviations: IV t-PA, intravenous tissue plasminogen activator; CE, Conformité Européene. Table entries sorted by publication date.

5.2.1 Applicability of included studies

Modelled cost-effectiveness studies were assessed using the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) questionnaire to assess the relevance and credibility of modelling studies. Relevance was assessed on the grounds of the study population, characteristics of the intervention, outcomes measured and the overall study context. The credibility of the results was considered using criteria related to the design, validation and analysis methods, the quality of the data used, as well as how the results were reported and interpreted and whether the authors had any conflicts of interest.

Four studies were considered of low applicability,[80-82, 85] five were of moderate applicability,[79, 83, 84, 88, 89] and one was graded as highly applicable.[87] A low applicability grading was associated with serious methodological issues (for example, a failure to apply discounting) and concerns over data sources (for example, data on recanalisation rates for the intervention and comparator coming from different sources). Studies graded as moderate applicability failed to adequately describe data sources or included data from a single trial where outcomes from multiple trials were available.

A lack of clear reporting was a common issue across studies, creating ambiguity regarding a number of parameters including the proportion of patients in the intervention arm receiving mechanical thrombectomy and the included costs.

5.2.2 Overview of studies

Four of the studies evaluated first-generation devices in the absence of RCT data to support estimates of clinical effectiveness.[79-82] Three of the four studies were presented as exploratory analyses due to the substantial uncertainty around the clinical effectiveness of endovascular treatment, and that RCT evidence was needed to confirm results.

Three early evaluations were US-based and used data from the Multi-MERCI trial.[79-81] All three studies took a societal perspective, applied a discount rate of 3% to costs and benefits, and used a 20 year or lifetime time horizon. The comparator differed across the three studies, variously defined as: standard therapy with anti-

platelet agents and supportive care, but excluding the use of thrombolytics such as tPA; best medical therapy outside the three hour window for IV t-PA; and IV t-PA alone. Long terms outcomes were modelled based on successful recanalisation and incidence of symptomatic intracerebral haemorrhage (SICH). The estimated incremental cost-effectiveness ratios (ICERs) ranged from $9,386 (€9,476) to $16,001 (€16,155) per QALY.

A Dutch study from 2013 was the last evaluation to be published based on evidence from first-generation devices.[82]. The comparator was IV t-PA alone. The assessment took a payer perspective and used time horizons of six months and lifetime. Parameter values for the economic model came from a variety of sources, including expert opinion for some of the key outcomes. The ICERs were €31,687 (€41,137) per QALY at six months and €1,922 (€2,495) per QALY at lifetime.

Subsequent studies used data from one or more of the five RCTs of second-generation mechanical thrombectomy devices published between 2013 and 2015.

Two US studies were published that used modified Rankin Score (mRS) outcome data from the MR CLEAN RCT.[83, 86] The first, by Leppert et al., was a cost-utility analysis comparing intra-arterial therapy (IAT) to IV t-PA alone for patients who received thrombolysis within 4.5 hours of symptom onset, and IAT within six hours [83]. Based on a payer perspective, a discount rate of 3% and a 30 year time horizon, the ICER for IAT was $14,137 (€12,921) per QALY. A cost-benefit analysis by Mangla et al. compared mechanical thrombectomy with IV t-PA alone.[86] The study did not apply discounting and there was no assessment of uncertainty.

Four evaluations used estimates of clinical effectiveness from data pooled across five RCTs of mechanical thrombectomy: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME and REVASCAT.[84, 85, 87, 88] The four studies all compared the intervention with IV t-PA alone and none of the studies specified treatment windows in relation to symptom onset. A UK study, adopting a payer perspective over a 20-year time horizon, estimated an ICER of $11,651(€8,966) per QALY.[84] A Canadian health technology assessment by Health Quality Ontario estimated an ICER of CA$11,990 (€8,345) based on a five-year time horizon and a discount rate of 5%.[87] Two Swedish evaluations were also published, both adopting a 20 year or lifetime time horizon. The first to be published, by Thurman et al., took a societal perspective and did not include discounting.[85] The ICER for mechanical thrombectomy was estimated at SEK45,000 (€4,231) per QALY. The second study, by Aronsson et al., found that mechanical thrombectomy dominated usual care – that is, was more effective and less costly than IV t-PA alone.[88]

Finally, a UK study used outcome data from the SWIFT PRIME study to estimate the cost-effectiveness of combined stent retriever thrombectomy and IV t-PA compared with IV t-PA alone.[89] Patients were assumed to receive the intervention within six hours of symptom onset. In addition to lifetime, time horizons of one, two and five years were also used. The intervention dominated IV t-PA alone at time horizons of two years, five years and lifetime. At a time horizon of one year, the ICER was £369 (€469) per QALY.

5.2.3 Applicability of the evidence

The studies can be classed as first- and second-generation device evaluations. The first-generation device assessments were carried out prior to the publication of a series of RCTs that compared thrombectomy with IV t-PA alone and derived outcome data from the Multi-MERCI trial or expert opinion. The Multi-MERCI trial was a single-arm trial of thrombectomy and hence did not collect information on the relevant comparator. As such, studies using the Multi-MERCI trial data estimated outcomes for the comparator using alternative sources, potentially introducing substantial bias. The assessments of second-generation devices used data from one or more of the eight RCTs of mechanical thrombectomy published between 2013 and 2015. In 2009 the recommended window for administering tPA changed from three hours to four and a half hours after symptom onset following publication of the ECASS trial. The majority of the RCT evidence was based on a 4.5 hour window for thrombolysis with tPA, whereas the Multi-MERCI trial was based on a three hour window. Studies based on second-generation devices were less likely to be affected by bias in the estimates of clinical effectiveness, and are more likely to be applicable to the Irish context.

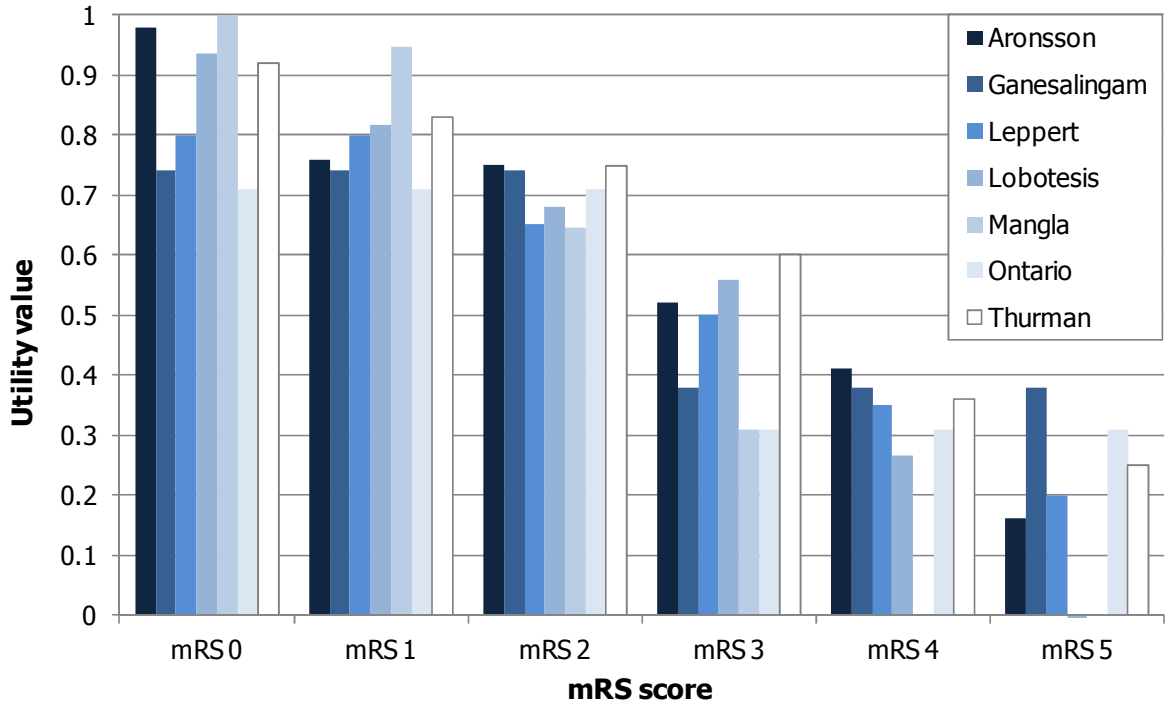
Of note is that mechanical thrombectomy devices are typically used in only a proportion of cases, as successful recanalisation may be achieved through IV t-PA. Some studies noted the proportion of patients that would receive mechanical thrombectomy as part of endovascular therapy. In terms of costs, in most of the studies it was not clearly stated whether it was assumed that costs took into account that not all patients would require mechanical thrombectomy.

The definition of the comparator varied, although across the studies based on second-generation devices the comparator was consistently best medical therapy including IV t-PA where appropriate. In most cases, trial patients were restricted to those eligible for IV t-PA within the recommended timeframe.

For evaluations of second-generation devices, clinical outcomes were expressed in terms of mRS at 90 days. Subsequent quality of life was estimated based on mRS at

90 days with some studies allowing for recurrent stroke and an associated potential for further reduced mRS. Quality of life was estimated by applying utilities to each mRS score, and the utility values used varied substantially across studies (Figure 5.1). For two of the studies, by Lobotesis et al. and Mangla et al., relative to the remaining studies the weights used are high for mRS scores of zero and one, but low for scores of four and five. The choice of utility weights in those two studies results in a greater benefit for mechanical thrombectomy than estimated in the remaining studies. In these economic evaluations, each study identified a single source for utility weights. Given the variation observed, a pooled estimate would perhaps have been more appropriate.

Figure 5.1 Utility weights used in the economic evaluations of second-generation devices



In the studies of first-generation devices, adverse events were specifically incorporated in the form of symptomatic intracerebral haemorrhage (SICH). In evaluations of second-generation devices, recognition of adverse events has been less clear. The study by Ganesalingam et al., for example, makes no reference to adverse events.[84] The HTA by Health Quality Ontario, on the other hand, explicitly pooled data on SICH and found no statistically significant difference between the intervention and comparator and therefore justified exclusion of SICH as an outcome.[87] Where treatment costs were collated from treatment data, it is possible that the mix of diagnosis-related groups (DRGs) reflects the rate of adverse events.

The link between adverse events and longer-term outcomes is unclear and rates of SICH may be reflected in mRS at 90 days, therefore incorporating complications through hospital costs may be sufficient.

Four of the eleven studies stated that they adopted a societal perspective,[79-81, 85] while the remainder adopted a payer perspective. In the context of stroke care, a payer perspective takes into account long-term care associated with patients who have poor functional outcomes, or lack independence. Given the debilitating nature of stroke, many patients surviving stroke may no longer be able to work. A societal perspective enables consideration of lost productivity. However, given that evaluations considered patients aged between 65 and 67 years at the time of first acute ischaemic stroke, most of the patients would no longer be part of the labour force. A payer perspective may be appropriate in this case, although it will fail to capture the impact on family and informal carers who may need to provide support to stroke survivors. Some of the studies adopting a societal perspective did not clearly incorporate societal costs, such as lost productivity, and it is possible that by stating 'societal' they were referring to non-hospital costs, such as rehabilitation or long-term care costs.

The time horizons adopted varied in the base-case analyses from five years to lifetime. The time horizon should be of sufficient duration to capture any meaningful differences in the future costs and outcomes likely to accrue to the intervention and comparator. The age at which stroke occurs must be taken into account when considering the appropriateness of the time horizons adopted. Studies estimated cost-effectiveness for patients aged 65 to 67 years at first stroke. Life expectancy in Ireland at age 65 years is 16.6 years for men and 19.8 years for women. Given the elevated risk of recurrent stroke in this cohort relative to the general population, it has to be assumed that life expectancy may be significantly shorter in this cohort. The lack of long-term follow up data for the RCT study populations must also be considered – hence outcomes over the time horizon are extrapolated based on outcomes at 90 days.

Costs and health outcomes that occur in the future should be discounted to present values to reflect society's rate of time preference. Discount rates vary across countries and some jurisdictions used differential discounting whereby different discount rates are applied to costs and benefits. In Ireland, a standard rate of 5% is applied to costs and benefits (correct as of January 2017). In the economic evaluations identified, the discount rates applied ranged from 3% to 5% with the exception of two studies that did not apply discounting. In all cases the same discount rate was applied to costs and benefits. The impact of a lower discount rate on the estimated cost-effectiveness depends on when costs and benefits accrue over

the time horizon. In the case of mechanical thrombectomy, the increased intervention costs occur at the outset whereas the savings accrue over the time horizon due to reduced health care costs for those with better functional outcomes. Benefits as measured by improved quality of life also accrue over the time horizon. As such, a reduced discount rate would be likely to favour the intervention in this case, as long-term benefits would be valued more highly. The Health Quality Ontario study used a 5% discount rate, the same as applies in Ireland.

Given the potentially high cost of post-stroke care, the applicability of the cost data to the Irish setting is an important consideration. A recent Irish HTA on atrial fibrillation collated data on the cost of care after stroke that can be used as a guide to the applicability of costs used in the evaluations of mechanical thrombectomy.[90] Costs in the identified studies included those associated with the acute hospital episode at the time of stroke, rehabilitation in the 90 days after stroke, and long-term care costs in relation to level of functional independence.

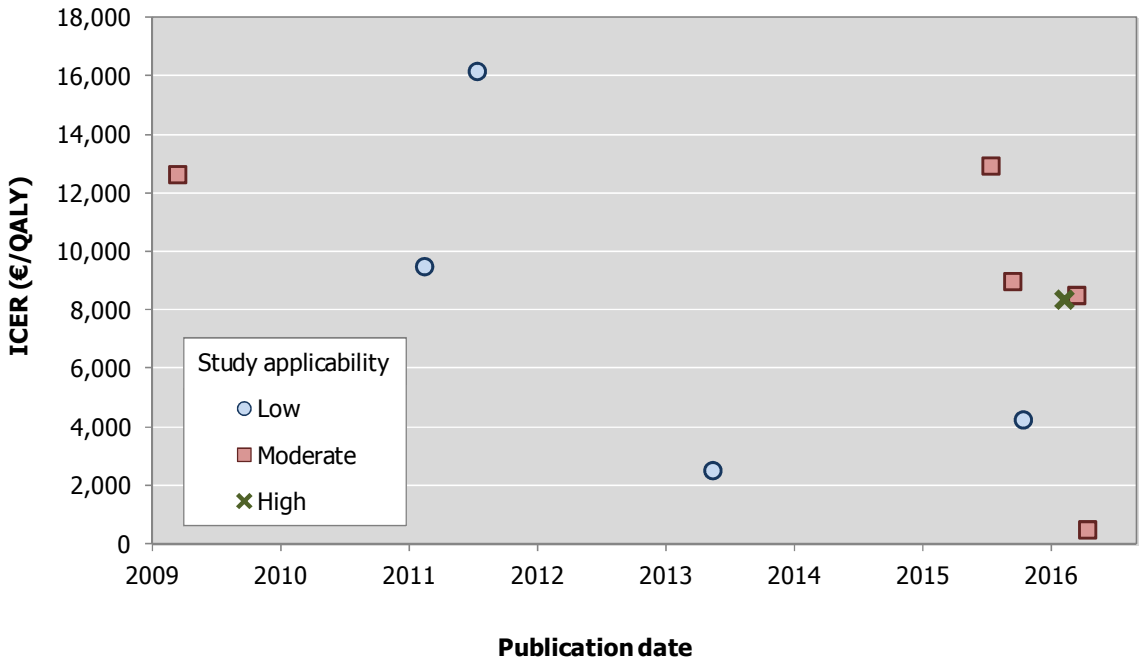
Regarding the cost of the initial acute hospital episode, there was substantial variation in the estimated cost of the intervention and the comparator (IV t-PA alone). The average reported cost for IV t-PA alone was €7,588 (range €1,261 to €16,228), compared with the estimated inpatient treatment cost of stroke patients in Ireland of €8,939. It must be borne in mind that, for analytical purposes, an evaluation might only consider the costs that differ between the intervention and comparator rather than estimating the full economic cost. The Ontario HTA, for example, estimated the additional cost of mechanical thrombectomy relative to IV t-PA alone, and did not report the cost of the comparator. The average reported additional cost of the intervention was €10,966 (range €3,734 to €18,129).

During the mechanical thrombectomy procedure, multiple passes of the device may be used. In some cases, multiple devices may be used. It is unclear if the reported intervention costs in the economic evaluations incorporated the use of multiple devices during an episode of care. The evaluation by Lobotesis et al., for example, states that an average 1.2 devices were used per procedure.[89] It does not state whether it is assumed that every patient in the intervention group receives mechanical thrombectomy. The lack of detail and clarity around the proportion receiving mechanical thrombectomy and the number of devices used per procedure mean that it is not possible to determine the accuracy or applicability of the quoted intervention costs.

Of the eleven evaluations identified, one was considered to be highly applicable, five were of moderate applicability and four were of low applicability. Three of the four low applicability studies were of first-generation thrombectomy devices. The one low

applicability study of second-generation devices was the Swedish study with poor reporting and an apparent failure to apply discounting.[85] The applicability of a study does not necessarily correlate with the accuracy of the results, but it does indicate a risk of bias. An assessment of reported ICERs by study applicability does not suggest a correlation with study applicability (Figure 5.2). Indeed, the reported ICERs tend to fall within a relatively narrow range, with all studies suggesting that mechanical thrombectomy is a cost-effective intervention relative to typical willingness-to-pay thresholds when compared with IV t-PA alone. The consistency of the results provides reassurance that study applicability may not have overly biased the estimates of cost-effectiveness.

Figure 5.2 Study applicability and the estimated incremental cost-effectiveness of mechanical thrombectomy



The majority of studies included here used probabilistic models in which parameter values were defined as distributions. It was therefore possible to explore the impact of parameter uncertainty on the estimated cost-effectiveness through one-way and multivariate sensitivity analysis. The parameters for which uncertainty consistently had a marked impact on the estimate of cost-effectiveness were the cost of the thrombectomy procedure, the cost of long term care, and the average age of patients. Mechanical thrombectomy was more cost-effective when the procedure cost was lower, when the cost of long term care was higher, and when patients

were younger at the time of stroke. However, within sensitivity analyses the intervention was generally found to be considered cost-effective or cost saving.

5.2.4 Considerations for applicability to the Irish setting

Cost-effectiveness incorporates the costs and benefits of the intervention, and the applicability of the cost-effectiveness data to the Irish setting therefore depends on the relevance of both the clinical and cost data used in the identified evaluations. In assessing the applicability of international findings to the Irish setting, it is important to consider whether any critical elements or parameters may be different in the Irish setting. As the assessments based on second-generation devices were all based on data from all or some of the five RCTs of second-generation devices, it is relevant to focus on the standard of care and patient populations described in those studies.

The economic evaluations discussed here all simulated patient populations that were aged between 65 and 67 at the time of stroke. The mean age of stroke in Ireland is 69 years for men and 75 years for women. Baseline quality of life and life expectancy both decrease with age. Furthermore, although not stated, the economic evaluations may have been restricted to patients with an mRS of zero at the time of stroke, thereby excluding people with disability due to a previous stroke. The Ontario study used a sensitivity analysis to estimate the cost-effectiveness of mechanical thrombectomy restricted to patients aged 70 years or older, and estimated an ICER of CA$29,899 (€20,811) per QALY. This finding suggests that mechanical thrombectomy may still be cost-effective for older patients. However, it is less clear whether mechanical thrombectomy would be cost-effective for patients with some level of disability prior to stroke.

Although pooled data from multiple high quality RCTs reflects the best level of evidence available, it is a measure of efficacy rather than effectiveness. Efficacy informs us of how well an intervention works under ideal circumstances. Effectiveness, on the other hand, is a measure of how well an intervention works under typical 'real world' conditions. The RCTs of mechanical thrombectomy included a variety of inclusion and exclusion criteria regarding the patients. For example, the SWIFT PRIME, REVASCAT and EXTEND-IA trials excluded patients with a baseline mRS of greater than one or a life expectancy of less than one year. The MR CLEAN study did not specify an upper age limit or specify baseline level of disability. Patients eligible for one of the five trials may not have been eligible in the other trials. The timing of interventions varied, as trials had different definitions of an acceptable time frame for administering IV t-PA and for commencement of mechanical thrombectomy. When a time window was specified in the RCTs, it was for IV t-PA to be administered within 4.5 hours and for mechanical thrombectomy to

start within six hours of symptom onset. As the economic evaluations used the RCT evidence to estimate clinical effectiveness, the estimates of cost-effectiveness only apply to patients treated under the conditions of trials. If treatment conditions are substantially different in Ireland due to health service infrastructure or patient characteristics, then the estimates of cost-effectiveness cannot be considered applicable under routine care conditions.

The cost associated with long-term care was typically subdivided into categories reflecting level of independence or stroke severity of the stroke survivors as measured by mRS at 90 days. The modified Rankin scale is used to measure the degree of disability, and ranges from zero (no symptoms) to six (dead). Studies differed in how they grouped mRS scores, with some considering three (moderate disability) as being synonymous with independence and others studies as reflecting dependence. For those with mild disability, functional independence or mRS values less than or equal to three, the mean annual cost of care was €5,478 (range €2,221 to €13,642). For patients with moderate to severe disability, functional dependence or mRS values greater than three, the mean annual cost of care was €24,014 (range €6,386 to €47,360). The estimated equivalent annual costs for long-term stroke in Ireland are €4,306 for mild stroke and approximately €23,110 for moderate to severe stroke. The average costs presented across studies was therefore broadly applicable to the Irish setting, although individual studies could differ quite substantially from the Irish figures.

Four of the eleven studies stated that they adopted a societal perspective, while the remainder adopted a payer perspective. In Ireland, the base-case analysis is typically based on the payer perspective. It was noted that for the studies adopting a societal perspective, this meant including long-term care costs which would be incorporated into an Irish evaluation. Of note is that for men in Ireland, 30% of strokes occur in those aged less than 65 years. These are men who are likely to participate in the workforce and functional impairment will have consequences for both the labour force and informal care. As such, a full societal perspective may be warranted.

The one identified high applicability study was the Health Quality Ontario HTA. The Ontario study used pooled data from five RCTs to estimate clinical effectiveness. Within the economic evaluation, it was assumed that the conditions in the five RCTs would apply to routine care. That is, more than 70% of patients received IV t-PA, irrespective of whether they were in the intervention or comparator arm, and 80% of patients in the intervention arm received mechanical thrombectomy. These figures are broadly in line with the case series of 93 patients treated at Beaumont Hospital in Dublin between 2010 and 2013; 67% received IV t-PA and 89% underwent

mechanical thrombectomy.[56] Of note, the Ontario study adopted a five-year time horizon. A sensitivity analysis was used to evaluate alterative time horizons and found that longer time horizons of 10 and 15 years resulted in similar ICERs. The sensitivity analyses also indicated that, with the exception of adopting a one year time horizon, mechanical thrombectomy was likely to be cost-effective under alternative parameterisations of the model.

Given that the long-term care costs used in the Ontario study were broadly similar to Irish costs and the same discount rate was applied, it can be assumed that the findings of the Ontario study are broadly applicable to the Irish setting if the standard of care described in the RCTs can be achieved in Ireland. However, it is noted that the published evaluations assumed sufficient neuroendovascular suite capacity as capital investment in additional biplane angiography suites was not included. These evaluations also omitted costs associated with patient transfer and redirection to comprehensive stroke centres resourced to provide mechanical thrombectomy procedures.

5.3 Summary

Based on a systematic review, eleven studies were identified that estimated the cost-utility or cost-benefit of mechanical thrombectomy relative to standard care. Studies could be dichotomised into evaluations of first- and second-generation devices. The clinical effectiveness of second-generation devices is supported by data from multiple RCTs, and is considered the best level of evidence. The cost of long-term stroke care used in the studies was found, on average, to be broadly consistent with estimates for Ireland. The applicability of the economic evaluations to the Irish healthcare system was mixed, but was generally poor or moderate.

One high applicability study was identified, a HTA by Health Quality Ontario. The Ontario HTA includes a detailed and comprehensive economic evaluation, and the costs are broadly similar to those in Ireland. The Ontario study found mechanical thrombectomy to be cost-effective relative to IV t-PA alone. Detailed sensitivity analysis suggest that other than by adopting a time horizon of one year, mechanical thrombectomy is likely to be considered cost-effective relative to a willingness-to-pay threshold of CAN$20,000 per QALY. The findings of the Ontario study in terms of cost-effectiveness are similar to the other identified studies, providing reassurance about the consistency of cost-effectiveness evidence.

Provided that a service in Ireland can replicate the treatment times observed in the RCTs, and assuming availability of comprehensive stroke care, it is possible that mechanical thrombectomy would be cost-effective in Ireland. In light of the

distribution of stroke services and population in Ireland, and the likely investment required to support the development of a national mechanical thrombectomy service, a cost-effectiveness analysis using Irish data was deemed necessary to support decision-making.

5.8 Key messages

- A systematic review of published economic evaluations was undertaken, identifying 11 published evaluations.
- Four studies evaluated the cost-effectiveness of first-generation devices while seven evaluated second-generation devices.
- The applicability of the studies was mixed, but was generally poor or moderate: there was one study with high applicability, five with moderate applicability and four with low applicability to the Irish healthcare setting.
- The estimates of cost-effectiveness were relatively consistent across studies, suggesting that mechanical thrombectomy is likely to be cost-effective or dominate standard medical care including IV t-PA where appropriate.
- If the international experience is applicable, mechanical thrombectomy may be cost-effective in Ireland assuming the availability of comprehensive stroke care and the delivery of mechanical thrombectomy within a six-hour time frame.
- The published evaluations excluded capital investment in equipment and costs associated with patient transfer to avail of this procedure. In light of the distribution of stroke services and population and the likely investment required to support a national thrombectomy service, a cost-effectiveness analysis using Irish data would provide more appropriate evidence by taking into account local context and the existing service.

6. Economic evaluation

The review of economic evaluations found seven studies evaluating second-generation devices, but the applicability of the evidence to the Irish setting was generally poor or moderate, and potentially insufficient for decision-making purposes. This chapter describes an economic model assessing the cost-effectiveness of a national emergency endovascular service providing mechanical thrombectomy for the treatment of acute ischaemic stroke in Ireland.

6.1 Economic analysis

In the absence of applicable published cost-effectiveness evidence from another setting, an economic model was developed specific to the Irish setting. The modelling approach was largely based on the Ontario HTA described in Chapter 5,[87] as this was considered most applicable to the Irish setting and captured the main costs and benefits relevant to this HTA.

6.1.1 Description of the economic model

A Markov decision-analysis model was built to compare the costs and benefits of a national emergency endovascular service providing mechanical thrombectomy with the current standard of medical care for acute ischaemic stroke in Ireland. The objective of the economic evaluation was to aid decision-making by estimating the incremental costs and benefits of adding mechanical thrombectomy to the current standard medical care, which includes provision of intravenous (IV) and or intra-arterial (IA) thrombolysis, where appropriate.

6.1.2 Study question

The study objective was to determine the cost-effectiveness and budget impact of a national emergency endovascular service providing mechanical thrombectomy to treat acute ischaemic stroke in Ireland.

6.1.3 Type of economic evaluation

A cost-utility analysis was also used, with benefits measured as quality-adjusted life years (QALYs) gained. Given the impact of the intervention on both quality and quantity of life, a cost-utility analysis was considered appropriate.

6.1.4 Study perspective

Costs and benefits were assessed from the perspective of the publicly-funded health and social care system. Only direct costs were included. Indirect costs such as productivity losses associated with mortality and morbidity as a result of stroke were excluded.

National guidelines for the economic evaluation of health technologies in Ireland recommend that the perspective of the publicly-funded health and social care system in Ireland should be adopted when assessing costs.[91] For this intervention, the majority of costs accrue to the health service, and hence it is appropriate to examine cost-effectiveness from the perspective of the publicly-funded health service only.

6.1.5 Technology

The technology being assessed is endovascular treatment using second-generation mechanical thrombectomy devices which could be used in combination with IV and or IA thrombolysis, or as an alternative to it in patients experiencing an acute ischaemic stroke who are not candidates for thrombolysis, or in patients in whom thrombolysis appears to have failed. See Chapter 2 for a more detailed description of the technology.

6.1.6 Choice of comparators

One comparator was included in the evaluation: standard medical care, which could include IV and or IA thrombolysis where appropriate. It is acknowledged that at present a limited mechanical thrombectomy service is provided. For the purposes of this assessment, the focus was on evaluating a full service relative to no service rather than a partial service.

6.1.7 Target population

The target population was adults aged 18 years or older who had acute large-artery ischemic stroke (in the anterior and or posterior region) with moderate-to-severe neurologic deficits. Based on data presented in Chapter 3 on the incidence of acute ischaemic stroke by age and gender in Ireland, it was assumed that the mean age at intervention was 70 years and that 57% of patients were male. It was further assumed that patients had functional independence prior to stroke onset and that occlusion was confirmed by imaging.

Consistent with the PICOS specified in Chapter 4 for identification of relevant studies in the systematic review of efficacy and safety, it was assumed that all patients were

first assessed for thrombolysis. Mechanical thrombectomy could then be used in combination with IV and or IA thrombolysis, or as an alternative to it in patients who were not candidates for thrombolysis, or in patients in whom thrombolysis appeared to have failed.

6.1.8 Time horizon

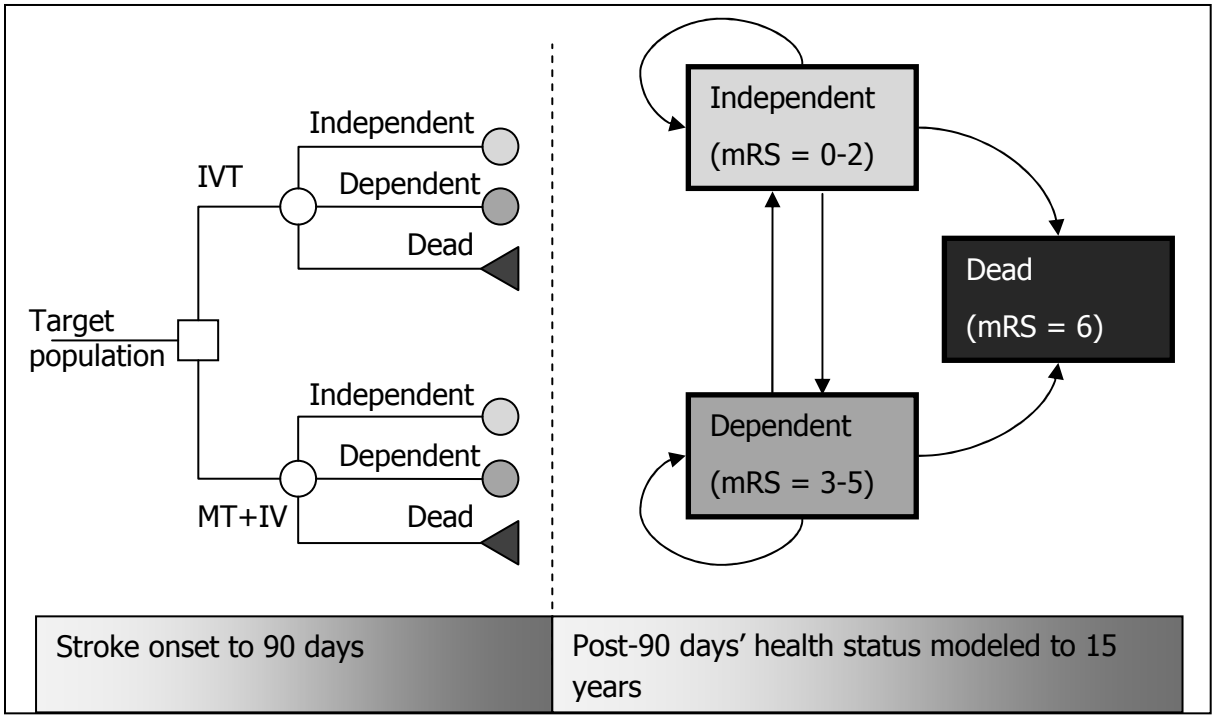
Costs and benefits were modelled to five years' follow-up. Given the mean age of patients at stroke onset and the substantial uncertainty regarding longer term outcomes for survivors of stroke, a short time frame was considered appropriate. Sensitivity analyses were used to model outcomes to 10 years.

6.1.9 Outline of the model structure

The model used a two-stage approach to modelling costs and outcomes, influenced by the fact that the main outcomes in the randomised controlled trials (RCTs) were reported at 90 days. The model estimated outcomes at three months using the pooled RCT outcomes for mortality and functional independence. The latter outcome was defined as a modified Rankin Scale (mRS) scores of zero, one or two.

The model then used a Markov decision-analytic approach to simulate transitions between three mutually exclusive states: functional independence (mRS 0-2); functional dependence (mRS 3-5); and death. Patients could transition between states in each monthly cycle. Being an absorbing state, patients could not transition out of the dead state.

Figure 6.1 Outline of model structure



The full model was developed in R 3.3.2[92] and validated against a basic model developed in Microsoft Excel 2010. The model was also populated with the Ontario model data to check against the Ontario HTA results. The model was fully probabilistic and used Monte Carlo simulation to allow parameter values to vary.

6.1.10 Model outputs

The outputs of the model included the number of survivors, number with functional independence, total costs, QALYs and life years gained for the two services modelled. Summary measures included the incremental cost-effectiveness ratio, and plots of the cost-effectiveness plane, cost-effectiveness acceptability curve, and the expected value of perfect information.

The incremental cost-effectiveness ratio (ICER) presents the additional costs divided by the additional benefits of one intervention relative to another. The ICER is typically considered in the context of a willingness-to-pay threshold, which represents the maximum a decision maker is willing to pay for a unit benefit, such as a life year gained or a quality-adjusted life year.

Cost-effectiveness acceptability curves (CEACs) are used as a method for summarising information on uncertainty in cost-effectiveness. A CEAC shows the probability that an intervention is cost-effective compared with the modelled alternatives for a range of willingness-to-pay thresholds.

The expected value of perfect information (EVPI) represents the amount a decision maker should be willing to pay to eliminate uncertainty about which intervention is the best option. As with the CEAC, the EVPI is calculated for a range of willingness-to-pay thresholds. The EVPI is an evaluation of how much the decision maker should be prepared to pay for perfect information.

In previous evaluations, willingness-to-pay thresholds of between €20,000 and €45,000 per QALY have typically been used as reference points against which estimates of cost-effectiveness are reported.

6.1.11 Sensitivity analysis

A probabilistic model was used that explicitly takes into account the uncertainty in the model parameters. All of the key parameters were varied within plausible ranges of values. Where possible, ranges were derived from published evidence. If published evidence was limited or unavailable, plausible ranges were derived with the support of the Expert Advisory Group. As the structure of the economic model presented here is inherently stochastic, the outputs are equivalent to a multivariate probabilistic sensitivity analysis.

Univariate, or one-way, sensitivity analysis facilitates examination of the impact of each variable in the study by varying it across a plausible range of values while holding all other variables constant at their 'best estimate' or baseline value. The resulting difference provides some indication of how sensitive the results might be to plausible changes in that parameter. Deterministic sensitivity analysis was used to examine this, where each parameter in turn was fixed at its upper and lower confidence bounds while all the other parameters are held at their average value. Any correlations between parameters were taken into account in the sensitivity analysis.

Scenario analyses were also used to look specifically at the impact of a number of key assumptions in relation to parameter values. In each analysis, one or more parameters were set at alternative and potentially justifiable point estimates.

6.1.13 Budget impact analysis

The budget impact analysis was conducted from the perspective of the publicly-funded health and social care system.[93] The analysis reports the incremental annual cost of the mechanical thrombectomy service relative to no mechanical thrombectomy service. As with the cost-effectiveness analysis, indirect costs due to productivity losses associated with stroke cases were not included. Costs used in the budget impact analysis were the same as those used in the economic analysis. A

budget impact analysis is inclusive of value-added tax (VAT) where applicable. VAT applies to non-oral medications, non-implantable medical devices, and to equipment when calculating amortised capital costs. In this case, VAT was applied to equipment used in the mechanical thrombectomy procedure and elements of the capital cost associated with the biplane angiographic suite.

Although the main comparison was between a national service and no service, defined as IVT only, for the budget impact it is also important to consider the existing ad hoc service. The budget impact was also estimated for a service that treats approximately 200 patients each year using existing resources.

6.2 Model parameters

The economic model required a range of input parameters that describe the cost of the mechanical thrombectomy procedure and associated service requirements, outcomes in terms of survival and disability, and ongoing costs associated with disability and long-term care.

The overall benefits and costs of a mechanical thrombectomy service were calculated by performing 10,000 model simulations. Randomly sampled individual parameter values were used in each simulation. Summarising across iterations provides an estimate of overall average costs and benefits, as well as the uncertainty associated with these values.

6.2.1 Discount rate

Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Discounting facilitates comparison between costs and benefits that occur at different times. Costs and benefits were discounted at the rate of 5% as set out by the Department of Finance.[91] The discount rate was fixed in the main analysis and varied from 1% to 7% in a univariate sensitivity analysis to test the impact of discounting.

6.2.2 Epidemiological measures

A variety of epidemiological parameters were required to model the use of mechanical thrombectomy and its impact on outcomes (Table 6.1).

In the first stage of the model, it was necessary to estimate the size of the target patient population. HIPE data indicate that, the number of hospitalised strokes per annum is in the region of 5,090, of which, on average, approximately 4,300 are ischaemic strokes. Based on prospective imaging data from the STOP-Stroke Study,

it is estimated that 46% of acute ischaemic strokes are due to large vessel occlusions.[94] Based on a three-year average from 2013 to 2015, HSE data indicate that approximately 12.3% of patients admitted with ischaemic strokes receive intravenous thrombolysis (IVT).[36-38] Based on the RCT data, only 77% of patients eligible for mechanical thrombectomy received IVT.

Using data from the RCTs of mechanical thrombectomy, the pooled percentage of patients in the intervention arm receiving mechanical thrombectomy was 84.5%. Not all patients eligible for mechanical thrombectomy undergo the treatment as successful reperfusion may have been achieved in the interim by IVT. The size of the target population eligible for mechanical thrombectomy was estimated at 316 (95% CI: 274 to 362) per annum, of which 268 (95% CI: 210 to 322) would undergo mechanical thrombectomy.

The estimated cohort of 268 reflects patients that present at a hospital with an ischaemic stroke due to a large vessel occlusion, are suitable for for mechanical thrombectomy, and can be transferred to one of the two treatment centres within six hours of stroke onset. Although it is anticipated that a small proportion of patients will arrive at a treatment centre outside the treatment window, it is assumed that eligibility or suitability for mechanical thrombectomy will be determined on the basis of imaging. The reason for including cases that would not require mechanical thrombectomy is that this cohort reflects the participants in the RCTs from which the clinical effectiveness was estimated.

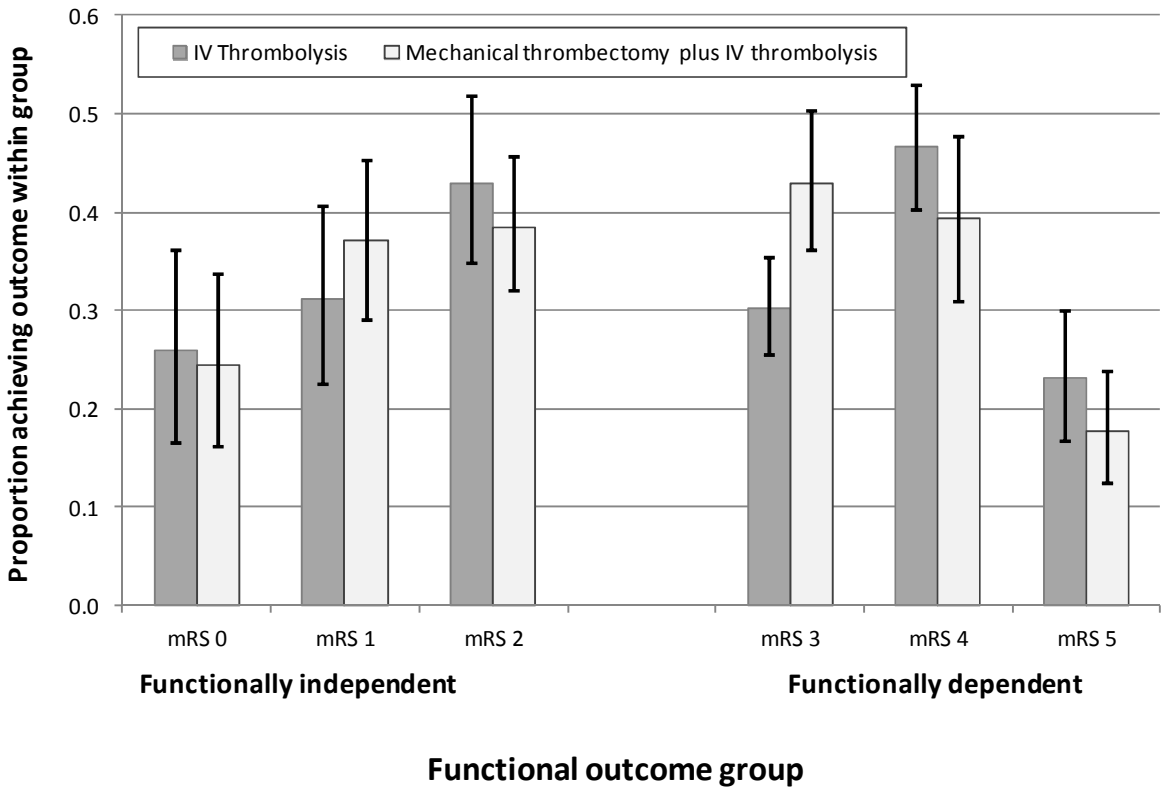
Treatment outcomes at 90 days were estimated using data from the six RCTs of second-generation devices. The proportion of patients dying (mRS=6) and achieving functional independence (mRS=0-2) for those undergoing IVT was estimated by pooling the control arm data from the trials. The relative risks of mortality and functional independence for those undergoing mechanical thrombectomy were based on the meta-analysis of trials presented in Chapter 4. For the main analysis, it was assumed that there was a difference in mortality between IVT and mechanical thrombectomy, although the pooled difference was not statistically significant. As the mean relative risk of mortality was 0.85, which is very clinically significant, it was important to consider the impact this effect could have on the estimate of cost-effectiveness. A sensitivity analysis was used to assess the impact of assuming no difference in mortality.

Quality of life was estimated for survivors of stroke to capture the benefits of achieving functional independence relative to functional dependence. Utilities for the two health states, functional independence and dependence, were estimated by pooling the utility values from studies cited in previous economic evaluations of

mechanical thrombectomy.[95-98] For each level of functional dependence, it was assumed that patients would be similarly distributed in terms of mRS scores within the outcome irrespective of the intervention used. That is to say, for example, that of those achieving functional independence, the proportion with an mRS score of 0 would be unaffected by the intervention used.

Based on pooled data from the six RCTs of second generation devices, there are potentially some differences in the proportions achieving different mRS scores (Figure 6.2). Most notably, for those achieving functional dependence (mRS: 3-5) at 90 days, a higher proportion of those who underwent mechanical thrombectomy plus IVT were classified as mRS 3 than for those who were treated by IVT alone. To account for this potential bias, a sensitivity analysis was carried out where utility scores were weighted separately for the two interventions to account for the potentially different distribution of mRS scores.

Figure 6.2 Patients achieving different mRS scores as a proportion of all patients with same broad functional outcome



Note: proportions sum to one within a functional dependence grouping for a given intervention.

From the review of clinical effectiveness in Chapter 4, there was a relative risk of 3.09 (p=0.08) associated with the adverse outcome of recurrent stroke in those who underwent mechanical thrombectomy. This outcome could potentially impact on treatment costs. However, the increased risk was strongly influenced by the inclusion of the MR CLEAN trial, which observed a risk ratio of 14.9 for recurrent stroke. The investigators in the MR CLEAN trial defined recurrent stroke as a new ischemic stroke in a different vascular territory. A proportion of patients in the mechanical thrombectomy arm of the MR CLEAN trial also underwent a simultaneous acute cervical carotid stenting (that is, a second revascularisation procedure). These issues suggest that the findings are subject to bias and that elevated rate of recurrent stroke may be unrepresentative. It was assumed that cases of recurrent stroke are likely to occur during the hospital episode associated with the initial stroke. Should recurrent stroke result in a poorer functional outcome, this should be captured in the outcomes at 90 days.

Table 6.1 Epidemiological parameters

Parameter	Mean	(95% CI)
Target population		
Number of hospitalised ischaemic strokes per annum	4,300	(4,209 to 4,475)
Proportion large vessel occlusions	0.462	(0.421 to 0.502)
Proportion stroke patients getting IVT	0.123	(0.115 to 0.131)
Proportion of patients eligible for MT receiving IVT	0.773	(0.709 to 0.832)
Proportion of eligible patients undergoing MT	0.849	(0.694 to 0.943)
Outcomes		
Probability of mortality at 90 days with IVT	0.181	(0.149 to 0.219)
Risk ratio of mortality at 90 days with MT	0.845	(0.668 to 1.069
Probability of functional independence at 90 days with IVT	0.323	(0.283 to 0.364)
Risk ratio of functional independence at 90 days with MT	1.563	(1.367 to 1.788)
Utilities		
Utility for functional independence	0.767	(0.681 to 0.844)
Utility for functional dependence	0.347	(0.257 to 0.443)

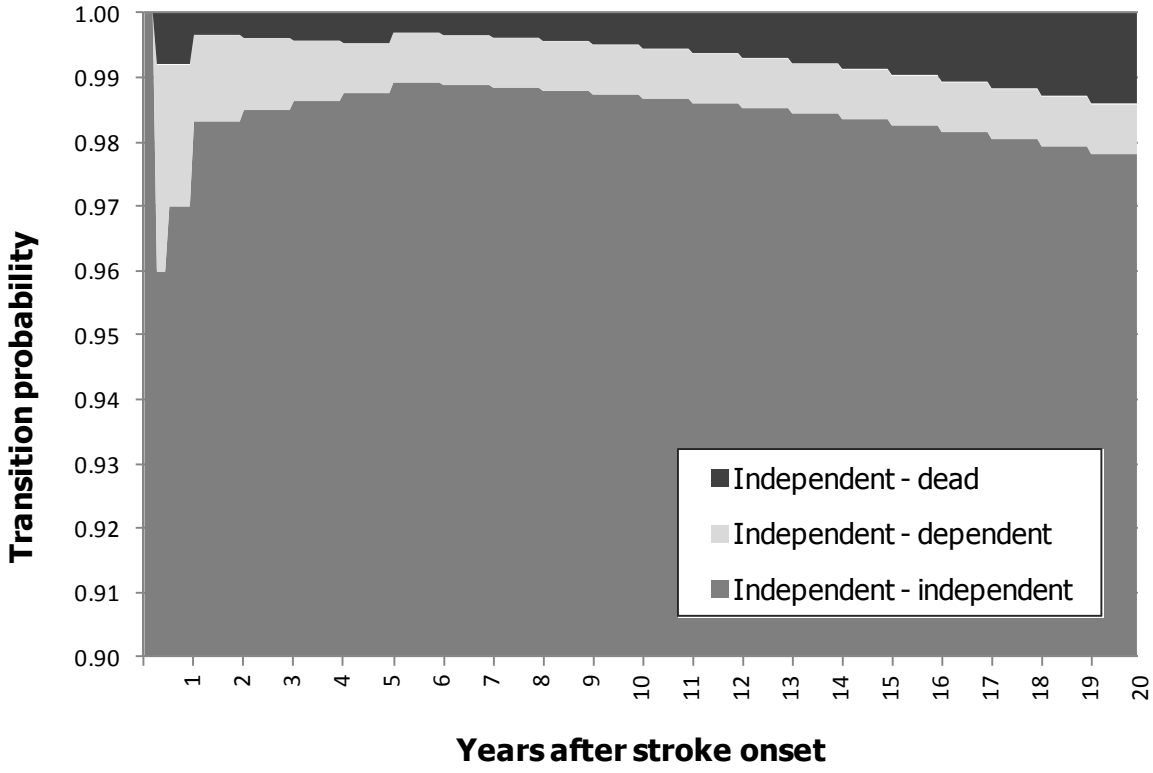
Notes: CI, confidence interval; IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

For the second phase of the economic model, a Markov model was used to allow those who survived to 90 days to move between the states of functional independence, dependence and death. The transition probabilities were derived from the Ontario HTA, which used data from the Oxford Vascular Study as part of a model-calibration exercise. As the model structure used here is an adaptation of the

Ontario HTA model, it was assumed that the transition probabilities used there would be applicable to this HTA.

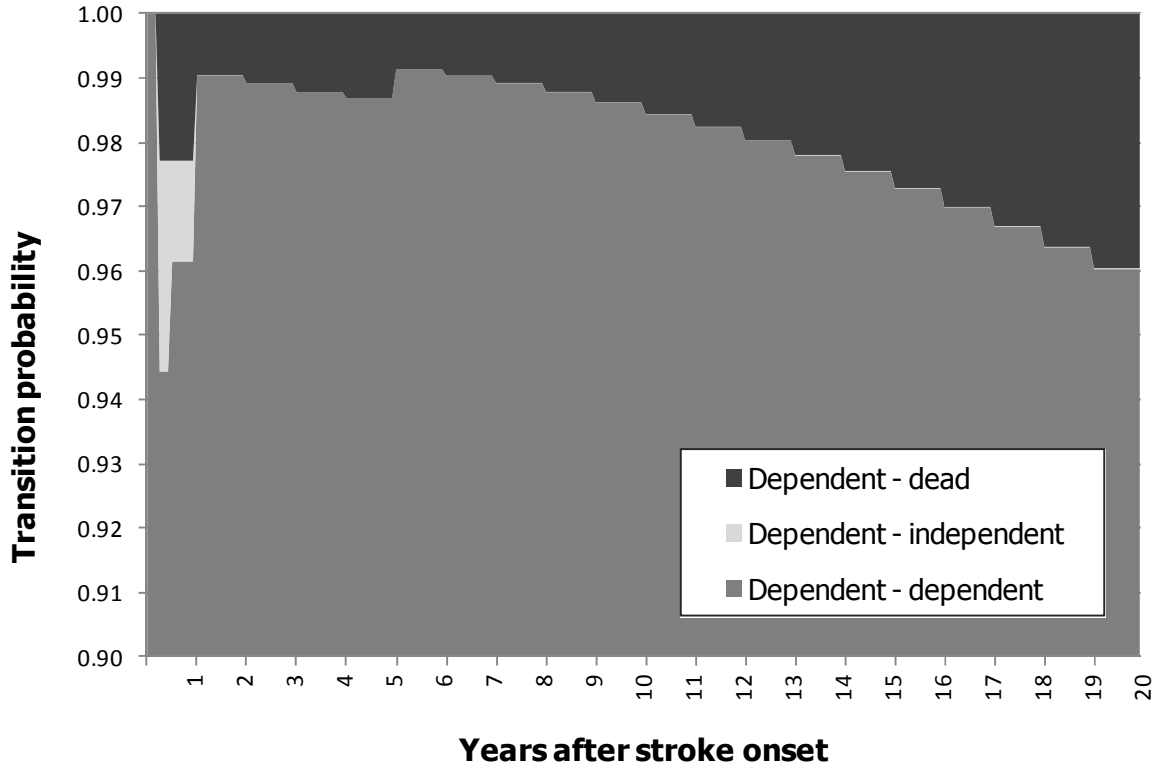
The monthly transition probabilities for those with functional independence are shown in Figure 6.3. In the period between three months and 12 months after stroke onset, there is an increased probability of transition to functional dependence or death. This reflects the fact that the risk of deterioration is greatest in the short term. The probability of transition to functional dependence is relatively stable after two years, but the probability of death increases reflecting the age profile of the cohort. It should be noted that in any cycle the most likely outcome for a patient with functional independence is to remain in that state.

Figure 6.3 Transition probabilities for those with functional independence



The monthly transition probabilities for those with functional dependence are shown in Figure 6.4. It is only possible to transition to functional independence in the period between three months and 12 months after stroke onset. There is also an increased probability of transition to death in the first year, again emphasising that the risk of deterioration is greatest in the short term. The probability of death increases steadily after five years reflecting the age profile of the cohort. It should be noted that in any cycle the most likely outcome for a patient with functional dependence is to remain in that state.

Figure 6.4 Transition probabilities for those with functional dependence



6.2.3 Estimates of cost

Costs were associated with transfer of patients to the treatment centres, treatments costs, and follow-up care costs. As the model calculated incremental costs, only cost items that were affected by the introduction of a mechanical thrombectomy service were included. As it was assumed that all patients undergoing mechanical thrombectomy would have first received IVT if appropriate, the cost of IVT was not included.

The cost of transferring patients was an important consideration, as it was assumed that all mechanical thrombectomy procedures will take place at one of two centres in Beaumont Hospital in Dublin and Cork University Hospital (Table 6.2). A large proportion of patients eligible for mechanical thrombectomy will therefore have to be transferred from the hospital in which they receive initial treatment. Data on the number of patients receiving IVT in each hospital were extracted from the Stroke Audit report.[99]

It was assumed that an emergency ambulance would have to travel from the nearest ambulance station to the hospital to collect the patient, drive to the nearest of the two planned treatment centres, hand over the patient to the treatment

centre, and then return to the originating ambulance station. The travel times between ambulance stations and hospitals, and between hospitals and treatment centres were computed using data from OpenStreetMap accessed through the osmr package in R.[100] Based on data from a 2015 HSE commissioned report on the capacity of National Ambulance Service,[101] it was assumed the call cycle would include 50 minutes in addition to driving time (five minutes from call to dispatch, 15 minutes at hospital receiving patient and 30 minutes at the treatment centre for patient handover). It was assumed that the ambulance would be available for dispatch once it signalled its availability on leaving the treatment centre. Repatriation of patients to their original treatment hospital was assumed to incur the same journey time, but not as an emergency transfer.

Based on 2015 data, the actual budget for the National Ambulance Service was €145.5 million, and the service responded to 303,502 call-outs.[36] The average call-cycle time is just over 85 minutes, suggesting an average cost of €5.85 per minute across all vehicle types. In the absence of formal data to support the estimate for a mean cost, a pragmatic estimate was generated. The mean cost was estimated based on an emergency vehicle trip costing twice as much as an urgent vehicle trip, which in turn was twice as much as a routine vehicle trip. The rationale for this estimate was that staff and equipment are scaled up in relation to the increasing complexity of cases dealt with.

These assumptions resulted in an estimated cost of €7.67 per minute. Upper and lower bounds were estimated to correspond approximately to almost the entire budget being spent on emergency vehicle trips and equal cost for all vehicles, respectively. The cost per journey for repatriation trips was determined using data from Beaumont Hospital regarding the repatriation of patients treated with mechanical thrombectomy by private ambulance, with an estimated average cost of €7.54 per minute. Although based on non-emergency vehicles, repatriation trips included the cost of an accompanying nurse and the transport for the nurse to return to the endovascular centre.

It was recognised that a proportion of patients may be transferred to a treatment centre by air ambulance. Based on the experience of the HSE's Acute Coronary Syndromes programme for patients requiring percutaneous coronary intervention for ST Elevation Myocardial Infarction (STEMI), approximately 7% of patients were transferred by air ambulance.[102] However, the treatment window for STEMI is 120 minutes, which is likely to create a greater demand for air transfer than mechanical thrombectomy. Based on one year of mechanical thrombectomy treatment data from Beaumont Hospital and Cork University Hospital, 5% of 200 hundred patients were brought by air ambulance.

For patients who are transferred to a treatment centre, it may be necessary to repeat the CT angiography if too much time has elapsed since the CT scan was carried out at the originating hospital. It was assumed that all patients whose transfer took more than 120 minutes would require a new CT angiography at the treatment centre. Based on combined data from Beaumont Hospital and Cork University Hospital, an estimated 29% of patients required a non-contrast enhanced CT scan prior to mechanical thrombectomy.

Table 6.2 Patient-transfer cost parameters

Parameter	Mean	(95% CI)
Proportion transferred from thrombolysis centre	0.877	(0.80 to 0.94)
Average transfer time (minutes)	125	(114 to 136)
Cost per minute of emergency ambulance transfer (€)	7.62	(6.26 to 9.27)
Cost per minute of ambulance for repatriation (€)	7.50	(6.17 to 9.12)
Proportion requiring air ambulance transfer	0.050	(0.024 to 0.084)
Cost per journey by air ambulance (€)	7,109	(5,844 to 8,648)
Proportion requiring extra head CT	0.290	(0.229 to 0.355)
Cost of CT angiography(€)	150	(123 to 182)

Notes: CT = computed tomography.

Based on the analysis of patient transfers, it was estimated that 65.5% (95% CI: 54.7% to 75.5%) of mechanical thrombectomy patients would be treated at the centre in Beaumont Hospital and the remainder at Cork University Hospital. This could vary if there is discretion regarding where to send patients coming from hospitals that are approximately equidistant from the two treatment centres. Equally, if treatment regions are defined for the two centres then the proportion of patients going to each centre could change. These proportions differ from those currently reported for mechanical thrombectomy in Ireland where 85% of patients are treated in Beaumont hospital; however, the current service has grown organically and as such may not be representative of the proportions achievable through a planned national service.

A mechanical thrombectomy service requires access to a biplane angiographic suite to carry out the procedure. While such facilities are available at Beaumont Hospital and Cork University Hospital, there may be insufficient capacity for a national service. In the main analysis, it was assumed that one new suite would have to be provided, and that it would be dedicated to acute management of stroke patients. It was anticipated that the suite would be used for other procedures for approximately 30% of the time. It was assumed that the service would leverage off existing capacity at the second site. That is, it would be prioritised for mechanical thrombectomy given the narrow treatment window for these procedures.

Two scenario analyses were undertaken: assuming two new suites, one at each centre; treating patients within existing capacity. It was assumed that, on average, 400 mechanical thrombectomy procedures could be carried out in a year in one suite. The capital costs associated with equipping the biplane angiography suite and necessary reconstruction costs were obtained from a business case developed by the Finance Department in Beaumont Hospital. The cost of a suite was amortised over 10 years. Consistent with usual practice, the cost of a maintenance contract averaging 10% of the purchase price of the equipment was applied to years two through 10 of the lifespan of the equipment.

The mechanical thrombectomy procedure requires the presence of a range of staff: consultant stroke physician, consultant interventional neuroradiologist, senior medical registrar, clinical nurse specialist, radiographer, radiology nurse, porter and cleaning staff. Based on data pooled from the published RCTs, the procedure from groin puncture to reperfusion takes an average of 73 minutes. This figure is approximately equivalent to the mean procedure time of 67 minutes published previously for mechanical thrombectomy procedures carried out at Beaumont Hospital.[103]

It was assumed that, on average, an additional 60 minutes of clinician and nursing time would be required in preparation for the procedure and immediately post-procedure. Porter and cleaning staff were costed for the 60 minutes of preparation and post-procedure time. An average of an additional 30 minutes of nurse time was included to monitor the patient in the radiology suite while awaiting admission to a ward or repatriation back to the originating hospital. Pay-Related Social Insurance (PRSI), pension and overheads were included as per the national guidelines. It was assumed that the clinical staff were full-time equivalents and that allowances apply.

The cost of procedure-related equipment was calculated using data from Beaumont Hospital for mechanical thrombectomy procedures carried out on 60 patients.[104] In the data a variety of mechanical thrombectomy devices were used, with an average cost of €2,830 per device. Other equipment used included catheters, stents and guidewires. The total equipment costs were an average of €4,250 per procedure.

Costs for hospital stay and long-term care were also estimated separately for mild stroke (mRS 0 to 2) and for moderate to severe stroke (mRS 3 to 5). These data reflect the differences in length of stay, complications, and complexity of care required depending on the functional status of the patient. Hospital and long-term care costs were derived from an economic evaluation of screening for atrial fibrillation.[105]

Table 6.3 Treatment and hospital cost parameters

Parameter	Mean	(95% CI)
Biplane angiographic suite		
Cost of biplane angiography suite and software (€)	2.00m	(1.96m to 2.04m)
Annual service/maintenance fee (after year 1) (€)	170,000	(163,433 to 176,784)
Number of new suites (base-case analysis)	1	
Number of new suites: scenario analysis 1	*2*	
Number of new suites: scenario analysis 2	*0*	
Proportion time dedicated to mechanical thrombectomy in new suites	0.70	(0.141 to 0.489)
Staff cost (€ per minute)		
Consultant stroke physician	3.08	(2.80 to 3.40)
Consultant interventional neuroradiologist	3.08	(2.80 to 3.40)
Senior medical registrar	2.23	(2.02 to 2.45)
Clinical nurse specialist	1.25	(1.14 to 1.38)
Radiographer	1.54	(1.40 to 1.70)
Radiology nurse	0.86	(0.78 to 0.95)
Porter	0.81	(0.74 to 0.89)
Cleaning staff	0.70	(0.64 to 0.77)
Hospital costs (€)		
MT procedure equipment	4,250	(3,854 to 4,698)
Duration of operation (mins)	73	(60 to 89)
Additional theatre time (mins)	60	(49 to 72)
Additional nurse time (mins)	30	(22.4 to 40.3)
Hospital stay for patient with functional independence	8,742	(7,154 to 10,602)
Hospital stay for patient with functional dependence	16,232	(13,292 to 19,642)
Hospital stay for patient that dies	14,299	(11,683 to 17,310)
Long-term care costs (€ per month)		
Cost of long term care with functional independence	360	(295 to 435)
Cost of long term care with functional dependence	2,229	(1,824 to 2,695)

6.3 Results of the cost-utility analysis

Stable estimates were obtained within 6,000 simulations, although the results presented here are based on the full 10,000 simulations.

6.3.1 Volume of patients

The analysis included an average of 268 (95% CI: 210 to 322) mechanical thrombectomy procedures a year (Table 6.4). The number of procedures was divided into 175 at Beaumont Hospital and 93 at Cork University Hospital. It was estimated that an average of 235 cases (95% CI: 180 to 286) would require ambulance transfer to one of the two treatment centres from the hospital where IV thrombolysis was initiated.

Table 6.4 Number of mechanical thrombectomy procedures by treatment centre

Location	Number of mechanical thrombectomy procedures	
	Mean	(95% CI)
Beaumont Hospital	175	(131 to 222)
Cork University Hospital	93	(61 to 129)
Total	268	(210 to 322)

It was estimated that ambulance transfers would generate 491 ambulance hours per annum (95% CI: 372 to 608) in each direction. That is, there would be an average of 491 emergency ambulance hours in transfers to the treatment centres, and an average of 491 hours of intermediate care vehicles hours for repatriation of patients.

6.3.2 Patient outcomes at three months

In the main analysis it was assumed that mechanical thrombectomy improved outcomes of functional independence and mortality at three months. The increase in numbers of patients achieving functional independence is shown in Table 6.5, indicating an additional 57 (95% CI: 38 to 78) patients achieving functional independence at three months.

Table 6.5 Patient outcomes at three months by treatment type

Treatment	Functional independence		Functional dependence	
	Cases	95% CI	Cases	95% CI
IV thrombolysis	102	(83 to 122)	156	(132 to 184)
Mechanical thrombectomy + IVT	159	(135 to 187)	108	(89 to 129)

6.3.3 Cost-utility analysis at five years

The main analysis was based on measuring outcomes at five years after stroke onset. The average cost per person was €2,626 more for mechanical thrombectomy plus IVT relative to IVT alone. In terms of outcomes, the intervention resulted in 0.187 more QALYs per person, on average, leading to an incremental cost-effectiveness ratio (ICER) of €14,016 per QALY.

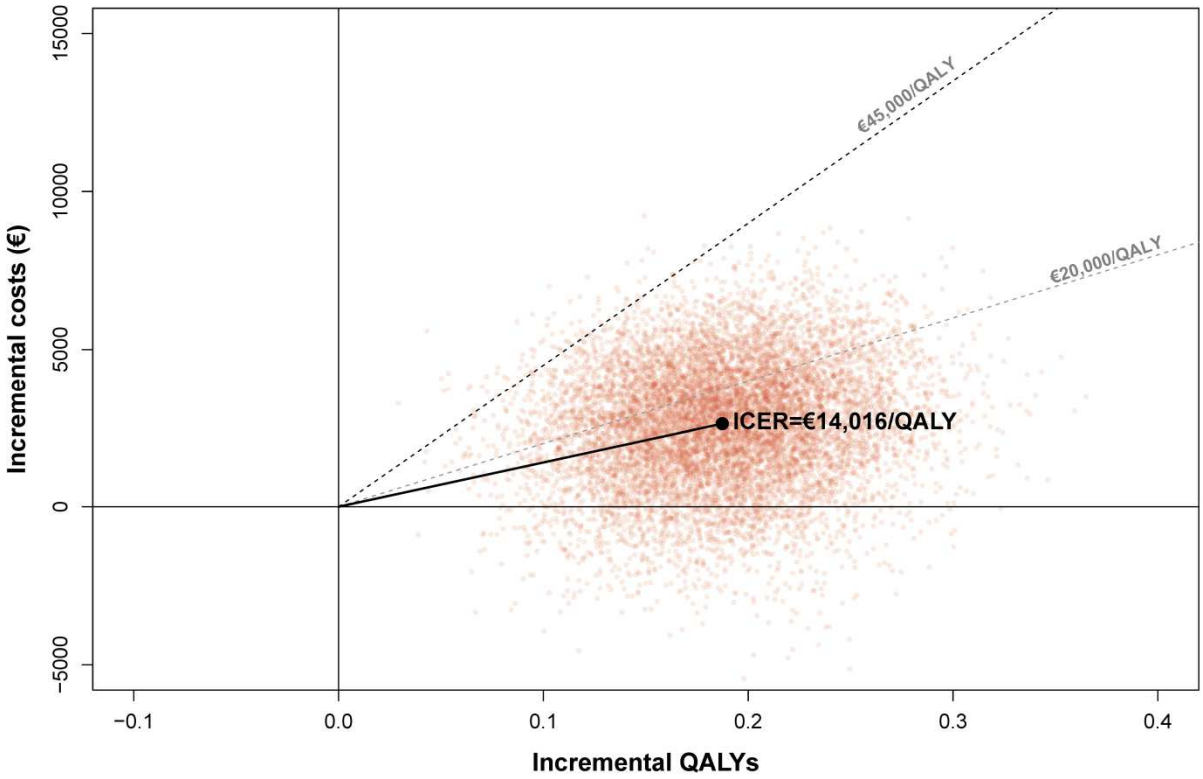
Table 6.6 Cost-effectiveness results based on QALYs

Treatment strategy	Cost (average per person)		QALYs (average per person)		ICER (€/QALY)
	Total	Incremental	Total	Incremental	
IV thrombolysis	€61,149		1.119		
Mechanical thrombectomy + IVT	€63,774	€2,626	1.306	0.187	14,016

Abbreviations: ICER, incremental cost-effectiveness ratio; IVT, intravenous thrombolysis; QALY, quality adjusted life year.

The cost-effectiveness plane shows the substantial variation around the estimates of incremental costs and benefits (Figure 6.5). In 70.1% of simulations, the ICER was less than €20,000 per QALY, and in 99.2% of simulations it was less than €45,000 per QALY. It should also be noted that there were no simulations in which mechanical thrombectomy plus IVT was less effective than IVT alone, and in 9.2% of simulations it was cost saving relative to IVT alone.

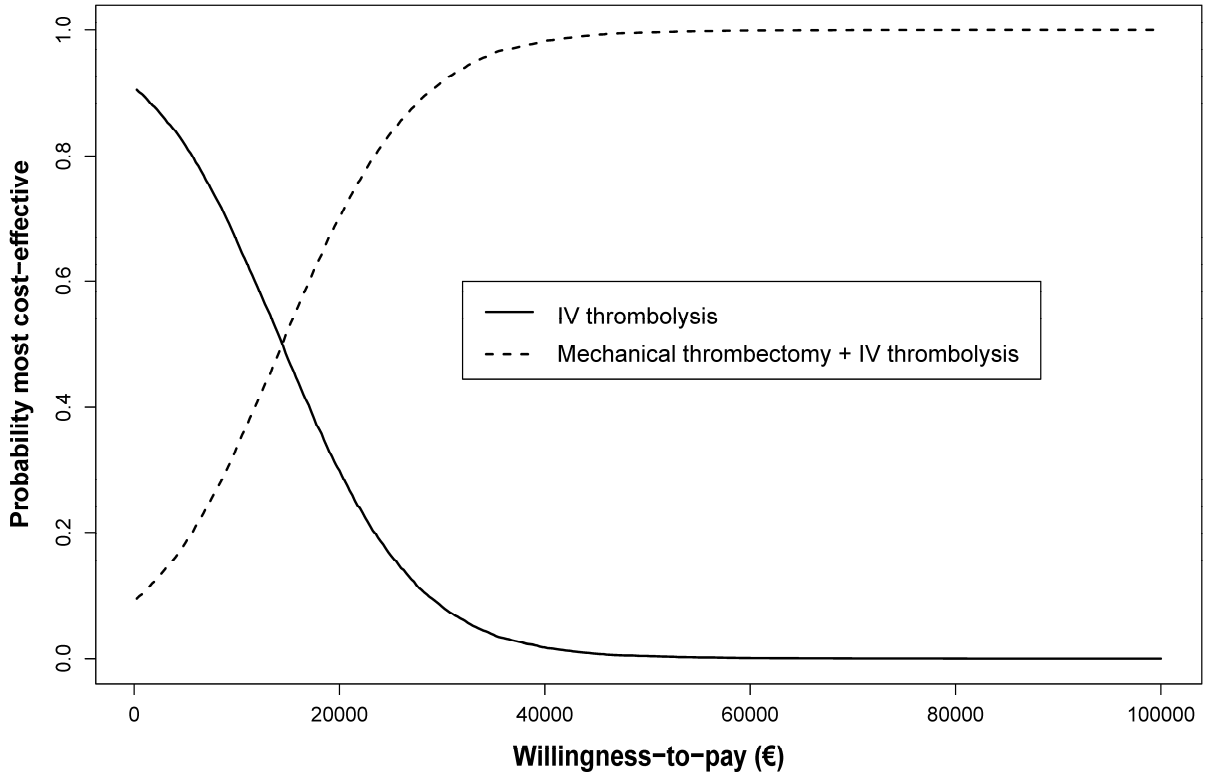
Figure 6.5 Cost-effectiveness plane for mechanical thrombectomy plus IV thrombolysis compared with IV thrombolysis alone



Notes: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

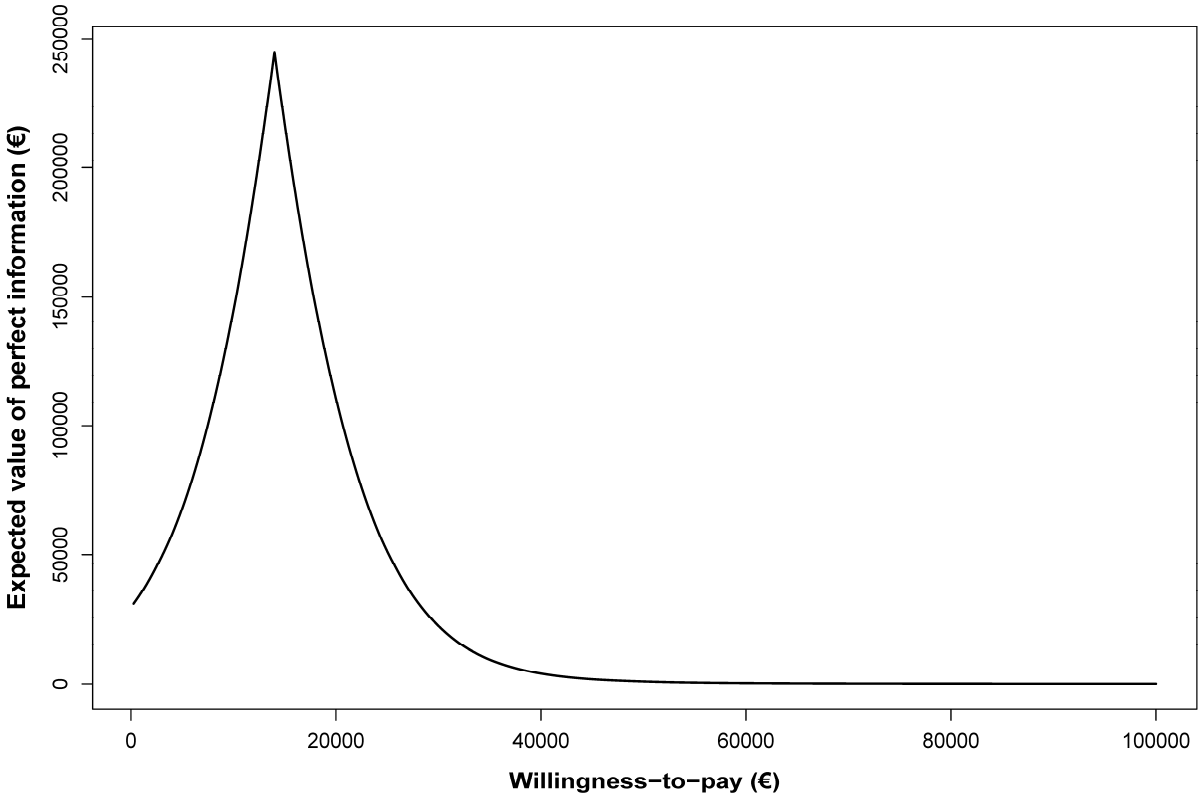
Up to a willingness-to-pay threshold of €14,250 per QALY, IVT has the highest probability of being the most cost-effective option (Figure 6.6). The probability of mechanical thrombectomy plus IVT being the most cost-effective option at thresholds of €20,000 and €45,000 per life year gained was 0.70 and 0.99, respectively.

Figure 6.6 Cost-effectiveness acceptability curve for mechanical thrombectomy plus IV thrombolysis compared with IV thrombolysis alone



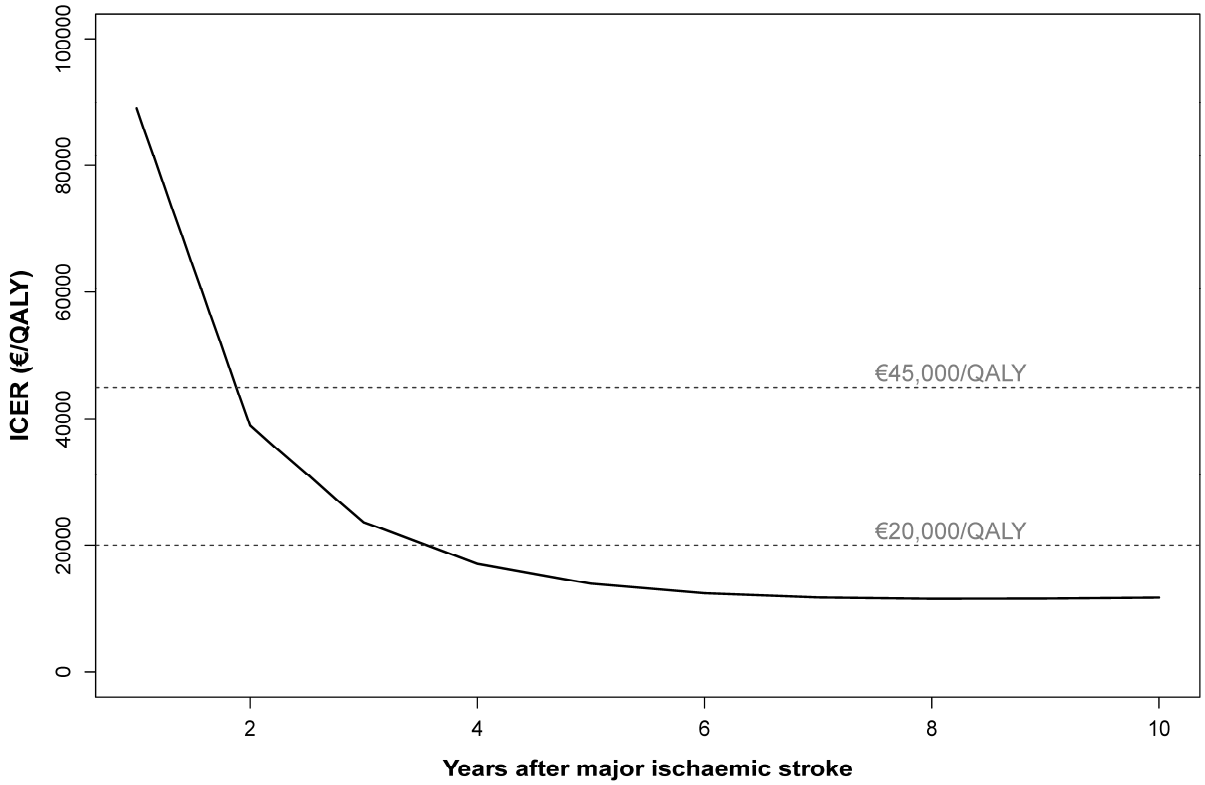
Corresponding to the cost-effectiveness acceptability curve, the expected value of perfect information reaches a peak of €244,977 at a willingness-to-pay threshold of €14,000 per QALY (Figure 6.7). The EVPI represents the amount a decision-maker should be willing to pay to eliminate uncertainty about which intervention is the best option.

Figure 6.7 Expected value of perfect information



The main results are reported at five years after stroke onset due to uncertainty regarding longer-term outcomes. The model was run over a longer time span to estimate the cost-effectiveness at up to 10 years after stroke onset (Figure 6.8). The ICER at 12 months after stroke onset is €89,014 per QALY. The high ICER is due to the additional up-front costs associated with the mechanical thrombectomy procedure, whereas QALY gains are accrued over many years. The ICER at three years is €23,613 per QALY after which it continues to fall to €11,807/QALY at year 10.

Figure 6.8 Incremental cost effectiveness ratios up to 10 years after stroke onset

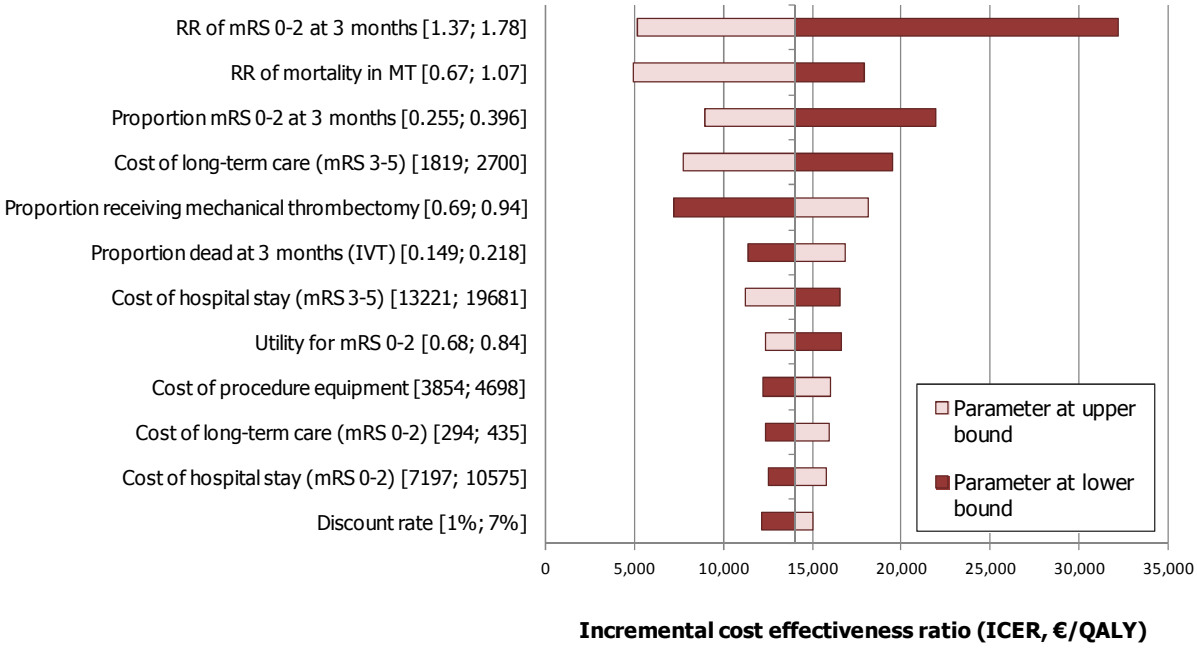


6.3.4 Univariate sensitivity analysis

A univariate sensitivity analysis was used to assess how sensitive the results were to fluctuations in each parameter. Given the uncertainty around the parameters themselves, the sensitivity analysis shows how that translates into uncertainty about the results.

The analysis investigated the impact of parameter variation on incremental cost-effectiveness (Figure 6.9). The parameters with most influence on the ICER related to the relative risk of functional independence at three months. If the risk ratio is above the mean then the ICER is reduced. At the upper bound for the risk ratio of 1.78, the ICER is an estimated €5,171 per QALY. The risk ratio associated with mortality is also an influential parameter. When the mortality rate is similar for IVT and mechanical thrombectomy, then the ICER is lower. This is because a lower mortality rate for mechanical thrombectomy implies a greater proportion of patients surviving with functional dependence. The poor QALY outcomes and substantial long-term care costs act to reduce the cost-effectiveness of mechanical thrombectomy.

Figure 6.9 Tornado plot of incremental cost-effectiveness ratio at five years



Note: only parameters that had a ±10% impact on the ICER are included in the tornado plot. All parameters were included in the analysis.

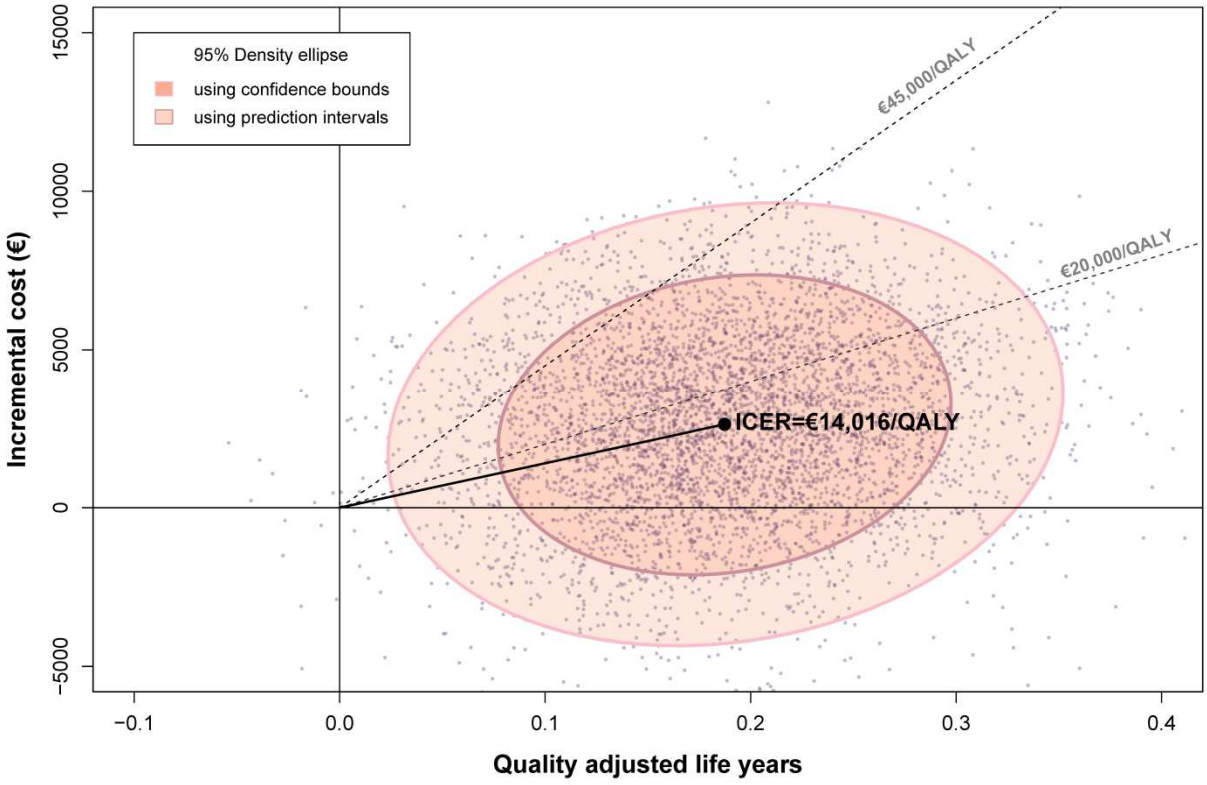
Only two parameters individually resulted in ICERs greater than €20,000 per QALY when set at their upper or lower bounds: the relative risk of functional independence at 90 days, and the proportion patients achieving functional independence at 90 days when treated with IVT alone. In both cases the ICER above €20,000/QALY was associated with the upper bound for the parameter value.

The three parameters with greatest influence on the ICER were obtained from RCT evidence. Given that these parameters are features of the performance rather than costs, it may be more difficult to predict or control what the observed values for these parameters will be in practice.

The uncertainty around the parameters defining patient outcomes from the RCTs was defined using the standard error of the treatment effects. The meta-analyses were based on random-effects analysis of six RCTs, and as such the standard error relates to the mean treatment effect. Alternatively, the prediction intervals can be considered. The prediction intervals provide an estimate of the distribution within which the treatment effect of a future study might fall. Prediction intervals tend to be wider than confidence bounds. Given that the anticipated volume of patients in Ireland is 268 per annum, which is not much larger than some of the trials included in the analysis, the use of prediction intervals may more appropriately capture the

uncertainty in treatment effect. Prediction intervals do not alter the mean treatment effect, only the width of the bounds of expected values. The base-case analysis was repeated using the prediction intervals for four parameters: probability of mortality at 90 days with IVT; risk ratio of 90 day mortality with mechanical thrombectomy; probability of functional independence with IVT in those surviving to 90 days; and risk ratio of functional independence with mechanical thrombectomy in those surviving to 90 days. The estimated ICER was unchanged, but the range of values increased markedly (Figure 6.10). There was a 17% chance of costing less than the standard of care (compared with 9% in the basecase analysis), and an 6.2% chance of having an ICER greater than €45,000 per QALY (compared with 0.8% in the basecase).

Figure 6.10 Cost-effectiveness plane for mechanical thrombectomy plus IV thrombolysis compared with IV thrombolysis alone with uncertainty in patient outcomes parameters defined using prediction intervals



In the evaluation of clinical effectiveness (Chapter 4), the difference in mortality was found to not be statistically significant. However, a 15% reduction in mortality can be considered highly clinically significant, particularly in the context of a mortality rate of 18% at 90 days. Had mortality been the only outcome of interest, then the lack of a statistically significant benefit would indicate a cost-minimisation analysis due to a lack of evidence of effect. In this analysis, it was found that assuming a

mortality benefit provided a conservative estimate of cost-effectiveness. The model was run assuming no difference in mortality resulting in an estimated ICER of €4,064/QALY at five years. Assuming no difference in mortality has the effect of reducing the proportion population with an outcome of functional dependence — an outcome associated with high long-term care costs and poor quality of life.

A final sensitivity analysis was used to explore the impact of differing distributions of mRS scores within functional groupings. Allowing the utility weights to vary between the two interventions had a small impact on the estimated incremental cost-effectiveness ratio. The ICER was €13,292 per QALY, which was slightly lower than the €14,016 calculated for the basecase analysis.

6.3.5 Scenario analysis

Two scenario analyses were considered: investing in a two biplane angiography suites; and only using capacity in existing angiography suites.

In the main analysis it was assumed that one new dedicated biplane angiography suite would be set-up for mechanical thrombectomy procedures only and existing angiography facilities may be used at the second site. Alternatively, two dedicated units may be developed. Under this scenario, costs would be increased with no expected change in patient outcomes under the assumption that timely access to the facilities is unaffected. The incremental costs increased from €2,626 in the main analysis to €3,175, resulting in an ICER of €16,947 per QALY at five years.

An alternative scenario would be that no dedicated biplane angiography suite would be developed at either centre, and instead existing facilities routinely available for other procedures are used. Again, it is assumed that patient outcomes would be unaffected. In this scenario the incremental costs were €2,318 and the estimated ICER was €12,374 per QALY.

The latter scenario analysis of reduced investment in biplane angiography suites assumes timely access to facilities within existing capacity at both treatment centres. Whether that is realistic would require an in-depth assessment of capacity.

6.4 Results of the budget impact analysis

A budget impact analysis was used to estimate the annual budget requirements of a national endovascular therapy service. The budget impact was calculated as the incremental budget impact for each of the first five years after the introduction of the service.

The cost of investment in the acquisition of a biplane angiographic suite and the associated construction works was accrued in the first year. The budget impact over five years was estimated at €7.2 million, with €3.3 million accruing in year one (Table 6.7). From year four onwards there is a potential for the endovascular service to be cost saving.

Table 6.7 Incremental budget impact of a national endovascular therapy service

Year	Budget impact (€ million) Mean	(95% CI)
1	3.29	(2.48 to 4.07)
2	1.23	(0.42 to 2.02)
3	1.00	(-0.01 to 1.95)
4	0.87	(-0.30 to 1.98)
5	0.81	(-0.51 to 2.07)
Total	7.21	(2.29 to 11.91)

As part of the budget impact, the staff resource requirements were also considered (Table 6.8). The calculations were based on the assumption that, on average, 65.5% of patients would be treated at Beaumont Hospital.

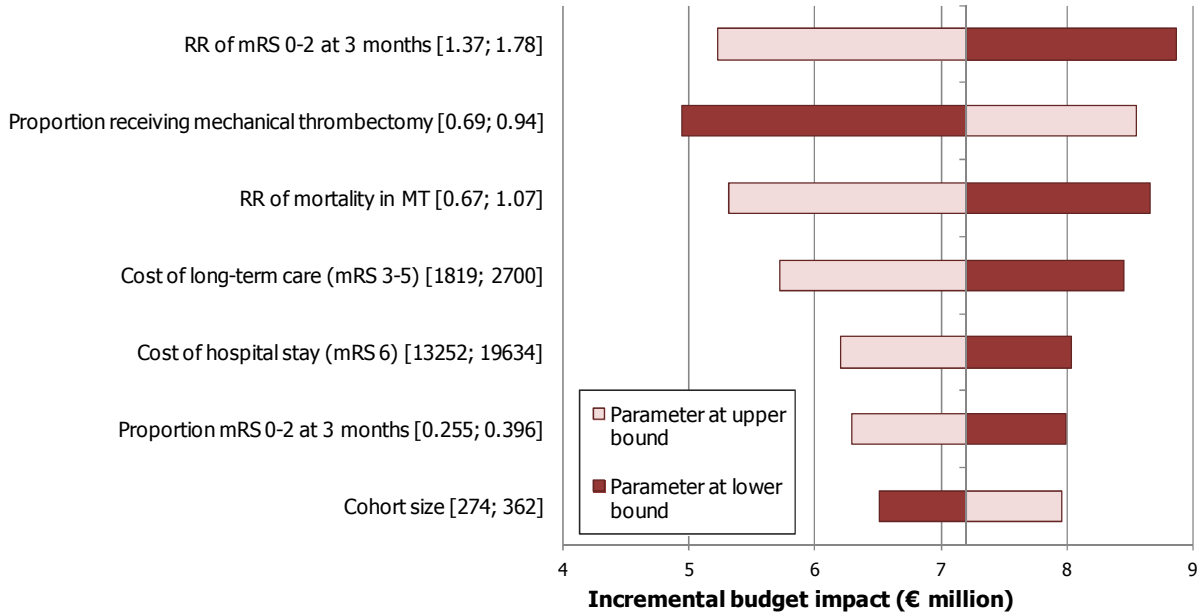
Table 6.8 Estimated number of whole-time equivalents required at each centre to deliver the national service

Grade	Beaumont Hospital Mean	(95% CI)	Cork University Hospital Mean	(95% CI)
Consultant stroke physician	0.24	(0.17 to 0.31)	0.13	(0.08 to 0.18)
Consultant neuroradiologist	0.24	(0.17 to 0.31)	0.13	(0.08 to 0.18)
Senior medical registrar	0.24	(0.17 to 0.31)	0.13	(0.08 to 0.18)
Clinical nurse specialist	0.24	(0.17 to 0.31)	0.13	(0.08 to 0.18)
Radiographer	0.24	(0.17 to 0.31)	0.13	(0.08 to 0.18)
Radiology nurse	0.29	(0.21 to 0.38)	0.15	(0.10 to 0.22)
Porter	0.11	(0.08 to 0.15)	0.06	(0.04 to 0.08)
Cleaning staff	0.11	(0.08 to 0.15)	0.06	(0.04 to 0.08)

A sensitivity analysis was used to evaluate the impact of different parameters on the estimated five-year incremental budget impact (Figure 6.11). The most influential parameter was the proportion of patients eligible for mechanical thrombectomy actually undergoing the procedure. As was observed for the incremental cost-effectiveness, varying the parameters for relative risk of functional independence and mortality at three months has a marked effect on budget impact. Set at their lower bounds, the parameters would increase the five-year budget impact to over €9

million, while at their upper bounds the budget impact would drop to below €6 million. Again, these parameters are all derived from RCT evidence.

Figure 6.11 Tornado plot of incremental budget impact over five years



Note: only parameters that had a ±10% impact on the incremental budget impact are included in the tornado plot. All parameters were included in the analysis.

The five-year budget impact was also estimated for the two scenario analyses (Table 6.9). Based on two dedicated units, the five-year budget impact would increase from €7.2 million to €9.3 million. Using only existing capacity and not investing in biplane angiography suites would reduce the budget impact to €5.9 million over five years. The latter scenario assumes that a national endovascular therapy service could be provided within existing capacity in terms of biplane angiography suites.

Table 6.9 Incremental budget impact of a national endovascular therapy service: scenario analyses

Year	Two dedicated units		Existing capacity	
	€ m	(95% CI)	€ m	(95% CI)
1	5.06	(3.90 to 6.12)	1.68	(1.02 to 2.35)
2	1.32	(0.52 to 2.10)	1.31	(0.48 to 2.12)
3	1.09	(0.09 to 2.04)	1.08	(0.06 to 2.05)
4	0.96	(-0.21 to 2.07)	0.95	(-0.24 to 2.08)
5	0.90	(-0.42 to 2.16)	0.89	(-0.44 to 2.16)
Total	9.33	(4.42 to 14.04)	5.91	(1.01 to 10.64)

The five-year budget impact was also estimated for the current ad hoc service (Table 6.10). The five-year budget impact of the proposed service with one new dedicated biplane angiography suite would be €2.78 million over the budget impact of the existing ad hoc service. Of the additional €2.78 million, €2.03 million will accrue in the first year arising out of the installation of a new biplane angiography suite.

Table 6.10 Incremental budget impact of a national endovascular therapy service: current ad hoc service versus proposed service

Year	Existing *ad hoc* service		Proposed service	
	€ m	(95% CI)	€ m	(95% CI)
1	1.26	(0.66 to 1.86)	3.29	(2.48 to 4.07)
2	0.98	(0.16 to 1.80)	1.23	(0.42 to 2.02)
3	0.81	(-0.26 to 1.84)	1.00	(-0.01 to 1.95)
4	0.71	(-0.57 to 1.94)	0.87	(-0.30 to 1.98)
5	0.67	(-0.80 to 2.06)	0.81	(-0.51 to 2.07)
Total	4.42	(-0.65 to 9.44)	7.21	(2.29 to 11.91)

6.5 Discussion

An economic model was presented in this chapter that was used to estimate the cost-utility of adding mechanical thrombectomy to standard medical care (that is, mechanical thrombectomy in conjunction with IV thrombolysis where appropriate) relative to standard medical care (IV thrombolysis alone) in the management of patients with acute ischaemic stroke. The parameters used in the model were derived from a wide variety of sources, some of which were subject to substantial uncertainty.

6.5.1 Main findings

Taking into account the assumptions used in the economic model and the uncertainty of the parameter values, the introduction of a national mechanical thrombectomy service involving one new biplane angiography suite would have an incremental cost-effectiveness ratio (ICER) of €14,016 per QALY.

Based on the evidence of six randomised controlled trials of second-generation mechanical thrombectomy devices, the intervention leads to substantially improved outcomes in terms of functional independence at three months. On the basis of 268 (95% CI: 210 to 322) patients treated with mechanical thrombectomy nationally, 57

(95% CI: 38 to 78) additional patients are predicted to achieve functional independence at three months (that is, increasing from 102 to 159 patients).

The probability of returning to functional independence when functionally dependent at three months is very low. The mortality rate is higher for functionally dependent stroke survivors than for those who are functionally independent. As such, mechanical thrombectomy in conjunction with IVT is associated with improved quality and quantity of life.

In terms of costs, the procedure has a substantial incremental cost over and above standard medical care (IVT alone), and this is reflected in the high incremental cost-effectiveness ratio at 12 months. However, as functional dependence results in markedly higher long-term care costs, the improved outcomes associated with mechanical thrombectomy mean that the ICER improves with longer time horizons. However, due to the substantial uncertainty in transition probabilities, the use of the five-year outcomes is advised for decision-making purposes.

6.5.2 Sensitivity and scenario analyses

Sensitivity analyses were used to identify which parameters had a substantial influence on the uncertainty in the estimated cost-effectiveness. The key parameters related to the proportion of patients achieving functional independence at three months, the mortality rate at three months and the proportion of patients undergoing the mechanical thrombectomy procedure.

The impact of varying the parameter values between their upper and lower bounds was substantial. These parameters were estimated using data from six randomised controlled trials. The trial sizes ranged from 70 to 500 participants, and thus were similar in size to the proposed national service. The most recently published trial, reporting the THRACE study, found a risk ratio of 1.27 for functional independence after mechanical thrombectomy. This figure was less than the lower bound used here. It was assumed for the analysis here that the average treatment effect across trials was relevant, but it must be borne in mind that the effect from any single trial could apply in practice.

The basecase analysis of cost-effectiveness and budget impact assumed the provision of one additional biplane angiography suite and a consistent volume of patients over time. Scenario analyses were used to investigate the impact of using only existing capacity to reduce the investment in dedicated biplane angiography suites, or to invest in two new suites. Leveraging off existing capacity reduced the ICER, although not substantially. Use of existing biplane angiography suite capacity for mechanical thrombectomy procedures may impact provision of other emergency

and elective endovascular procedures. Given the narrow timeframe within which mechanical thrombectomy is effective, other procedures may need to be delayed or deferred resulting in delays in treatment for these patients. With increasing numbers of stroke patients treated, it is inevitable also that more than one acute stroke case may present at a time creating delays to treatment for the second patient if only one suite is available. Investment in two new suites would increase the ICER and budget impact of a national emergency endovascular service. In the event that the number of eligible patients increases over time, then it may become necessary to consider the provision of a second dedicated biplane suite to ensure timely access and to minimise disruption to other services.

Further analyses looked at the impact of changing how patient outcomes parameters were defined in the model. Increasing the uncertainty in those parameters increased the uncertainty around the ICER. Using an assumption of no difference in mortality on the grounds that the difference observed in the trials was not statistically significant reduced the ICER to €4,064 at five years.

6.5.3 Limitations

Any economic analysis is subject to numerous limitations. Two key issues are the applicability of the included data and the structure of the model. The model used here was adapted from a model used for the Ontario HTA. The model was subject to rigorous calibration and was considered applicable to the Irish setting. The key differences in the model were the inclusion of additional costs relating to transfer of patients from other stroke centres and capital equipment.

The key parameters impacting on uncertainty in the ICER came from six randomised controlled trials. Only one of those six trials recruited the planned number of participants, the other trials stopping early. Although the trials typically stopped according to pre-specified criteria and on foot of planned interim analyses, it is still the case that trials that stop early are at risk of bias. In the event that the trials over-estimated the effectiveness of mechanical thrombectomy, that would have a negative impact on the estimated cost-effectiveness, although it is likely that the ICER would stay below €45,000 per QALY.

The nature of stroke is that its occurrence is unpredictable and requires rapid treatment. Ireland has a dispersed population who access thrombolysis via 27 sites around the country. The majority of patients require emergency ambulance transfer to an endovascular treatment centre. In the analysis, the cost of ambulance transfer was included both to and from the treatment centres. It was estimated that based on treating 268 (95% Ci: 210 to 322) patients a year, an average of 235 cases (95%

CI: 180 to 286) would require ambulance transfer, generating 491 ambulance hours both to and from the endovascular centres per annum. Although the cost of transfers was included, the National Ambulance Service is operating under capacity constraints such that investment may be required to enable the volume of transfers envisaged. The cost of such investment was not incorporated into the analysis.

The estimates of cost-effectiveness presented here are potentially conservative for a number of reasons. We included an estimated mortality benefit for mechanical thrombectomy, although the effect has not been shown to be statistically significant. Inclusion of a mortality benefit reduces the estimated cost-effectiveness by increasing the proportion of patients who are functionally dependent at 90 days. Under the assumption of no mortality benefit, the ICER is reduced to €4,064 at five years. This approach to estimating cost-effectiveness corresponds to the methodology used in other assessments, where the effect of mortality was not included on the grounds that it is not statistically significant.

Ambulance times were calculated as driving times on the road network. The driving times were not for emergency transfer, and may therefore overestimate the times in practice. Shorter driving times would reduce the costs of transfers and thereby reduce the ICERs, although such a change would have a limited impact on the ICER. The other conservative assumption regarded reporting results at five years. With longer time horizons, the cost-effectiveness improves. The average age of the cohort was assumed to be 70 years at onset of stroke. The life expectancy at age 70 years is 13 years for males and 16 years for females. For individuals achieving functional independence, a 10-year time horizon could be justified. Although reporting cost-effectiveness at five years is a conservative estimate, given the lack of data on life expectancy for people post-stroke, this approach was justifiable for the main reporting.

6.6 Key messages

- A Markov model was developed to simulate a cohort from stroke onset to 10 years post-stroke to determine the costs and benefits associated with providing mechanical thrombectomy in conjunction with standard medical care.
- An estimated 268 (95% CI: 210 to 322) thrombectomy procedures would take place in a year.
- With a national thrombectomy service, an estimated 57 (95% CI: 38 to 78) more patients would have regained functional independence at three months after stroke onset, increasing from 102 to 159 of 268 patients.
- The cost-utility of a national mechanical thrombectomy service with one new

dedicated biplane angiography suite was an estimated €14,016 per QALY.

- The estimated five year incremental budget impact of a national mechanical thrombectomy service assuming one new dedicated suite was €7.21 million, with €3.29 million accruing in the first year.
- The estimated five-year budget impact of moving from the existing ad hoc service (approximately 200 patients treated through exisiting facilities) to an organised national service is estimated to be €2.8 million (of which €2.0 million would be incurred in the first year).
- The calculated cost-utility is sensitive to the clinical effectiveness of mechanical thrombectomy in terms of achieving functional independence and mortality at 90 days. Although the underlying trials demonstrate a treatment effect, there is uncertainty about the magnitude of that effect. Under the assumption of no treatment effect on mortality, the incremental cost-effectiveness is €4,064/QALY.
- An estimated 235 cases (95% CI: 180 to 286) would require ambulance transfer from the hospital in which IV thrombolysis was initiated to one of the two proposed centres carrying out mechanical thrombectomy. The transfers would generate 491 (95% CI: 372 to 608) emergency ambulance hours per annum in transfers to the treatment centres, and the same number of hours again to repatriate patients by intermediate care vehicle to the referring hospitals.

7. Organisational and social aspects

This chapter provides a review of the potential implications of changes to stroke care within the Irish health system and for society as a whole. The purpose of this review is to identify and discuss any broader issues relevant to the decision-making process, and to highlight potential changes to the organisation or delivery of services required to support changes to stroke care. This chapter was developed broadly in line with the structure described in the EUnetHTA Core Model.[128]

7.1 Organisational aspects

The review of clinical effectiveness in this assessment suggests that mechanical thrombectomy is effective and safe in the management of acute ischaemic stroke. However, to incorporate the procedure into the routine management of acute ischaemic stroke in Ireland, there are a number of issues that must be considered in planning and delivering stroke services.

As noted in Chapter 2, to be consistent with the clinical trial evidence and international consensus guidelines, mechanical thrombectomy should be confined to comprehensive stroke centres with access to neurosurgical care, advanced brain imaging and appropriate neuroendovascular expertise. Currently, such access is limited in Ireland, with interventions provided in just two hospitals (Beaumont Hospital and Cork University Hospital [CUH]).

In 2016, 85% of all procedures (170 out of 200) were performed in Beaumont Hospital, which provides a 24-seven service. The service in CUH is currently only resourced to provide a 9am to 5pm service, Monday to Friday, so has limited capacity to accept patient transfers.[39] There are a number of issues which need to be addressed if patients with acute ischaemic stroke who could potentially benefit from mechanical thrombectomy are to be facilitated in receive it. These may be categorised into pre-hospital, individual hospital and system-wide (including community) factors.

A key consideration in assessment of eligibility for mechanical thrombectomy is the time elapsed from symptom onset to the time of intervention. The evidence presented in the meta-analysis is based on trials involving cohorts of patients who were managed within six hours of symptom onset. It is therefore concerning that the time of onset of symptoms is unknown in 38% of patients presenting with acute stroke in Ireland (33% in the UK) and that nationally the median time from onset of symptoms to presentation varies appreciably by hospital (national median 2 hours 26

minutes, range 1 hour 32 minutes to 4 hours 24 minutes).[39] Indeed, 22% of patients arrive at hospital more than six hours after symptom onset.[39]

One possible explanation for these delays is that less than two out of three patients who experience a stroke in Ireland present by ambulance to hospital. This is substantially less than the 82% observed in the UK in 2014.[55] The European Stroke Guidelines specify that public recognition of stroke is a vital part of successful stroke care and plays an important role in the stroke 'chain of survival'.[7]

The FAST campaign (2010-2015) funded by the Irish Heart Foundation aimed to improve awareness of the symptoms of stroke among the general public, thereby promoting timely presentation to hospital. This was regarded as a success in the short term, however, its effects have not been sustained over the longer term.[106] If the numbers of patients eligible for mechanical thrombectomy are to be improved, then the general public must continue to be educated on the importance of presenting early following onset of symptoms and, consequently, a new public awareness campaign on recognising stroke symptoms may be required.

In addition to public awareness, the other 'pre-hospital' factor that influences stroke care is the ability of the ambulance service to swiftly transport patients to appropriate receiving hospitals. The National Ambulance Service implemented a 'bypass protocol' for patients experiencing acute stroke in 2014; the protocol facilitates the rapid transfer of a suspected acute stroke patient to a hospital with a designated thrombolysis service. While the effectiveness of this protocol has not yet been audited, it is likely to provide a template upon which to base the transportation of patients to centres performing thrombectomy.

Evidence of the ability of the National Ambulance Service to swiftly transport patients to appropriate receiving hospitals may also be evident from its management of ST elevation myocardial infarction (STEMI) patients. A bypass protocol was put in place for these patients in October 2012, so that these patients can be transferred directly to one of nine Primary Percutaneous Coronary Intervention Centres (PPCIs) nationally, located in Cork, Dublin, Galway, Limerick and Waterford. Once a STEMI patient is identified, the goal is to transport the patient by land or air to a PPCI centre in less than 90 minutes. In line with criteria set out by the European Society of Cardiology, the treatment window from first medical contact to treatment is 120 minutes. In 2015, 88.5% of STEMI patients without contraindication to reperfusion therapy obtained PPCI. Transporting these patients is different to that of the acute stroke patient as the patients may be transported directly from the field rather than via another hospital and because

there are a larger number of receiving hospitals, allowing for shorter transport distances. The treatment window is, however, shorter.

Use of existing ambulance capacity to transfer patients, either by transferring patients from one acute hospital to a tertiary referral centre or by bypassing an acute hospital creates logistical issues for the National Ambulance Service. Aside from the economic cost of the transfer, there is an opportunity cost because deploying existing ambulances to transfer patients potentially long distances (for example, from Mayo General Hospital to Beaumont Hospital) leaves the referring area with reduced or no ambulance cover for the total duration of the ambulance trip.

The number of additional thrombectomy patients requiring transfer may be insufficient to justify additional ambulance capacity in the individual National Ambulance Service-defined areas. However, it is evident that in response to reorganisation of services by the Health Service Executive (HSE), the implementation of bypass protocols by the National Ambulance Service is growing, with such protocols already in place for thrombolysis and STEMI patients. Implementing bypass protocols for acute trauma cases and emergency hip replacement following a fractured neck of femur have also been discussed. On aggregating numbers across these protocols there may be sufficient cases on a weekly basis in certain areas to justify additional ambulance capacity for a transfer service.

In planning any additional National Ambulance Service capacity, the availability of trained emergency medical services staff will also need to be considered. It has been noted that there is an existing national shortage of paramedic staff and given the time to fully train new paramedics (up to two years), this may represent a capacity constraint in the short to medium term.

If patients are encouraged to present without delay following onset of symptoms, then the hospitals to which they present must equally be equipped to manage their pathology in a timely manner. As seen in the data presented in this HTA, access to appropriate and timely imaging is central to maximising outcome. Moreover, in a 2016 sub-analysis of the ESCAPE trial, it has been demonstrated that every 30-minute increase in CT-to-reperfusion time reduces the probability of achieving a functionally independent outcome by 8.3%.[107] Unfortunately, while all hospitals managing stroke in Ireland have 24-hour access to on-site CT scanning, the median time from onset of symptoms to performance of neuroimaging is 15 hours and 44 minutes, and over 30% of patients are not scanned within 24 hours. While some of this delay is due to patients presenting late at the hospital, there is also evidence of substantial delays in care within institutions — the 2015 National Stroke Audit

reported that the median time from presentation to scan ('door to scan time') is 9 hours and 23 minutes.[39]

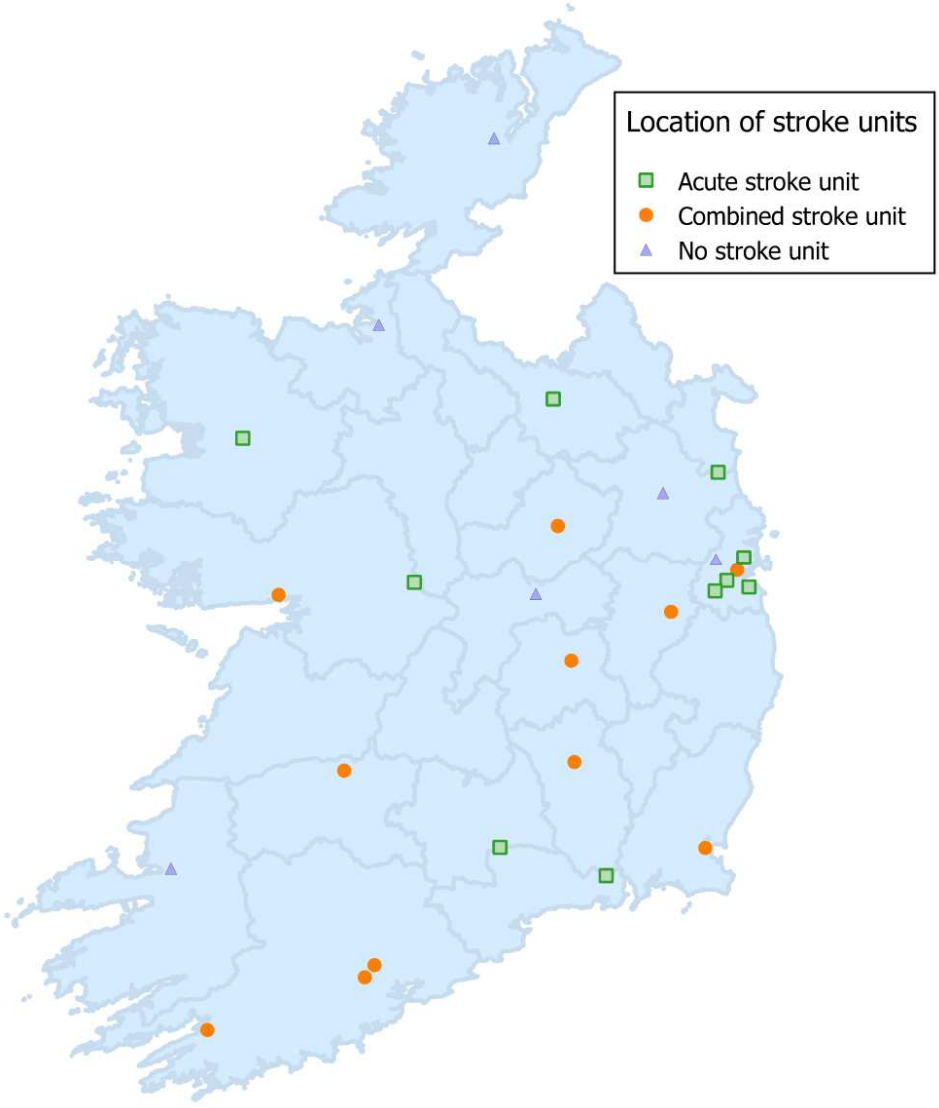
Imaging is just one component of the care pathway in mechanical thrombectomy, but the issues outlined above are illustrative of the challenges faced by individual units providing care for stroke patients. The majority of the hospitals that participated in the randomised controlled trials (RCTs) included in this analysis are high-volume stroke centres where the procedures were carried out in ideal circumstances.[53] It is doubtful whether the stroke management systems in place in these institutions could be replicated on a widespread basis in hospitals around Ireland.

While stroke units are available in 78% of receiving hospitals (21 of 27, see Figure 7.1), less than one in three patients (29%) are admitted to these units at presentation.[39] Even if all patients were admitted to these units at presentation, it is unrealistic to expect that each of these units would have appropriately trained clinicians capable of delivering endovascular procedures on-site or that the volume of patient throughput at multiple individual sites would be sufficient to maintain expertise. Such expertise would, for example, include interventional neuro-radiologists, a dedicated neurointensive care unit and neurosurgical (including vascular) expertise.

Furthermore, it will not be feasible from a health system perspective to provide 24-hour, seven day cover for mechanical thrombectomy in all of these stroke units. Therefore, if the encouraging results demonstrated in this meta-analysis are to be replicated in Ireland, the procedure will need to be developed and offered in a small number of centres that are adequately resourced and sited to maximise patient access, workforce expertise and coverage.

One potential solution is the development of a 'hub and spoke' model with referral to 'comprehensive' centres of excellence helping to improve workflow, treatment times and, ultimately, clinical outcomes.[108] The most appropriate configuration of this model for Ireland remains to be made clear, but there are precedents upon which to base this, not least of which is the aforementioned Acute Coronary Syndromes Model of Care which designated six hospitals as Primary Percutaneous Coronary Intervention (PPCI) centres in 2012.[109] A mapping exercise undertaken as part of the rollout of this Model reported that 81% of the Irish population, aged over 55 years, lives within a 90-minute drive time to Dublin, Cork and Galway.[109]

Figure 7.1 Locations of public acute hospitals treating patients with acute stroke in Ireland



The case series published by Beaumont Hospital in 2015 also provides evidence in support of a 'hub and spoke' model. Of 93 patients included in that case series, 57 were transferred from another institution; the authors reported similar outcomes in terms of 90-day function, symptomatic haemorrhage, and 90-day mortality for the direct and transferred groups. This was despite a slightly longer time from symptom onset to first pass of endovascular device in the transferred group (288 minutes) than in the directly presenting group (254 minutes).[56] It is also noted that mechanical thrombectomy is being performed in Belfast at present. There may be value in considering how this service might contribute to the development of an all-island approach to providing mechanical thrombectomy.[110]

Therefore, a combination of approaches — raising public awareness of the need for timely presentation, formalising pre-hospital arrangements for emergency care and transport, and designation of comprehensive stroke centres whose workflow practices have been maximised — can ensure that a substantial majority of those who would benefit from mechanical thrombectomy receive it.

Coordination of these approaches and, in particular, designation and efficient working of 'comprehensive' stroke centres will require a number of 'foundation stones', as was evidenced during roll-out of the acute coronary syndromes model of care [(109)]:

- ensure national agreement
- implement the programme robustly
- ensure readiness in pre-hospital sector
- understand and deal with the knock-on effects on various parts of the system
- understand and plan for staffing requirements
- clarify costs of implementation
- set out clear monitoring and evaluation parameters.

Many of these elements are already in place for stroke care in Ireland. The National Clinical Programme for Stroke was launched in 2010 and has resulted in improvements in the organisation and delivery of stroke care in Ireland. This is perhaps best illustrated by improvements in rates of thrombolysis nationally. Between 2007 and 2015, there was a tenfold increase in these rates, with 12.3% of patients with acute ischaemic stroke now benefiting from this treatment, a figure comparable with that reported internationally (12% in the UK in 2014).[(36-39, 55)] However, the implementation of a coordinated national service for mechanical thrombectomy will bring unique and additional challenges, and the exact model for its delivery in Ireland has yet to be refined.

It is in this context that an assessment of the cost-effectiveness, budget impact and resource implications for the Irish healthcare setting was undertaken with a view to informing decision-making. The model assessed was based on providing a national acute endovascular service from two sites: Beaumont Hospital in Dublin and Cork University Hospital (CUH). Both are tertiary referral sites for endovascular procedures, although CUH is only resourced to provide a 9am to 5pm, Monday to Friday service and thus has only limited capacity to accept transfers. While potentially insufficient for providing the number of procedures required by an organised national service, both have the minimum necessary equipment and access to experienced neurointerventional radiologists capable of undertaking these

procedures. The estimates of cost-effectiveness and budget impact were based on a minimum number of staff being present when the procedure is being undertaken. This staffing was outlined in Chapter 6, Table 6.3 and included the following clinical staff: a consultant stroke and neuroradiology staff, a medical registrar, two nursing staff and a radiographer. As noted in Chapter 3, data from the 2015 National Stroke Audit indicate that 55% of acute stroke patients present to the emergency deparment outside of office hours (Monday to Friday, 9am-5pm). Given time delays associated with the initial diagnosis and management of patients at their local acute stroke service and transportation to the tertiary treatment site, and the limited treatment window for mechanical thrombectomy, timely access to this procedure will depend on these sites being resourced to provide 24-seven access to thrombectomy.

Taking into account the assumptions used in the economic model and the uncertainty of the parameter values, the introduction of a national mechanical thrombectomy service involving one new dedicated biplane angiography suite was found to be cost-effective under typical willingness-to-pay thresholds applied in Ireland. As the procedure has a substantial incremental cost over and above current standard of care (IVT alone), a high incremental cost-effectiveness ratio (ICER) was found at 12 months. However, as functional dependence results in markedly higher long-term care costs, the improved outcomes associated with mechanical thrombectomy mean that within five years the ICER fell to €14,016 per QALY, declining to €11,807 per QALY when 10-year outcomes are used. Given the substantial uncertainty in transition probabilities, the use of the five-year outcomes is advised for decision-making purposes.

While mechanical thrombectomy procedures have been provided to date (200 procedures in 2016) using the existing facilities in Beaumont Hospital and Cork University Hospital. Use of existing biplane angiography suite capacity impacts delivery of other emergency and elective therapeutic endovascular procedures (for example, coiling of cerebral aneuyrsms). Data from Beaumont Hospital indicate that it provides on average 350 therapeutic interventional procedures and 500 to 700 cerebral angiograms each year using one neurovascular biplane angiography suite. Increasing use of this existing suite for acute stroke cases, means that other emergency procedures are delayed and elective procedures rescheduled, with potential consequences for the timely and efficient provision of care for these patients. The basecase analysis of cost-effectiveness and budget impact assumed the provision of one additional biplane angiography suite and a consistent volume of patients over time. In the event that the number of eligible patients increases over time, then it may become necessary to consider the provision of a second dedicated biplane suite to ensure timely access and to minimise disruption to other services.

This meta-analysis of clinical effectiveness demonstrated the rapid pace with which endovascular technologies are evolving. As with any technology or service, this evidence base will continue to evolve, so there is a need to ensure that key performance indicators (KPIs) are identified and that reporting against these measures takes place. Much of the background work for this is already in place though the National Audit of Stroke Care,[39] the Hospital In-Patient Enquiry Reporting (HIPE) Scheme[111] and specifically through the National Stroke Register, which is based on data recorded within the HIPE system.[51] It is recommended that KPIs for mechanical thrombectomy are identified and that the National Stroke Register is used to audit practice against these.

Finally, the meta-analysis demonstrated improved outcomes for patients with acute ischaemic stroke in relation to disability, morbidity and function at 90-day follow-up. The benefits of this at the individual and societal level are obvious. However, if more patients are being discharged back in to the community (as opposed to step-down or long-term residential care facilities) this may place additional burden on community-based post-stroke service provision. A 2012 study of this service in Ireland noted that there were, 'major gaps in the provision of community-based inter-disciplinary team services for people with stroke…. (and) where services existed, they were generic in nature, rarely inter-disciplinary in function and either deficient in (or completely deprived of) input from salient disciplines.'[112]

Just as integration of pre-hospital and hospital-based care is essential to improving outcomes in the acute phase of stroke management, so too must hospital and community-based services be integrated to ensure optimal outcomes in the post-acute phase. As noted in the 2011 National Policy and Strategy for the Provision of Neuro-Rehabilitation Services in Ireland, 'neuro-rehabilitation teams cannot function successfully without close links and associated referral pathways forged with other sectors of the HSE not directly involved in neuro-rehabilitation.'[113]

To optimise outcomes for survivors of stroke, the proposals contained in the Policy for the Provision of Neuro-Rehabilitation Services would need to be considered. In particular, consideration should be given to its central recommendation — that regional and local neuro-rehabilitation networks should be developed — in order that stroke survivors are able to fully participate physically, psychologically, socially and economically in everyday life in Ireland.

7.2 Key messages

- Currently, there is limited access to mechanical thrombectomy in Ireland with interventions provided in just two hospitals: 85% of procedures (that is approximately 170 out of 200 procedures) were performed in Beaumont Hospital in Dublin in 2016.
- If all patients who could benefit from mechanical thrombectomy are to be given this opportunity, then a series of pre-hospital, hospital and system-wide factors need to be addressed in any service expansion to achieve timely, efficient delivery of safe and effective care.
- Effective care is predicated on the timely delivery of the intervention with only a narrow treatment window available between the onset of stroke symptoms and the time that treatment must be started. Delays in the presentation of patients to the hospital can occur due to poor awareness of the symptoms and management of stroke, or due to transport and logistical issues. These delays need to be minimised.
- Development of a national mechanical thrombectomy service has potentially significant organisational and resource implications for the National Ambulance Service in order to ensure timely transport of patients to the appropriate receiving hospitals and to facilitate repatriation of the patients post-intervention.
- Within hospitals there is a need for timely imaging and assessment to facilitate treatment initiation, the availability of appropriate expertise in the delivery of the intervention and the management of the patient in the hyperacute period. This will necessitate having a trained, resourced workforce which is capable of delivering a mechanical thrombectomy service that achieves comparable outcomes to those observed in the published clinical trials.
- An equitable, efficient and cost-effective national thrombectomy service is contingent on the procedure being offered in a small number of centres that are adequately resourced and sited to maximise patient access, workforce expertise and geographical coverage.
- Expanded access to mechanical thrombectomy has potential implications for community-based services with the potential requirement for increased availability of community-based rehabilitation to ensure patients can achieve optimal outcomes in the post-acute phase.
- An organised mechanical thrombectomy service will necessitate detailed service planning to ensure it adheres to requisite quality standards. This includes the development of quality key performance indicators to measure performance against targets or expectations.

8. Ethical issues

This chapter considers the key ethical issues that should be considered in relation to providing mechanical thrombectomy in Ireland. This chapter was developed broadly in line with the structure described in the EUnetHTA Core Model.[114] It should be noted that mechanical thrombectomy procedures have been carried out in Ireland since 2010, including as part of one of the randomised controlled trials (ESCAPE) reported in the clinical effectiveness chapter.

8.1 Balance of benefits and harms

Based on the review of clinical effectiveness, under the current standard of care (IV t-PA alone) approximately 33% of patients have functional independence and 18% have died 90 days after stroke. The remaining 49% of patients survive with moderate or severe functional impairment and require some degree of care assistance. It is assumed that 90-day functional status does not improve over the longer term, and may in fact deteriorate. From this, it can be seen that based on standard medical care, only a minority of people experiencing stroke will be functionally independent after rehabilitation.

The mechanical thrombectomy procedure is associated with improved functional outcomes, with approximately 51% of patients having functional independence at 90 days, and roughly 33% having functional dependence. From the analysis of safety, mechanical thrombectomy was shown to be associated with a higher rate of any cerebral haemorrhage and there was some evidence of a higher rate of recurrent stroke at 90 days. However, the intra-procedural and longer-term adverse effects do not outweigh the benefits of improved functional outcomes.

Disability due to stroke gives rise to demand for long-term care in the form of community services, residential care, and care in the home. Care in the home may place a significant burden on family members through the provision of informal care and support. An intervention that improves functional outcomes and reduces the need for long-term support provides a clear benefit not only to the survivors of stroke, but also to their families and society.

The estimates of benefits and harms are derived from pooled randomised controlled trial (RCT) evidence, which represents the highest level of evidence. A salient lesson from the poorer outcomes associated with the first three published RCTs is that the appropriate selection of patients and the time to treatment are critical to treatment success. The populations included in the trials, and the manner in which the intervention was delivered, may differ from the current profile of service provision in

Ireland. However, published evidence from the main hospital currently providing this service in Ireland suggests that practice and outcomes are broadly in line with that reported in the clinical trials.

8.2 Autonomy and respect for persons

In the medical context, respect for autonomy, or self-rule, is of vital significance in relation to consulting with and informing patients about their healthcare and their choices. With the exception of cases of incapacity or medical emergency, it requires doctors to obtain informed consent from patients before any treatment or intervention. Stroke is an acute event and timely treatment is essential to improve outcomes. Standard medical care, IV t-PA, must be administered within 4.5 hours of symptom onset to be effective. Symptoms of stroke include difficulty with speech, confusion, and paralysis of the face, arm or leg. It may not be possible to obtain informed consent from the individual prior to the provision of the medical intervention. In this regard, mechanical thrombectomy is not different to other thrombolysis or endovascular procedures in that the patient's condition may preclude them from giving informed consent.

As mechanical thrombectomy is proposed as an adjunct to standard medical care, it is a procedure that will be used if IV t-PA is contraindicated or in the event that successful thrombolysis is not achieved using IV t-PA. A potential additional benefit of mechanical thrombectomy is the extension of the window for treatment for certain selected patients relative to thrombolysis which must be initiated within 4.5 hours of stroke onset. In selected patients, RCT indicate that mechanical thrombectomy is a safe and effective procedure when provided within six to 12 hours of stroke onset. There may be a considerable lag between the onset of symptoms and confirmation that the individual has experienced a stroke (including so-called 'wake up strokes'), mechanical thrombectomy provides some additional prospects for successful treatment in selected cases with favourable imaging.

The infrastructure for stroke care and endovascular treatment is likely to be such that patients may receive IV t-PA at a stroke centre before a decision is made to transfer the patient to another centre for mechanical thrombectomy. Consideration should be given to the potential impact of transferring patients over potentially large distances, and whether this could adversely affect outcomes relative to the benefits of mechanical thrombectomy.

There is strong professional support for the provision of mechanical thrombectomy. On the basis of the RCT evidence, there a consensus that mechanical thrombectomy should form a critical component in the treatment of acute ischaemic stroke. It is

recommended that the use of endovascular therapy be limited to centres with advanced neuroimaging capability, coordinated stroke care, specialist stroke teams including expertise in the performance of interventional neuroradiology, and a stroke unit to provide appropriate care after the hyperacute period. A potential impact on clinicians is that patients under their care may be transferred to other stroke centres for mechanical thrombectomy. However, there is precedence as with standard medical care, patients may be transferred to avail of other endovascular or specialist stroke services.

8.3 Justice and equity

Mechanical thrombectomy is an endovascular procedure like intra-arterial thrombolysis, which is already available. Given the demonstrated efficacy of mechanical thrombectomy, equity issues could arise if the procedure is not made available to all eligible patients. In Ireland this may occur due to geographic disparities in timely access to specialist stroke care in the hyperacute period (first six to 12 hours) and disparities in onward referral to stroke centres providing mechanical thrombectomy. Older people have a higher risk of stroke, and Ireland has a substantial rural elderly population. The time frame for providing mechanical thrombectomy is longer than for IV t-PA. While geographic disparities may be reduced for some selected patients than for the current standard of care which must be provided within a 4.5 hour window, the additional time associated with transferring patients to tertiary treatment centres means that disparities in access are likely to persist unless the variation in initial access to stroke care is addressed.

A well-functioning and coordinated ambulance service is necessary to ensure that patients are brought to the appropriate centres and, if necessary, transferred to centres providing mechanical thrombectomy. The use of existing ambulance services to transfer patients to tertiary referral centres, however, has potentially significant implications for other patients in that region as it may leave the area with a reduced ambulance service for the duration. Consideration must be given to how ambulance bypass and transfer protocols are implemented across a range of services to ensure that the other patients in any given area are not adversely impacted by these arrangements.

The equitable provision of mechanical thrombectomy must be supported by a reorganisation of stroke services. These infrastructural changes will have benefits not only for patients with acute ischaemic stroke, but as such should be viewed as an opportunity to improve outcomes for all those who experience stroke.

The provision of a new intervention may require investment or additional cost that may result in disinvestment in other aspects of health services. This displacement may adversely affect the care of patients with other conditions. The introduction of mechanical thrombectomy may be costly at the outset in terms of both staff and facilities. However, the evidence from the cost-effectiveness review suggests that mechanical thrombectomy is likely to be cost-effective over relatively short time horizons.

8.4 Ethical consequences of HTA

This technology assessment has reviewed evidence regarding the clinical and cost-effectiveness of mechanical thrombectomy. The clinical effectiveness was evaluated on the basis of nine RCTs published between 2013 and 2016, and in particular the subset of six RCTs relating to second-generation stent retriever devices published between 2015 and 2016. The economic evaluations identified in the review of cost-effectiveness were also largely based on evidence of efficacy reported in these RCTs. As such, the findings of this report are heavily influenced by the results of a limited number of trials. The accuracy and applicability of the HTA findings must therefore be considered in terms of the accuracy and applicability of the RCT evidence.

Thrombolysis with IV t-PA was defined as the standard of care for patients with acute ischaemic stroke in the RCT, with mechanical thrombectomy only provided to those eligible for IV t-PA within 4.5 hours of stroke onset. Standard medical care for acute stroke in Ireland includes the use of IV t-PA, and while there is variability in thrombolysis rates across centres, the national thrombolysis figure in Ireland — that is an average of 12.3%— is comparable with that reported internationally.

The provision of mechanical thrombectomy may give rise to expectations of improved outcomes that may not be observed in practice because the conditions of the RCTs are not recreated on the ground. For example, it is assumed that post-procedure care is comparable to that in the trial sites, with appropriate access to rehabilitation services in the acute period. As noted in Chapter 3, while stroke units and services have been developed in Ireland, these vary in their resourcing and level of service offered with only 29% of patients with an acute stroke admitted to a stroke unit on presentation and only 54% admitting to at any time during the course of their hospitalisation.

Issues also may apply in relation to so-called 'indication creep'. For example, most of the RCTs specifically excluded patients who were not functionally independent prior to having the stroke. In reality, some of the patients treated may be functionally dependent at the time of stroke (such as in cases of recurrent stroke), and the

potential to benefit is lower for these individuals. As with any evolving technology, it is likely that the indications for mechanical thrombectomy will expand to include patients with a lower capacity to benefit. This would have potential implications for the clinical and cost-effectiveness of the intervention. It is important that the evidence underpinning any expansion of indication continues to be assessed and that a formal process of audit and evaluation is in place.

The data from the trials provided information on outcomes at 90 days whereas the economic evaluations modelled outcomes to 20 or 30 years. Substantial assumptions are required when using short-term outcomes to model long-term benefits. However, due to the use of sensitivity analyses and by incorporating the risk of recurrent stroke, it is likely that the long-term predictions of the economic evaluations are broadly accurate.

8.6 Summary

In examining the ethical issues associated with the provision of mechanical thrombectomy, we considered issues under four broad headings: benefit-harm balance; autonomy and respect for persons; justice and equity; and ethical consequences of the HTA.

Under standard medical care, only a minority of patients achieve functional independence at 90 days (approximately 31%). Mechanical thrombectomy is associated with improved functional outcomes such that an estimated 48% of eligible patients achieve functional independence at 90 days. There is evidence to suggest that mechanical thrombectomy is associated with a higher rate of any cerebral haemorrhage and there was some evidence of a higher rate of recurrent stroke at 90 days. However, the intra-procedural and longer-term adverse effects do not outweigh the benefits of improved functional outcomes.

An important consideration in the provision of any medical intervention is whether patients are particularly vulnerable and whether they can provide informed consent. While not a disease confined to older people, stroke patients tend to be elderly and experience symptoms of confusion, partial paralysis and difficulty with speech. Obtaining informed consent from the patient may not be possible. However, this is also the case for standard medical care and other endovascular procedures which are used in the treatment of stroke currently.

Geographic accessibility is the factor most likely to affect the equitable provision of mechanical thrombectomy. The number of patients likely to benefit from thrombectomy is largely predicated by thrombolysis rates which reflect accessibility

of specialist stroke care at local acute stroke centres. For reasons of safety and quality, mechanical thrombectomy is likely to be provided at a limited number of centres. Those living furthest from those centres may face additional difficulties in accessing centres in a timely manner.

The introduction of mechanical thrombectomy may have to be as part of service reorganisation which will require some degree of investment and disruption. However, reorganisation will benefit not just patients eligible for mechanical thrombectomy but also stroke patients generally. Furthermore, mechanical thrombectomy is estimated to be cost-effective over relatively short time horizons.

In basing the HTA findings on a small number of RCTs, it is possible that the estimated benefits may overstate what might be achieved in practice. This could occur, for example, if the patient population in Ireland is systematically different from those included in the trials. The assessment may therefore give rise to false expectations about the benefits that might be observed if mechanical thrombectomy is provided to eligible patients.

8.7 Key messages

- Mechanical thrombectomy when used as an adjunct to standard medical care has a favourable risk-benefit profile.
- While there may be difficulty obtaining informed consent, this is also the case for standard medical care and other endovascular procedures that are used in the treatment of stroke currently.
- Geographical accessibility may impact on the equitable provision of mechanical thrombectomy. The number of patients that may benefit from mechanical thrombectomy each year is largely predicated by the national thrombolysis rate. While nationally a rate of 12.3% has been achieved, there is considerable regional variation which will manifest also in thrombectomy rates unless this variation in access is addressed.
- It is assumed that for patients to achieve comparable outcomes to those observed in the clinical trials, that they receive comparable care post-procedure. Nationally while stroke units and services have been developed, these vary in their resourcing and level of service offered which may impact on patient outcomes.
- The introduction of mechanical thrombectomy may have to be as part of a service reorganisation that is likely to benefit stroke patients generally. While an

initial investment may be required, mechanical thrombectomy is estimated to be cost-effective over relatively short time horizons.

- In basing the HTA findings on a small number of RCTs, it is possible that the estimated benefits may overstate what might be achieved in practice.

9. Discussion

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided. The purpose of this HTA was to examine the evidence for mechanical thrombectomy plus current standard of care as a treatment strategy for acute ischaemic stroke in Ireland. This HTA considered the following domains: description of technology, burden of stroke, the clinical effectiveness and safety, a review of the cost-effectiveness literature, organisational issues, and ethical and social issues.

9.1 Description of the technology

Although thrombolysis with intravenous (IV) tissue-plasminogen activator (t-PA) remains the standard medical treatment for acute stroke, it has been shown to have modest clinical efficacy in severely affected patients. In order for IV t-PA to be effective and provide maximum benefit, it must be administered within 4.5 hours of the onset of stroke symptoms. However, rates of recanalisation following treatment are dependent on the particular vessel affected and the location of the thrombus within that vessel. Thrombolysis has a limited impact on larger, more proximally situated thrombi and successful recanalisation of large vessel occlusions with thrombolysis alone is infrequent. The narrow time window and strict exclusion criteria associated with thrombolysis has meant that only a small portion of patients experiencing acute ischaemic stroke receive thrombolysis.

Endovascular treatment with mechanical thrombectomy within 6–12 hours of stroke onset has been suggested as an effective and safe adjunct to standard medical care, which includes thrombolysis with IV t-PA. These devices can also be considered in terms of their time of development and approval for use, and may be separated into 'first-' and 'second-generation' retrieval devices and devices whose mechanism of action is based on suction or aspiration. As of August 2015, fifteen mechanical thrombectomy devices had been CE-marked (that is, they carry a mark indicating a manufacturer's declaration that the produce complies with the essential requirements of the relevant European health, safety and environmental protection legislation). Consistent with the clinical trial evidence and international consensus guidelines, delivery of this procedure is confined to comprehensive stroke centres with access to neurosurgical care, advanced brain imaging and appropriate neuro-endovascular expertise.

9.2 Burden of disease

Diseases of the circulatory system, stroke and other circulatory diseases are the most common cause of death in Ireland, and accounted for 8,899 deaths or just over one in three deaths (34% of all mortality) in Ireland in 2014. An estimated 2,000 people die as a result of stroke each year in Ireland, giving an age-standardised death rate of 34.6 per 100,000 population. A 2014 HSE report predicted 20% increases in the prevalence of major chronic diseases by 2020 primarily due to population aging, with the number of people with stroke predicted to increase by between 4% and 5% each year between 2015 and 2020.

In Ireland, more than half (approximately 55% to 57%) of strokes occur in men. Ischaemic stroke accounts for approximately 85% of all acute strokes resulting in hospitalisation in Ireland, amounting to approximately 4,300 cases annually. The average age for patients experiencing an acute stroke is approximately 75 years, with incidence increasing with age. However, stroke is not a condition confined to old age. In 2014, 27% of stroke cases occurred in those aged under 65 years.

Following major changes in the organisation and delivery of stroke care by the HSE, there have been substantial improvements in acute stroke care in Ireland over the past eight years resulting in significant reductions in mortality. Thrombolysis rates have improved to a national average of 12.3%, although there is considerable variation between acute hospitals, not all of which have established 24-seven local access or protocols for patient transfer and redirection to an acute stroke unit. Stroke units and services vary in their resourcing and the level of service offered. In 2015, stroke units were available in 78% of the 27 receiving hospitals, although less than one in three patients (29%) were admitted directly to these units at initial presentation.

At present in Ireland, endovascular procedures using mechanical thrombectomy is available on an ad hoc basis in two hospitals, with one hospital providing 85% of all such procedures (170 out of 200) in 2016.

9.3 Clinical effectiveness and safety

A systematic review was carried out to identify relevant studies of the effectiveness and safety of mechanical thrombectomy in the treatment of acute ischaemic stroke in Ireland. Patient outcomes were evaluated using a meta-analysis of randomised controlled trials.

Based on the available evidence, mechanical thrombectomy using second-generation (stent retriever) devices is a safe and effective procedure when provided as an

adjunct to standard medical care within six to 12 hours of stroke onset. This evidence is conditional on the procedure being used in conjunction with non-invasive arterial imaging in selected patients with anterior circulation acute ischaemic stroke.

Mechanical thrombectomy is significantly more likely to result in functional independence (RR: 1.56, 95% CI: 1.37–1.78) as measured by the modified Rankin Score (mRS) and may have a positive effect on health-related quality of life (EQ-5D) compared with standard medical care alone. It is not associated with an increased risk of all-cause mortality at 90 days (RR 0.85, 95% CI 0.67–1.07), or symptomatic intracranial haemorrhage SICH (RR 1.07, 95% CI 0.67–1.71). Pooled data from three trials does not suggest that the intervention is associated with a higher overall rate of recurrent ischaemic stroke within 90 days (RR 3.09, 95% CI 0.86–11.11). While individual studies reported adverse events and or serious adverse events, a lack of clarity regarding what constitutes 'serious' events and inconsistencies in reporting makes comparative analysis across studies difficult.

The data obtained from the published randomised controlled trials represents the best available evidence and are likely to be broadly accurate for those currently receiving thrombectomy Ireland. However, it is noted that most of the participating hospitals in the trials included in this analysis are high-volume stroke centres where the procedures were carried out in idealised circumstances. There is currently insufficient evidence to determine the applicability of this evidence to the larger, heterogeneous cohort of patients with acute ischaemic stroke who are treated in the real-world setting. Such patients may be ineligible for IV t-PA, arrive outside of the time window for treatment and or are managed in non-specialised settings.

This is particularly relevant in the Irish context where the 2015 Irish National Stroke Audit showed that most of those who currently experience a stroke in Ireland would be ineligible for mechanical thrombectomy as they could not receive it within an appropriate time frame from the onset of stroke symptoms due to delays in presentation to emergency departments and in timely access to imaging and specialist stroke care within hospitals. The evidence regarding mechanical thrombectomy continues to evolve, and it is likely that the patient population who are deemed eligible to benefit from this intervention will expand over time. Therefore, it is essential that as further evidence emerges and the technology becomes more widely available, that quality key performance indicators are developed and measures put in place to audit and evaluate the effectiveness and safety of a national service.

9.4 Review of cost-effectiveness

Based on a systematic review, 11 studies were identified that estimated the cost-utility or cost-benefit of mechanical thrombectomy relative to standard medical care alone. Studies could be dichotomised into evaluations of first- and second-generation devices. The clinical effectiveness of second-generation devices is supported by data from multiple randomised controlled trials, and this is considered the best level of evidence. The cost of long-term stroke care used in the studies was found, on average, to be broadly consistent with estimates for Ireland. The applicability of the economic evaluations was mixed, but generally was poor or moderate.

One high-applicability study was identified, a HTA by Health Quality Ontario in Canada. The Ontario HTA includes a detailed and comprehensive economic evaluation, and the costs are broadly similar to those in Ireland. The Ontario study found mechanical thrombectomy to be cost-effective relative to IV t-PA alone. Detailed sensitivity analysis suggest that other than by adopting a time horizon of one year, mechanical thrombectomy is likely to be considered cost-effective relative to a willingness-to-pay threshold of €20,000 per QALY. The findings of the Ontario study in terms of cost-effectiveness are similar to the other identified studies, providing reassurance about the consistency of the cost-effectiveness evidence.

Evidence from the review of cost-effectiveness literature therefore suggested that, providing that a service in Ireland can replicate the treatment times observed in the RCTs, and assuming availability of comprehensive stroke care, mechanical thrombectomy would be cost-effective in Ireland. However, in light of the distribution of stroke services and population in Ireland, and the likely investment required to support a national mechanical thrombectomy service, a cost-effectiveness analysis using Irish data was deemed necessary to support decision-making.

9.5 Economic evaluation

An economic evaluation was undertaken to determine the cost-effectiveness and budget impact of a national emergency endovascular service providing mechanical thrombectomy for treating acute ischaemic stroke in Ireland. The objective of this evaluation was to aid decision-making by estimating the incremental costs and benefits of adding this therapy to current standard medical care, which includes provision of IV and or IA (intra-arterial) thrombolysis, where appropriate. In the base-case analysis, it was assumed that one additional dedicated biplane angiography suite would be needed to provide sufficient capacity for a national endovascular stroke service. It was assumed that existing national arrangements for

thrombolysis would prevail and that eligible thrombectomy patients would be transferred from local stroke centres to one of two tertiary emergency endovascular stroke referral centres.

Based on this analysis, it was estimated that with a national thrombectomy service, 268 (95% CI: 210 to 322) thrombectomy procedures would take place each year. An estimated 57 (95% CI: 38 to 78) more patients would regain functional independence at three months after having a stroke. Using a five-year time horizon, the cost-utility of a national mechanical thrombectomy was an estimated €14,016 per quality-adjusted life year gained, which, in light of the conservative estimate used for a number of parameters, is within typical willingness-to-pay thresholds in Ireland.

The calculated cost-utility is sensitive to the clinical effectiveness of mechanical thrombectomy in terms of achieving functional independence. Although the underlying trials demonstrate a treatment effect, there is uncertainty about the size of the effect due to heterogeneity in the trials informing the estimate. The estimate of cost-effectiveness presented here is conservative due to the short time-horizon and inclusion of a treatment effect on mortality. Based on the meta-analysis of the clinical trials, the effect on mortality was not statistically significant. If no effect is assumed, then the incremental cost-effectiveness ratio is €4,064 per quality-adjusted life year.

The budget impact of moving from no service to a national emergency endovascular service for acute stroke was estimated to be €7.2 million over five years. The budget impact in the first year was estimated at €3.3 million based on the provision of one additional dedicated biplane angiography suite which would be required to ensure sufficient capacity for a national service without impacting on other endovascular services. Annual costs thereafter were estimated at between €1.2 million and €0.8 million based on treating 268 (95% CI 210 to 322) patients each year. The five-year budget impact of moving from the current ad hoc service (200 patients per annum provided through the existing facilities) to a national service was estimated to be €2.8 million (of which €2.0 million would be incurred in the first year). The introduction of the service will have implications for 24-seven availability of appropriate staff at the two treatment centres.

The basecase analysis of cost-effectiveness and budget impact assumed the provision of one additional biplane angiography suite and a consistent volume of patients over time. In the event that the number of eligible patients increases over time, then it may become necessary to consider the provision of a second dedicated biplane suite to ensure timely access and to minimise disruption to other services.

It was estimated that 235 cases (95% CI: 180 to 286) would require ambulance transfer from the hospital in which IV thrombolysis was started to and from one of the two proposed tertiary referral centres carrying out mechanical thrombectomy in Ireland. The transfers are equivalent to 491 emergency ambulance hours (95% CI: 372 to 608) each year, and also 491 intermediate care vehicle hours (95% CI: 372 to 608) for the return journeys. This would have resource implications for the HSE's National Ambulance Service both in terms of the initial transfer of the patient and their subsequent repatriation to their local acute stroke unit once they were clinically stable post-procedure.

9.6 Organisational and social aspects

To achieve comparable levels of efficacy and safety to those observed in randomised controlled trials, delivery of mechanical thrombectomy for treating acute ischaemic stroke must be confined to comprehensive stroke centres with access to neurosurgical, and neurocritical care. These centres must have appropriate neuro-endovascular expertise and access to advanced brain imaging. Two hospitals (Beaumont Hospital, Dublin and Cork University Hospital [CUH]) currently meet these criteria.

As a national emergency endovascular service for acute stroke has not been established, there are no formalised protocols for the inter-hospital transfer of patients to ensure safe and equitable access to mechanical thrombectomy. Mechanical thrombectomy is provided on an ad hoc basis in Beaumont Hospital and CUH, with a 24-seven service available in Beaumont Hospital only. This hospital provided 85% of all such procedures (approximately 170 cases out of 200) in 2016.

Ireland faces a number of challenges in ensuring appropriate access to mechanical thrombectomy for eligible patients. Many of these hurdles have been partially addressed through the development of the HSE's National Clinical Programme for Stroke and, in particular, the efforts which have gone into improving the management of patients in the hyperacute period (the first 6 to 12 hours after a stroke) as manifested by improved thrombolysis rates. Effective care is predicated on the timely delivery of the intervention with only a narrow treatment window available between the onset of stroke symptoms and the time that treatment must be started.

Delays in the presentation of patients to the hospital can occur due to poor awareness of the symptoms and management of stroke, or due to transport and logistical issues. These delays need to be minimised. Within hospitals, there is a need for rapid imaging and assessment to allow appropriate treatment to start in a

timely fashion. Appropriate expertise in the delivery of mechanical thrombectomy and the management of the patient in the hyperacute period is also required.

An equitable, efficient and cost-effective national thrombectomy service can only be delivered if the procedure is offered in a small number of centres that are adequately resourced and sited to maximise patient access, workforce expertise and geographical coverage. Expanded access to mechanical thrombectomy has implications for both acute hospital- and community-based stroke services. Additional community-based rehabilitation may potentially be needed to ensure patients can achieve optimal outcomes in the post-acute phase.

Developing a national mechanical thrombectomy service has potentially significant organisational and resource implications for the National Ambulance Service. This is in order to ensure patients are transported quickly to the appropriate receiving hospitals and to facilitate repatriation of clinically stable patients back to their local acute stroke unit after they have undergone the procedure. Use of existing ambulance capacity to transfer patients potentially long distance creates logistical issues as it may leave the referring area with reduced or no ambulance cover for extended periods. Resource implications include therefore adequate availability of both ambulances and trained emergency medical services staff. Given the existing national shortage of paramedic staff and the time to fully train new paramedics (up to two years), this may represent a capacity constraint in the short to medium term.

An organised national mechanical thrombectomy service will necessitate detailed service planning to ensure it adheres to requisite quality standards. This includes the development of quality key performance indicators to measure performance against targets or expectations.

9.7 Ethical considerations

By their nature, public healthcare programmes raise a range of ethical issues which require consideration by policy makers. While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a way that is equitable, non-discriminatory, transparent and, as far as possible, non-coercive.

Mechanical thrombectomy is associated with improved functional outcomes, with an estimated 51% of eligible patients regaining functional independence at 90 days compared with 33% using standard medical care. Although mechanical thrombectomy may be associated with a higher rate of certain peri-procedural adverse events, these do not outweigh the benefits of improved functional outcomes.

While stroke is not a condition confined to old age, stroke patients tend to be elderly and experience symptoms of confusion, partial paralysis and difficulty with speech. Obtaining informed consent from the patient may not be possible. However, this is also the case for standard medical care and other endovascular procedures that are used in the treatment of acute ischaemic stroke currently.

The factor most likely to affect the equitable provision of mechanical thrombectomy is geographic accessibility. While the treatment window for mechanical thrombectomy is longer than that for thrombolysis — and there is cohort of patients that may benefit from thrombectomy, but for whom thrombolysis is contraindicated — mechanical thrombectomy rates are largely predicated on the initial thrombolysis rates that are achieved. Poor access to specialist stroke teams or poor management of patients in the hyperacute period in hospitals receiving these patients will limit the number of otherwise eligible patients that could benefit from mechanical thrombectomy.

As noted, on average 12.3% of acute stroke patients receive thrombolysis, although there is considerable variability between hospitals, not all of which have established 24-seven local access or protocols for patient transfer and redirection. Similarly, while stroke units and services have been developed, their resources and services vary. Results from the economic evaluation undertaken in this HTA indicate that mechanical thrombectomy would be cost-effective given typical willingness-to-pay thresholds. Introduction of a national endovascular service for mechanical thrombectomy may have to be as part of a service reorganisation, which would likely benefit stroke patients generally.

In basing the HTA findings on a small number of randomised controlled trials, it is possible that the estimated benefits may overstate what might be achieved in practice. This could occur, for example, if the patient population in Ireland is systematically different from those included in the clinical trials or if the trial conditions cannot be mimicked in the Irish healthcare service. The assessment may therefore give rise to false expectations about the benefits that might be observed if mechanical thrombectomy is provided to eligible patients. Audit against key performance indicators will be necessary to ensure a national service is meeting requisite effectiveness and safety levels.

9.8 Conclusions

Bearing in mind the estimates and assumptions that were used in this analysis, a number of conclusions may be drawn. Evidence from a systematic review of randomised controlled trials, conducted as part of this HTA, suggest that mechanical thrombectomy is significantly more likely to result in functional

independence (mRS) compared with standard medical care. The evidence is conditional on mechanical thrombectomy being used in conjunction with non-invasive arterial imaging, in selected patients within six to 12 hours of onset of anterior circulation acute ischaemic stroke, and when using second-generation (stent retriever) devices.

An economic evaluation was undertaken in order to determine the cost-effectiveness and budget impact of a national emergency endovascular service providing mechanical thrombectomy for treating acute ischaemic stroke in Ireland. Taking into account the assumptions used in the economic model and the uncertainty of the parameter values, the introduction of a national mechanical thrombectomy service involving one dedicated biplane angiography suites would be cost-effective under typical willingness-to-pay thresholds applied in Ireland with a five-year budget impact of €7.2 million compared to no thrombectomy service. The five-year budget impact of moving from the current ad hoc service (200 patients per annum provided through the existing facilities) to a national service is estimated to be €2.8 million (of which €2.0 million would be incurred in the first year).

Assuming an estimated 268 thrombectomy procedures would take place nationally each year, 57 more patients (that is increasing from 102 to 159) would regain functional independence 90 days after stroke onset.

An organised national service would, however, necessitate detailed service planning to ensure it adheres to the requisite quality standards. This includes the development of quality key performance indicators to measure performance against targets or expectations.

An equitable, efficient and cost-effective national thrombectomy service is contingent on the procedure being offered in a small number of centres that are adequately resourced and sited to maximise patient access, workforce expertise and geographical coverage. Expanded access to mechanical thrombectomy has potential implications for the HSE's National Ambulance Service to ensure timely transfer and repatriation of patients and to ensure ambulance access can be maintained for other patients while ambulances are deployed to transfer patients. Expanded access also has implications for community-based rehabilitation services to ensure patients can achieve the best possible outcomes after their acute care had ended.

Glossary

Adverse event	Any noxious, pathological or unintended change in anatomical, physical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of a clinical study whether or not considered treatment related. It includes exacerbation of pre-existing conditions or events, intercurrent illnesses, accidents, drug interaction or the significant worsening of disease.
Autonomy	The patient's right of self-determination concerning medical care. It may be used in various senses including freedom of action, effective deliberation and authenticity. It supports such moral and legal principles as respect for persons and informed consent. Making decisions for oneself, in light of a personal system of values and beliefs.
Bias	In general, any factor that distorts the true nature of an event or observation. In clinical investigations, a bias is any systematic factor other than the intervention of interest that affects the magnitude of (that is to say, tends to increase or decrease) an observed difference in the outcomes of a treatment group and a control group.
Budget impact analysis	The financial impact of the introduction of a technology or service on the capital and operating budgets of a government or agency.
Casemix	The mix of patients treated by a hospital in terms of treatment complexity. Reimbursement for the cost of patient care in the Irish public hospital system is based on casemix.
Clinical outcome	An outcome of major clinical importance that is defined on the basis of the disease being studied (for example, fracture in osteoporosis, peptic ulcer healing and relapse rates).

Clinical significance	A conclusion that an intervention has an effect that is of practical meaning to patients and healthcare providers.
Cohort study	An observational study in which outcomes in a group of patients that received an intervention are compared with outcomes in a similar group, that is to say, the cohort, either contemporary or historical, of patients that did not receive the intervention.
Comparator	The technology to which an intervention is compared.
Complication	A secondary disease or condition that develops in the course of a primary disease or condition and arises either as a result of it or from independent causes.
Confidence interval (CI)	Depicts the range of uncertainty about an estimate of a treatment effect.
Contraindication	A clinical symptom or circumstance indicating that the use of an otherwise advisable intervention would be inappropriate.
Cost per QALY	A measure used in cost-utility analysis (CUA) to assist in comparisons among programmes; expressed as monetary cost per unit of outcome.
Cost-effectiveness analysis (CEA)	A comparison of alternative interventions in which costs are measured in monetary units and outcomes are measured in non-monetary units, e.g. reduced mortality or morbidity. (See also Cost per QALY).
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis of alternative interventions in which costs are measured in monetary units and outcomes are measured in terms of their utility, usually to the patient, for example, using QALYs.
Discount rate	The interest rate used to discount or calculate future costs and benefits so as to arrive at their present values, for example, 3% or 5%. This is also known as the opportunity cost of capital investment.
Discounting	The process used in cost analyses to reduce mathematically future costs and/or benefits/outcomes to their present value.
Economic evaluation	The comparative analysis of alternative courses of action, in terms of their costs and consequences.

Economic model	In healthcare, a mathematical model of the patient pathway that describes the essential choices and consequences for the interventions under study and can be used to extrapolate from intermediate outcomes to long-term outcomes of importance to patients.
Effectiveness	The benefit (for example, to health outcomes) of using a technology for a particular problem under general or routine conditions.
Efficacy	The benefit of using a technology for a particular problem under ideal conditions, for example, in a laboratory setting or within the protocol of a carefully managed randomised controlled trial.
Efficiency	The extent to which the maximum possible benefit is achieved out of available resources.
Epidemiology	The study of the distribution and determinants of health-related states or events in specified populations.
Equity	Fairness in the allocation of resources or treatments among different individuals or groups.
Ethics	A general term for what is often described as the science of morality. In philosophy, ethical behaviour is that which is good. The goal of a theory of ethics is to determine what is good, both for the individual and for society as a whole.
EU27	EU-27 is the European Union of 27 Member States: Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the UK.
Evidence-based medicine	The use of current best evidence from scientific and medical research to make decisions about the care of individual patients. It involves formulating questions relevant to the care of particular patients, systematically searching the scientific and medical literature, identifying and critically appraising relevant research results, and applying the findings to patients.
Forest plot	A plot showing a series of lines and symbols which

	represent the results of a meta-analysis.
Funnel plot	A graphical display of sample size plotted against effect size that can be used to investigate publication bias.
Health outcomes	The results or impact on health of any type of intervention (or lack of), for example, a clinical procedure, health policy or programme, and so on.
Health-related quality of life (HRQoL)	A multi-dimensional measure comprising the physical and mental health perceptions of a patient in terms of health status, health risks, functional status, social support, and socioeconomic status.
Health technology	Any intervention that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. This includes the pharmaceuticals, devices, procedures and organisational systems used in healthcare.
Health technology assessment (HTA)	Health technology assessment (HTA): the systematic evaluation of properties, effects, and/or impacts of healthcare technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in healthcare. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.
Heterogeneity	In meta-analysis, heterogeneity refers to variability or differences in the estimates of effects among studies. Statistical tests of heterogeneity are used to assess whether the observed variability in study results (effect sizes) is greater than that expected to occur by chance.
Hierarchy of evidence	Studies are often grouped into a hierarchy according to their validity or the degree to which they are not susceptible to bias. The hierarchy indicates which studies should be given most weight in an evaluation.
HTA	Health technology assessment.
Iatrogenic	An adverse condition in a patient resulting from treatment by a physician or surgeon.
Incidence	The rate of occurrence of new cases of a disease or

	condition in a population at risk during a given period of time, usually one year.
Incremental cost	The additional costs that one intervention imposes over another.
Incremental cost-effectiveness ratio (ICER)	The ratio of incremental costs to incremental benefits (difference in effect of patient outcome) obtained when comparing two technologies, for example, additional cost per QALY.
Indication	A clinical symptom, risk factor, or circumstance for which the use of a particular intervention would be appropriate as determined or specified.
Informed consent	The legal and ethical requirement that no significant medical procedure can be performed until the competent patient has been informed of the nature of the procedure, risks and alternatives, as well as the prognosis if the procedure is not done. The patient must freely and voluntarily agree to have the procedure done.
Justice	The principle that states that fairness requires equals to be treated equally.
Literature review	A summary and interpretation of research findings reported in the literature. May include unstructured qualitative reviews by single authors as well as various systematic and quantitative procedures such as meta-analysis. (Also known as overview.)
Meta-analysis	Systematic methods that use statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome.
Outcomes	Components of patients' clinical and functional status after an intervention has been applied.
p value	In hypothesis testing, the probability that an observed difference between the intervention and control groups is due to chance alone if the null hypothesis is true.
Prevalence	The number of people in a population with a specific disease or condition at a given time, usually expressed as a proportion of the number of affected people to the

	total population.
Quality of evidence	Degree to which bias has been prevented through the design and conduct of research from which evidence is derived.
Quality of life (QOL)	See Health-related quality of life.
Quality-adjusted life year (QALY)	A unit of healthcare outcomes that adjusts gains (or losses) in years of life subsequent to a healthcare intervention by the quality of life during those years.
Random effects model	A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.
Randomised controlled trial (RCT)	An experiment of two or more interventions in which eligible people are allocated to an intervention by randomisation. The use of randomisation then permits the valid use of a variety of statistical methods to compare outcomes of the interventions.
Relative risk (RR) (risk ratio)	The ratio of (statistical) risk in the intervention group to the risk in the control group. A relative risk of one indicates no difference between comparison groups. For undesirable outcomes an RR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.
Risk assessment	The qualitative or quantitative estimation of the likelihood of adverse effects that may result from exposure to specified health hazards or from the absence of beneficial influences.
Risk factor	An aspect of a person's condition, lifestyle or environment that increases the probability of occurrence of a disease. For example, cigarette smoking is a risk factor for lung cancer.
RR	See Relative Risk.
SD	See Standard deviation.
Sensitivity analysis	A means to determine the robustness of a mathematical model or analysis (such as a cost-effectiveness analysis

	or decision analysis) that tests a plausible range of estimates of key independent variables (for example, costs, outcomes, probabilities of events) to determine if such variations make meaningful changes to the results of the analysis.
Standard deviation (SD)	A measure of the dispersion of a set of data from its mean.
Statistical significance	Statistical significance: a conclusion that an intervention has a true effect, based upon observed differences in outcomes between the treatment and control groups that are sufficiently large so that these differences are unlikely to have occurred due to chance, as determined by a statistical test.
Stochastic	A stochastic process is one that involves random elements so that the outcome varies each time the process is repeated.
Study validity	The degree to which the inferences drawn from the study are warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn (internal and external validity, applicability, generalisability).
Systematic review (systematic overview)	A form of structured literature review that addresses a question that is formulated to be answered by analysis of evidence, and involves objective means of searching the literature, applying predetermined inclusion and exclusion criteria to this literature, critically appraising the relevant literature, and extraction and synthesis of data from the evidence base to formulate findings.
Utility	In economic and decision analysis, the desirability of a specific level of health status or health outcome, usually expressed as being between zero and one (e.g. death typically has a utility value of zero and a full healthy life has a value of one).
Validity	The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic

	errors). Also, the degree to which a measure or parameter accurately reflects or assesses a concept of interest.
Willingness-to-pay (WTP)	The maximum amount that a person is willing to pay: (i) to achieve a particular good health state or outcome, or to increase its probability of occurrence; or (ii) to avoid particular bad health state or outcome, or to decrease its probability.

Appendix 1 Search details for clinical effectiveness

Search strategy for Pubmed (Medline), Date of Search 13th April 2016

((((((embolectomy[Title/Abstract]) OR "mechanical thrombus removal"[Title/Abstract]) OR "mechanical embolus removal"[Title/Abstract]) OR "endovascular intervention"[Title/Abstract]) OR "mechanical device"[Title/Abstract]) OR "endovascular recanalisation"[Title/Abstract]) OR "endovascular embolectomy"[Title/Abstract]
OR
(((((((((stroke[MeSH]) OR stroke[tiab])) OR "Cerebrovascular accident"[Title/Abstract]) OR "Large vessel occlusion"[tiab]) OR "Large artery occlusion"[tiab])) AND ((((((((((((thrombectomy[MeSH terms] OR Thrombectomy[Text Word])))) OR (("mechanical thrombolysis"[MeSH terms] OR mechanical thrombolysis[Text Word])))) OR (("endovascular procedures"[MeSH terms] OR endovascular procedures[Text Word])))) OR ((angioplasty[MeSH terms] OR angioplasty[Text Word])))) OR "endovascular therapy"[Title/Abstract]) OR "revascularization"[Title/Abstract]) OR "stent retriever"[Title/Abstract]) OR "mechanical recanalization"[Title/Abstract]) OR "stent recanalization"[Title/Abstract]) OR "clot retrieval"[Title/Abstract]) OR "retrievable stent"[Title/Abstract]) OR "intra-arterial"[Title/Abstract])))
AND
((((((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR drug therapy [sh]) OR randomly [tiab]) OR trial [tiab]) OR groups [tiab])) NOT ((animals [mh] NOT humans [mh])))) AND ((((((((embolectomy[Title/Abstract]) OR "mechanical thrombus removal"[Title/Abstract]) OR "mechanical embolus removal"[Title/Abstract]) OR "endovascular intervention"[Title/Abstract]) OR "mechanical device"[Title/Abstract]) OR "endovascular recanalisation"[Title/Abstract]) OR "endovascular embolectomy"[Title/Abstract]) AND ("2005/01/01"[PDat] : "3000/12/31"[PDat]))

Search strategy for EMBASE, Date of Search 13th April 2016

1	**'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR 'randomi?ed controlled' NEXT/1 trial* OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR allocated NEAR/2 random OR single NEXT/1 blind* OR double NEXT/1 blind* OR (treble OR triple) NEAR/1 blind* OR placebo***

2	**'thrombectomy'/exp OR 'thrombectomy'**
3	**'endovascular therapy':ab,ti**
4	**'revascularisation':ab,ti**
5	**'stent retriever':ab,ti**
6	**'mechanical recanalization':ab,ti**
7	**'stent recanalization':ab,ti**
8	**'clot retrieval':ab,ti**
9	**'retrievable stent':ab,ti**
10	**'intra-arterial':ab,ti**
11	**'mechanical thrombectomy'/exp OR 'mechanical thrombectomy'**
12	**'endovascular procedure'/exp OR 'endovascular procedure'**
13	**'angioplasty'/exp OR 'angioplasty'**
14	2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15	**'stroke'/exp OR 'stroke'**
16	**'cerebrovascular accident':ab,ti**
17	**'large vessel occlusion':ab,ti**
18	**'large artery occlusion':ab,ti**
19	15 OR 16 OR 17 OR 18
20	**1 AND 14 AND 19 AND [2005-2016]/py**
21	**'embolectomy':ab,ti**
22	**'endovascular recanalization':ab,ti**
23	**'endovascular embolectomy':ab,ti**

24	**'mechanical thrombus removal':ab,ti**
25	**'mechanical embolus removal':ab,ti**
26	**'endovascular intervention':ab,ti**
27	**'mechanical device':ab,ti**
28	21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27
29	1 AND 28 **AND [2005-2016]/py**
30	29 OR 20

Search strategy for International Clinical Trials Registry Platform (ICTRP)

Date of Search 13th April 2016
Condition: Stroke or cerebrobascular accident
AND
Intervention: thrombectomy OR mechanical OR endovascular OR angioplasty OR revascularization OR stent OR embolectomy 01/01/2005 to present

Search strategy for MetaRegister of Controlled Trials (mRCT)

Date of Search 13th April 2016
Not available. Directed to ICTRP and UKCTG (this latter one pools data from ICTRP and clinicaltrials.gov and therefore not searched).

Search strategy for Stroke Trials Registry

Date of Search 13th April 2016
Search terms: thrombectomy OR mechanical OR endovascular OR angioplasty OR revascularization OR stent
Limited to randomized trials
Thrombectomy
Mechanical Thrombolysis
Mechanical
Endovascular
Angioplasty
Revascularization
Stent
Embolectomy
Mechanical thrombus removal
Mechanical embolus removal

Search strategy for Cochrane register of controlled trials

Date of search: 13th April 2016
'("stroke" OR "cerebrovascular accident") AND ("thrombectomy" OR "endovascular" OR "stent" OR "mechanical" OR "angioplasty" OR "revascularization" OR "embolectomy") in Record Title in Trials' 2005 to present.

Search strategy for ClinicalTrials.gov

Date of search: 13th April 2016
("stroke" OR "cerebrovascular accident") AND ("thrombectomy" OR "endovascular") | Adult, Senior | received on or after 01/01/2005

Appendix 2

Table App2.1Study characteristics of nine included randomised controlled studies

Author Year published Name	Objective	Comparator	Inclusion Criteria						Exclusion Criteria (Imaging/other)
			Age	Location of Stroke	Pre Stroke FA	Baseline NIHSS	IV t-PA	Thromb-ectomy	
Kidwell 2013 MR RESCUE	Determine if patients selected for revascularization on basis of penumbral-imaging pattern have better outcomes than patients treated medically or those with nonpenumbral imaging patterns	Standard medical care	18-85	Anterior circulation	mRS≤2	≥ 6 & < 30	Within 4.5hrs of onset	Within 8hrs of onset	Proximal ICA occlusion, proximal carotid stenosis > 67% or dissection on MRA, CTA
Broderick 2013 IMS III	Determine efficacy of endovascular therapy after IV t-PA	IV t-PA (0.9 mg/kg body weight administered over a 1-hour period; maximum dose, 90 mg)	18-82	M1, ICA or Basilar Artery	mRS≤2	≥10 at start of IV t-PA or >7 and <10 with occlusion seen in M1/ICA/Basilar artery on CTA	Within 3hrs of onset	Within 5hrs of onset	Large (> 1/3 of the MCA) regions of clear hypodensity on baseline imaging. (ASPECTS < 4 used as guideline when evaluating >1/3 region of territory involvement)
Ciccone 2013 SYNTHESIS Expansion	To assess whether endovascular treatment, including the options of a mechanical device and IA t-PA, is more effective than the currently available treatment with IV t-PA	IV t-PA, 0.9 mg/kg body weight (maximum, 90mg for patients with a body weight of ≥100 kg) - to be delivered within 1 hour	18-80	-	-	-	Within 4.5hrs of onset in control group	Within 6hrs of onset	Intra-cranial haemorrhage
Berkhemer 2015 MR CLEAN	To test if IA treatment plus usual care is more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation	Usual care alone (which could include IV t-PA	18+	Intracranial ICA, M1 or M2, ACA	-	NIHSS ≥ 2	-	Within 6hrs of onset	Intra-cranial haemorrhage

Author Year published Name	Objective	Comparator	Inclusion Criteria						Exclusion Criteria (Imaging/other)
			Age	Location of Stroke	Pre Stroke FA	Baseline NIHSS	IV t-PA	Thrombectomy	
Campbell 2015 EXTEND IA	To test whether endovascular thrombectomy will improve outcomes in patients with anterior circulation ischaemic stroke selected within 4.5hrs of stroke onset	IV t-PA (0.9 mg/kg body weight)	18+	Anterior Circulation	mRS≤2	-	Within 4.5hrs of onset	Within 6hrs of onset	Irreversibly injured brain on CT perfusion imaging (diagnosed if the relative cerebral blood flow was <30% that in normal tissue)
Jovin 2015 REVASCAT	To determine efficacy & safety of neurovascular thrombectomy with the Solitaire™ stent retriever	Medical therapy alone	18-80	Proximal anterior circulation	mRS≤1	≥6	-£	Within 8hrs of onset	ASPECTS score <7 on non-contrast CT or ASPECTS score <6 on DWI MRI
Saver 2015 SWIFT PRIME	To establish the efficacy and safety of rapid neurovascular thrombectomy with the stent retriever in conjunction with IV t-PA versus IV t-PA alone	IV t-PA alone	18-80	Intracranial ICA, M1 or both	mRS≤1	≥8	Within 4.5hrs of onset	Within 6hrs of onset	ASPECTS score <6 on non-contrast CT or DWI MRI*
Goyal 2015 ESCAPE	To test if patients selected on the basis of results of CT and CTA, would benefit from rapid endovascular treatment	Current Standard of Care	18+	Proximal anterior circulation	Barthel Index ≥90	-	-£	Within 12hrs of onset	ASPECTS score <6 on non-contrast CT or CTA
Bracard 2016 THRACE	To assess whether endovascular treatment, including the options of a mechanical device and IA t-PA, is more effective than the standard treatment with IV t-PA alone	Standard treatment with IV t-PA alone	18-80	Intracranial ICA, M1 or superior third of BA	-	≥10 and ≤25	First 80 patients: Within 3hrs of symptom onset Remainder: Within 4hrs of symptom onset	Within 5hrs of symptom onset	Hyperdensities or other signal abnormalities suggesting haemorrhage regardless of severity; Infarct with a mass effect causing midline shift already visible on CT or MRI FLAIR· indicating an error in amount of time since symptom onset;

Key: ACA = Anterior Cerebral Artery; BA = Basilar Artery; CTA = Computed Tomographic Angiography; DSA = Digital Subtraction Angiography; FA = Functional Ability; IA = intra-arterial, IV = intravenous; ICA = internal carotid artery; M1 = first segment of middle cerebral artery; MRA = Magnetic Resonance Angiography; mRS = modified Rankin Scale

* Before imaging entry criteria revision, this criterion stated: "Core Infarct and hypoperfusion: a) MRI- or CT-assessed core infarct lesion greater than 50 cc; b) Severe hypoperfusion lesion (10 sec or more Tmax lesion larger than 100 cc); c) Ischaemic penumbra < 15 cc and mismatch ratio ≤1.8." After imaging entry criteria revision, sites could enrol based on ASPECTS findings only, but were still encouraged to obtain perfusion imaging and use this information if available. A total of 71 patients were enrolled under the initial imaging entry criteria and 125 patients under the revised imaging entry criteria.

£ Eligibility for IV thrombolysis was not mandatory in REVASCAT or ESCAPE.

Table App2.2 Patient characteristics of nine included randomised controlled trials

Author Yr Published Name	No. Patients	Age (Mean)	Sex % Male	Pre Stroke NIHSS (Median (IQR))	Pre Stroke mRS	Proportion of intervention group who received... (%)			
						M.T.	GA	IV tPA	IA tPA
Kidwell 2013 MR RESCUE	I: 64 C: 54	I: 64 C: 67	I: 47 C: 50	I: 16 (12-18) AND 19 (17-22) C: 16 (11-18) AND 20.5 (17-23)	-	100[+] (64/64)	-	43.7	12.5
Broderick 2013 IMS III	I: 434 C: 222	I: 69 (Md) C: 68 (Md)	I: 50 C: 55	I: 17 (range 7-40) C: 16 (range 8-30)	mRS 0 = I – 87.3% C – 88.7%	39.2 (170/434)	-	100	61
Ciccone 2013 SYTHESIS Expansion	I: 181 C: 181	I: 66 C: 67	I: 59 C: 57	I: 13 (9-17) C: 13 (9-18)	-	30.9 (56/181)	12	0	-
Berkhemer 2015 MR CLEAN	I: 233 C: 267	I: 66 (Md) C: 66 (Md)	I: 58 C:59	I: 17 (14-21) C: 18 (14-22)	mRS 0 = I - 81.5% C - 80.1%	81.5 (190/233)	37.8	87.1	84.1
Campbell 2015 EXTEND IA	I: 35 C: 35	I: 69 C: 70	I: 49 C: 49	I: 17 (13-20) C: 13 (9-19)	All mRS < 2	77.1 (27/35)	36	100	-
Jovin 2015 REVASCAT	I: 103 C: 103	I: 66 C: 67	I: 53 C: 52	I: 17 (14-20) C: 17 (12-19)	mRS 0 = I - 83.5% C – 80.6%	95.1 (98/103)	6.7	68	1*
Saver 2015 SWIFT PRIME	I: 98 C: 98	I: 65 C: 66	I: 47 C: 55	I: 17 (13-19) C: 17 (13-20)	mRS 0 or 1 = I – 98% C – 99%	88.7 (87/98)	37	-	-
Goyal 2015 ESCAPE	I: 165 C: 150	I: 71 (Md) C: 70 (Md)	I: 48 C: 47	I: 16 (13-20) C: 17 (12-20)	-	91.5 (151/165)	9.1	72.7	-
Bracard 2016 THRACE	I: 204 C: 208	I: 66 (Md) C: 68 (Md)	I: 50 C: 57	I: 18 (15-21) C: 17 (13-20)	-	71.1‡ (145/204)	33.8‡	100‡	7.4‡

Key: I = Intervention Group, C = Controls, Md = Median, MT = Mechanical Thrombectomy, GA = General Anaesthetic, IV = intravenous, IA = intra-arterial, tPA = tissue plasminogen activator

[+]Per-protocol analysis.

*The authors state that 1 patient received IA t-PA outside of protocol – it is unclear whether any other patients in the intervention group received IA t-PA.

‡ Figures are calculated as a proportion of those randomised and not a proportion of those who underwent thrombectomy.

Table App2.3 Timing characteristics of nine included randomised controlled trials

Author Year published Name	Median Time in minutes from stroke onset to.... (median and IQR, unless otherwise stated)			Duration of Procedure (median and IQR)
	Thrombolysis	Randomisation	Groin Puncture	
Kidwell 2013 MR RESCUE	-	I: 318 +/- 96 (mean, SD) C: 346 +/-69 (mean, SD)	I: 381 +/- 74 (mean, SD)	-
Broderick 2013 IMS III	I: 122.4 +/-33.7 (mean, SD) C: 121.2 +/-33.8 (mean, SD)	Within 40minutes of initiation of IV t-PA	I: 208 +/- 46.7 (mean, SD)	-
Ciccone 2013 SYTHESIS Expansion	I: NA C: 165 (140-200)	I: 148 (124-190) C: 145 (119-179)	I: 225 (194-260)	-
Berkhemer 2015 MR CLEAN	I: 85 (67-110) C: 87 (65-116)	I: 204 (152-251) C: 196 (149-266)	I: 260 (210-313)	-
Campbell 2015 EXTEND IA	I: 127 (93-162) C: 145 (105-180)	I: 29 (23-46) C: 36 (18-55) (this is the time from initiation of IV t-PA to randomisation)	I: 210 (166-251)	I: 43 (24-53)
Jovin 2015 REVASCAT	I: 117.5 (90.0–150.0) C: 105.0 (86.0–137.5)	I: 223 (170–312) C: 226 (168–308)	I: 269 (201–340)	I: 75 (50-114)
Saver 2015 SWIFT PRIME	I: 110.5 (85-156) C: 117 (80-155)	I: 190.5 (141-249) C: 188 (130-268)	I: 224 (165-275)	-
Goyal 2015 ESCAPE	I: 110 (80-142) C: 125 (89-183)	I: 169 (117-285) C: 172 (119-284)	Time from stroke onset to study CT: I: 134 (77-247) Time from study CT to groin puncture I: 51 (39-68)	-
Bracard 2016 THRACE	I: 150 (120-178) C: 153 (124-180)	I: 168 (143-195) C: 170 (138-199)	I: 250 (210-290)	GA: 45(28-70) LA or conscious sedation: 56 (24-86)

Key: C = Controls; GA = General Anaesthetic; I = Intervention Group; LA = Local Anaesthetic; NA = not applicable.

Note Re Kidwell, 2013: The intervention and control groups were split into those with and without favourable penumbral patterns.

Table Ap2.4 Effectiveness outcomes of nine included randomised controlled trials

Author Year published Name	mRS ≤2 at 90 days	Mortality at 90 days	NIHSS	Barthel Index at 90 days	mTICI score on final angiography
Kidwell 2013 MR RESCUE	I: 8/64 C: 10/54	I: 12/64 C: 13/54	-	-	2a-3 at day 7 I: 40/56
Broderick 2013 IMS III	I: 177/415 C: 86/214	I: 83/434 C: 48/222	-	-	2b-3 by vessel ICA occlusion: 38% M1 occlusion: 44% M2 occlusion: 44% Multiple M2 occlusions: 23%
Ciccone 2013 SYNTHESIS Expansion	I: 76/181 C: 84/181	I: 26/181 C: 18/181	≤6 at day 7 I: 97/181 C: 100/181	-	-
Berkhemer 2015 MR CLEAN	I: 76/233 C: 51/267	I: 49/233 C:59/267	Median (IQR) at 24hrs I: 13 (6-20) C: 16 (12-21)	≥95 I: 99/215 C: 73/245	2b-3 I:115/196
Campbell 2015 EXTEND IA	I: 25/35 C: 14/35	I: 3/35 C: 7/35	A reduction of ≥8 points on NIHSS or a score of 0-1 at 3 days I: 28/35 C: 13/35	-	2b-3 I:25/29
Jovin 2015 REVASCAT	I: 45/103 C: 29/103	I: 19/103 C: 16/103	A reduction of ≥8 points on NIHSS or a score of ≤ 2 at 24 hrs I: 59/100 C: 20/100	≥95 I: 47/82 C: 23/87	2b-3 I:82/103
Saver 2015 SWIFT PRIME	I: 59/98 C: 33/93	I: 9/98 C:12/97	Mean change at 27hrs I: -8.5 (+/- 7.1) (n = 97) C: -3.9 (+/- 6.2) (n = 92)	Median (IQR) I: 100 (10-100) (n = 88) C: 90 (0-110) (n = 77)	2b-3 I:73/83
Goyal 2015 ESCAPE	I: 87/164 C: 43/147	I: 17/164 C: 28/147	Median (IQR) at 24hrs I: 6 (3-14) C: 13 (6-18)	≥95 I: 94/163 C: 49/146	2b-3 I:113/156
Bracard 2016 THRACE	I: 106/204 C: 85/208	I: 24/204 C: 27/208	Median (IQR) at 24hrs I: 9 (4-18) C: 12 (6-19)	≥95 I: 92/152 C: 79/161	2b-3 I: 95/138

Key: C, Controls; I, Intervention Group; ICA = internal carotid artery; IQR, Interquartile Range; M1, first segment of middle cerebral artery; M2, second segment of middle cerebral artery; mRS, modified Rankin Scale; mTICI, modified Treatment in Cerebral Ischaemia; NIHSS, National Institutes of Health Stroke Scale.

Appendix 3 Cochrane risk of bias checklist

Study: Kidwell et al, MR RESCUE		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from protocol): "employing a biased coin technique (weighted randomization to provide balanced assignments while maintaining uncertainty regarding next allocation)" or else "permuted block sequence" if there is a failure.
Allocation Concealment (selection bias)	Low	Randomisation occurred after imaging.
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Unclear	Trial is described as a "blinded-outcome evaluator trial," but there is no clear description of this in the protocol or main paper other than "core laboratories completed primary neuroimaging analyses blinded to treatment assignment before database lock".
Incomplete outcome data (attrition bias)	High	9/127 excluded from the per protocol analysis (Intervention group 6; control group 3)
Selective reporting (reporting bias)	Low	Primary and secondary outcomes reported.
Other bias	Unclear	Quote (from main paper): "The trial was funded by Covidien and designed and led by a steering committee that included academic investigators and representatives of the sponsor. The site investigators gathered the data, with monitoring and database maintenance performed by the sponsor"

Study: Broderick et al, IMS III		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from protocol): "Randomization is implemented using a combination of a web-based minimization + biased coin scheme"
Allocation Concealment (selection bias)	Low	Quote (from protocol): "sealed randomization envelopes placed at each clinical site"
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	The assessor was blinded
Incomplete outcome data (attrition bias)	Unclear	mRS analysis on 415/434 in intervention group; 214/222 – in control group. Unfavourable imputation applied for 27 patients
Selective reporting (reporting bias)	High	EQ-5D, trail making test and Barthel Index all mentioned in protocol but no mention in the paper
Other bias	Low	Quote (main paper): "None of the industry sponsors were involved in the study design, study conduct, manuscript review, or protocol review, except to make sure that the specified use of devices in the study followed the instructions for use approved by the Food and Drug Administration (FDA)"

Study: Ciccone et al, SYNTHESIS Expansion		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from main paper): "The study protocol provided for centralized, simple randomization online. A single randomization list was prepared with the use of a hardware system, available at www.random.org. All patients underwent randomization within 4.5 hours after symptom onset."
Allocation Concealment (selection bias)	Unclear	Not stated when randomisation was carried out.
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Quote (from protocol): "A long-term patient's clinical condition is evaluated by a single neurologist, blinded to treatment allocation"
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	Low	Primary and secondary outcomes reported.
Other bias	Low	Quote (from main paper): "There was no industry support for or industry involvement in this trial."

Study: Berkhemer et al, MR CLEAN		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from protocol): "The randomization procedure is computer- and web-based, using permuted blocks. Full-time back-up by telephone is provided."
Allocation Concealment (selection bias)	Low	Quote (from protocol): "Randomization is allowed when the intracranial occlusion has been established by CTA, MRA or DSA" and "Treatment assignment cannot be determined before inclusion and randomization."
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Quote (from protocol): "Information on outcome at 3 months will be assessed with standardized forms and procedures, in a structured telephone interview by an experienced research nurse at the central trial office who is not aware of treatment allocation. Assessment of outcome on the mRS will be based on this information, by assessors who are blind to the allocated and actually received treatment. Results of neuroimaging will also be assessed by blinded observers."
Incomplete outcome data (attrition bias)	Low	No loss to follow-up.
Selective reporting (reporting bias)	Low	Primary outcomes all reported. Most secondary outcomes reported.
Other bias	Low	Quote (from main paper): "The study sponsors were not involved in the study design, study conduct, protocol review, or manuscript preparation or review."

Study: Campbell et al, EXTEND IA		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from protocol): "randomization via a centralized website" with clinical assessment prior to randomisation.
Allocation Concealment (selection bias)	Unclear	Centralised website - not clear if investigators would have known what the next person out would be (intervention or control)
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Quote (from protocol): "All those involved in the subsequent clinical and imaging assessment of outcomes will be blinded to treatment allocation."
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	Low	Primary, secondary and tertiary outcomes reported.
Other bias	Unclear	Trial stopped early after unplanned interim analysis. Study sponsorship. Quote (from main paper): "Covidien supplied the Solitaire FR device and an unrestricted grant to support trial infrastructure, but the company was not involved in the study design or conduct or in the preparation of the manuscript, except to review the protocol to ensure that the specified use of devices in the study followed the approved instructions for use."

Study: Jovin et al, REVASCAT		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	From protocol: web-based real-time randomisation based on minimisation
Allocation Concealment (selection bias)	Low	From protocol: randomisation is carried in real-time at point of confirming eligibility
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Primary endpoint of mRS evaluated by blinded assessors. Quote (from protocol): "All neuroimaging secondary end-points including recanalisation at 24 hours, infarct volume and haemorrhage will be determined by the CT/MR core-lab, which will be also blinded to treatment allocation."
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	Low	Primary outcomes all reported. Most secondary outcomes reported.
Other bias	Low	Quote (main paper): "The study was funded by an unrestricted grant from the manufacturer of the stent retriever (Covidien), which was not involved in the design or conduct of the study or in the writing of the protocol or the manuscript."

Study: Saver et al, SWIFT PRIME		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Unclear	"Subject allocation to treatment will be accomplished by using an interactive web response or interactive voice response system." Further detail on how this was actually done would have been preferable.
Allocation Concealment (selection bias)	Unclear	Not reported.
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Quote (from protocol): "The 90-day mRS will be assessed by study personnel certified in the scoring of the mRS using the RFA-A and will be blinded to treatment assignment" and "the Core Lab will assess all CT and MR imaging blinded to treatment assignment"
Incomplete outcome data (attrition bias)	Unclear	Loss to follow-up in control arm (5 of 98). Last outcome carried forward (LOCF) used for 1/98 in intervention arm and 3/98 in control arm.
Selective reporting (reporting bias)	Low	Primary and secondary outcomes reported.
Other bias	Unclear	Trial stopped early after unplanned interim analysis. Study sponsorship. Quote (from main paper): "The trial was funded by Covidien and designed and led by a steering committee that included academic investigators and representatives of the sponsor. The site investigators gathered the data, with monitoring and database maintenance performed by the sponsor."

Study: Goyal et al, ESCAPE		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from protocol): "Patients will be randomized using a real-time, dynamic Internet-based, minimal sufficient balance (MSB) randomization method"
Allocation Concealment (selection bias)	Low	Quote (from protocol): "Because randomization will occur dynamically in real-time, it will be fully concealed."
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Quote (from protocol): "After enrolment...the site will designate a blinded evaluator to perform the 3-month follow-up evaluation including the primary end-point (mRS).This individual cannot be involved in care of the subject and must remain blinded to treatment assignment of the subject. Pts will be instructed not to disclose their treatment group to the evaluator. All neuroimaging secondary end-points will be determined by the CT core laboratory blinded to treatment allocation."
Incomplete outcome data (attrition bias)	Low	Loss to follow-up (1 case, 3 controls) represents small proportion of participants (165 cases, 150 controls).
Selective reporting (reporting bias)	Low	Primary outcomes all reported. Most secondary outcomes reported.
Other bias	Unclear	Trial stopped early after unplanned interim analysis. Study sponsorship. Quote (from main paper): "The study funders, including Covidien, were not involved in the design or conduct of the study, the preparation or review of the protocol, the collection or analysis of the data, or the preparation or review of the manuscript. All the authors collected data, provided comments on the analysis, contributed to the writing of the manuscript, and were independent of the sponsors."

Study: Bracard et al, THRACE		
Bias	**Authors` Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from main paper): "Randomisation was done at the coordination centre by a computer analyst who was masked to the investigation centres and to the patients. Randomisation was done with a computer-generated sequence and was stratified by centre, and sequential minimisation with a factor of 85% was used to avoid imbalance in treatment."
Allocation Concealment (selection bias)	Low	Quote (from main paper): "Participants were enrolled by local investigators and assigned to the trial group according to the random number."
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Partly, although not for mRS. CT and MRI images were reviewed by an independent committee of four experienced neuroradiologists who were masked to randomisation group and patient clinical outcome. Three other experienced independent interventional neuroradiologists who were masked to patient clinical outcome and other imaging data reviewed the angiograms before and after thrombectomy and provided a consensus evaluation. Cerebral perfusion was assessed with the mTICI scale. 19 Clinical assessments were done by vascular neurologists who were not masked to the treatment to which the patients had been allocated.
Incomplete outcome data (attrition bias)	Low	Loss to follow-up (2 cases, 2 controls) and missing data (2 cases, 4 controls) represents small proportion of participants (204 cases, 208 controls).
Selective reporting (reporting bias)	Low	Primary outcomes all reported. Most secondary outcomes reported.
Other bias	Unclear	Trial stopped early after unplanned interim analysis. Study sponsorship – the study was funded by the French Ministry for Health. Quote (from main paper): "The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report."

Appendix 4 GRADE assessment: effectiveness and safety of mechanical thrombectomy devices

Outcome	No. Studies	Study Design	Bias	Consistency	Directness	Imprecision	Other Factors	Quality	Importance
mRS at 90 days	9	RCTs	Moderate Risk[1]	Serious inconsistency[2]	No serious indirectness	Moderate imprecision	5 studies stopped early	Low[4]	Critical
All cause mortality at 90 days	9	RCTs	Moderate Risk[1]	No serious inconsistency	No serious indirectness	Moderate imprecision	5 studies stopped early	Moderate	Critical
Barthel Index at 90 days	4	RCTs	Moderate Risk[1, 3]	No serious inconsistency	No serious indirectness	Moderate imprecision	2 studies stopped early	Moderate	Critical
SICH	9	RCTs	Moderate Risk[1]	No serious inconsistency	No serious indirectness	Serious imprecision	5 studies stopped early	Moderate	Critical
Any Haemorrhage	8	RCTs	Moderate Risk[1]	Serious inconsistency	No serious indirectness	Serious imprecision	4 studies stopped early	Low	Critical
Recurrent Stroke at 90 days	4	RCTs	Low Risk[1]	No serious inconsistency	No serious indirectness	Serious imprecision	3 studies stopped early	Low	Critical

1. See Risk of bias table
2. Lack of consistency between earliest three and latest five studies. Also lack of consistency in result with wide variation in % getting mRS≤2
3. One of the RCTs, IMS III, had planned to analyse Barthel Index at 90 days but did not report on this outcome measure
4. The overall quality of the eight trials is deemed as low because of the serious inconsistency between earlier and later trials. If analysis was confined to studies which commenced after 2010, the evidence would be deemed moderate.

Appendix 5 Search details for economic evaluations

Inclusion criteria

Studies will be included if they compare the costs and consequences of mechanical thrombectomy added to usual care compared to routine care alone for people with acute ischaemic stroke in the anterior and/or posterior region. The studies have to report the cost-effectiveness of the intervention. The studies must be randomised controlled trials (RCTs), observational studies, or economic modelling studies.

Population	Adults aged 18 years or older with acute ischaemic stroke in the anterior and/or posterior region.
Intervention	Mechanical thrombectomy alone or in combination with intravenous (and/or intra-arterial) thrombolysis or as an alternative to it in patients experiencing an acute ischaemic stroke who are not candidates for thrombolysis or in whom thrombolysis appears to have failed.
Comparator	Standard of care (which may include intravenous and/or intra-arterial thrombolysis where appropriate).
Outcomes	Cost-utility or cost-effectiveness.
Study design	Randomised controlled trials (RCTs), observational studies, or economic modelling studies.

Search strategy

The search for economic evaluations will be carried out in PubMed, EMBASE and the Cochrane Library. The search will include articles published between January 1st 2005 and the date of the search. A search of the main HTA agency websites and Google will also be used. In addition, systematic reviews of the clinical effectiveness of mechanical thrombectomy will be hand-searched for primary studies that included cost or economic outcomes.

The Consensus on Health Economic Criteria (CHEC)-list will be used to assess the quality of the studies. For studies that include an assessment of cost-utility or an economic modelling approach, assessment of the relevance of the studies and their credibility will be considered using a questionnaire from the International Society of Pharmacoeconomic Outcomes Research (ISPOR).

PubMed

(((((((embolectomy[Title/Abstract]) OR "mechanical thrombus removal"[Title/Abstract]) OR "mechanical embolus removal"[Title/Abstract]) OR "endovascular intervention"[Title/Abstract]) OR "mechanical device"[Title/Abstract]) OR "endovascular recanalisation"[Title/Abstract]) OR "endovascular embolectomy"[Title/Abstract])

OR

(((((((((stroke[MeSH]) OR stroke[Title/Abstract])) OR "Cerebrovascular accident"[Title/Abstract]) OR "Large vessel occlusion"[Title/Abstract]) OR "Large artery occlusion"[Title/Abstract])) AND ((((((((((((thrombectomy[MeSH terms] OR Thrombectomy[Text Word])))) OR (("mechanical thrombolysis"[MeSH terms] OR mechanical thrombolysis[Text Word])))) OR (("endovascular procedures"[MeSH terms] OR endovascular procedures[Text Word])))) OR ((angioplasty[MeSH terms] OR angioplasty[Text Word])))) OR "endovascular therapy"[Title/Abstract]) OR "revascularization"[Title/Abstract]) OR "stent retriever"[Title/Abstract]) OR "mechanical recanalization"[Title/Abstract]) OR "stent recanalization"[Title/Abstract]) OR "clot retrieval"[Title/Abstract]) OR "retrievable stent"[Title/Abstract]) OR "intra-arterial"[Title/Abstract])))

AND

((((((((((((((((((models, economic[mesh]) OR "economics, pharmaceutical"[mesh]) OR "economics, medical"[mesh]) OR "health care costs"[mesh]) OR "decision support techniques"[mesh]) OR "cost-benefit analysis"[mesh]) OR "Cost of illness"[mesh]) OR "cost savings"[mesh]) OR "Hospital costs"[mesh]) OR "economic"[ti]) OR ("costs and cost analysis"[mesh])) OR economic evaluation*[ti]) OR economic analy*[ti]) OR cost analy*[ti]) OR cost eff*[ti]) OR cost benefit*[ti]) OR cost utilit*[ti]) OR ("economics"[mesh])) OR cost*[ti/ab])

EMBASE

embolectomy:ab,ti OR 'mechanical thrombus removal':ab,ti OR 'mechanical embolus removal':ab,ti OR 'endovascular intervention':ab,ti OR 'mechanical device':ab,ti OR 'endovascular recanalisation':ab,ti OR 'endovascular embolectomy':ab,ti

OR

((stroke/exp OR stroke:ab,ti) OR 'Cerebrovascular accident':ab,ti OR 'Large vessel occlusion':ab,ti OR 'Large artery occlusion':ab,ti) AND ((thrombectomy/exp OR Thrombectomy.tw) OR ('mechanical thrombolysis'/exp OR mechanical thrombolysis.tw) OR ('endovascular procedures'/exp OR endovascular procedures.tw) OR (angioplasty/exp OR angioplasty.tw) OR 'endovascular therapy':ab,ti OR 'revascularization':ab,ti OR 'stent retriever':ab,ti OR 'mechanical recanalization':ab,ti OR 'stent recanalization':ab,ti OR 'clot retrieval':ab,ti OR 'retrievable stent':ab,ti OR 'intra-arterial':ab,ti)

AND

(models, AND economic OR 'economics'/exp OR 'economics, pharmaceutical'/exp OR 'economics, medical'/exp OR 'health care costs'/exp OR 'decision support techniques'/exp OR 'cost benefit analysis'/exp OR 'cost of illness'/exp OR 'cost savings'/exp OR 'hospital costs'/exp OR 'economic':ab,ti OR 'costs and cost analysis'/exp OR cost*:ab,ti OR (economic AND evaluation*:ab,ti) OR (economic AND analy*:ab,ti) OR (cost AND analy*:ab,ti) OR (cost AND eff*:ab,ti) OR (cost AND benefit*:ab,ti) OR (cost AND utilit*:ab,ti))

Cochrane

#1	MeSH descriptor: [thrombectomy] explode all trees
#2	thrombectomy:ti,ab,kw
#3	endovascular therapy:ti,ab,kw
#4	revascularisation:ti,ab,kw
#5	stent retriever:ti,ab,kw
#6	mechanical recanalization:ti,ab,kw
#7	stent recanalization:ti,ab,kw
#8	clot retrieval:ti,ab,kw
#9	retrievable stent:ti,ab,kw
#10	intra-arterial:ti,ab,kw
#11	mechanical thrombectomy:ti,ab,kw
#12	~~MeSH descriptor: [mechanical thrombectomy] explode all trees~~
#13	endovascular procedure:ti,ab,kw
#14	MeSH descriptor: [endovascular procedure] explode all trees
#15	angioplasty:ti,ab,kw
#16	MeSH descriptor: [angioplasty] explode all trees
#17	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18	stroke:ti,ab,kw

#19	MeSH descriptor: [stroke] explode all trees
#20	cerebrovascular accident:ti,ab,kw
#21	large vessel occlusion:ti,ab,kw
#22	large artery occlusion:ti,ab,kw
#23	(#18 OR #19 OR #20 OR #21 OR #22)
#24	(#17 AND #23)
#25	embolectomy:ti,ab,kw
#26	endovascular recanalization:ti,ab,kw
#27	endovascular embolectomy:ti,ab,kw
#28	mechanical thrombus removal:ti,ab,kw
#29	mechanical embolus removal:ti,ab,kw
#30	endovascular intervention:ti,ab,kw
#31	mechanical device:ti,ab,kw
#32	(#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31)
#33	MeSH descriptor: [Models, Economic] explode all trees
#34	MeSH descriptor: [Economics] explode all trees
#35	MeSH descriptor: [Economics, Pharmaceutical] explode all trees
#36	MeSH descriptor: [Economics, Medical] explode all trees
#37	MeSH descriptor: [Health Care Costs] explode all trees
#38	MeSH descriptor: [Decision Support Techniques] explode all trees
#39	MeSH descriptor: [Cost-Benefit Analysis] explode all trees
#40	MeSH descriptor: [Cost of Illness] explode all trees
#41	MeSH descriptor: [Cost Savings] explode all trees
#42	MeSH descriptor: [Hospital Costs] explode all trees
#43	economic:ti,ab,kw (Word variations have been searched)
#44	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#45	cost*:ti,ab,kw (Word variations have been searched)

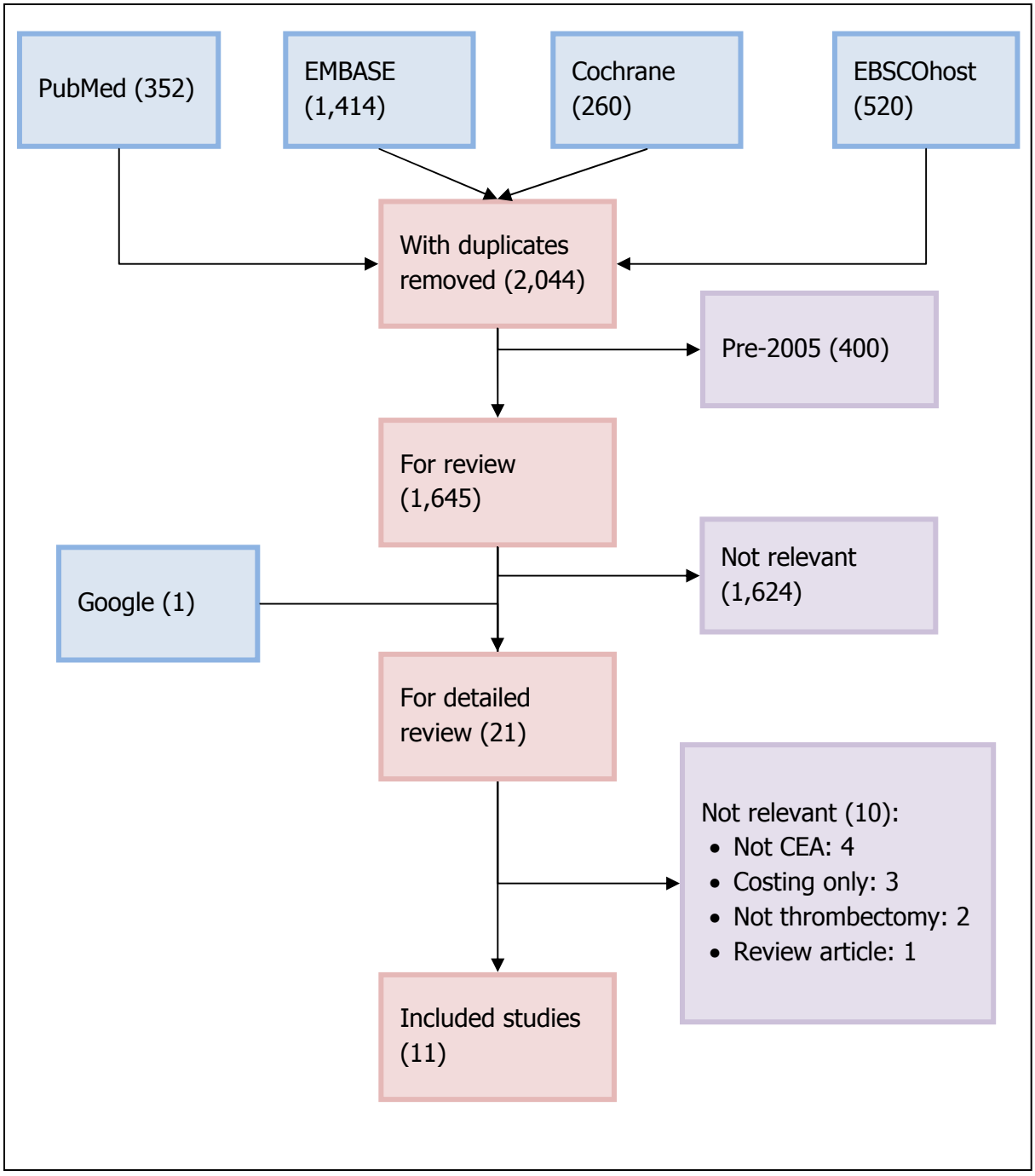
#46	economic evaluation*:ti,ab,kw (Word variations have been searched)
#47	economic analy*:ti,ab,kw (Word variations have been searched)
#48	cost analy*:ti,ab,kw (Word variations have been searched)
#49	cost eff*:ti,ab,kw (Word variations have been searched)
#50	cost benefit*:ti,ab,kw (Word variations have been searched)
#51	cost utilit*:ti,ab,kw (Word variations have been searched)
#52	(#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51)
#53	#24 OR #32
#54	#52 AND #53

EBSCOhost (Academic Search, CINAHL, EconLit)

S1	SU thrombectomy OR TI thrombectomy OR AB thrombectomy
S2	TI endovascular therapy OR AB endovascular therapy
S3	TI revascularisation OR AB revascularisation
S4	TI stent retriever OR AB stent retriever
S5	TI mechanical recanalization OR AB mechanical recanalization
S6	TI stent recanalization OR AB stent recanalization
S7	TI clot retrieval OR AB clot retrieval
S8	TI retrievable stent OR AB retrievable stent
S9	TI intra-arterial OR AB intra-arterial
S10	SU mechanical thrombectomy OR TI mechanical thrombectomy OR AB mechanical thrombectomy
S11	SU endovascular procedure OR TI endovascular procedure OR AB endovascular procedure
S12	SU angioplasty OR TI angioplasty OR AB angioplasty
S13	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S14	SU stroke OR TI stroke OR AB stroke
S15	TI cerebrovascular accident OR AB cerebrovascular accident
S16	TI large vessel occlusion OR AB large vessel occlusion
S17	TI large artery occlusion OR AB large artery occlusion
S18	S14 OR S15 OR S16 OR S17
S19	S13 AND S18
S20	TI embolectomy OR AB embolectomy
S21	TI endovascular recanalization OR AB endovascular recanalization
S22	TI endovascular embolectomy OR AB endovascular embolectomy
S23	TI mechanical thrombus removal OR AB mechanical thrombus removal

S24	TI mechanical embolus removal OR AB mechanical embolus removal
S25	TI endovascular intervention OR AB endovascular intervention
S26	TI mechanical device OR AB mechanical device
S27	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26
S28	SU Models, Economic
S29	SU Economics
S30	SU Economics, Pharmaceutical
S31	SU Economics, Medical
S32	SU Health Care Costs
S33	SU Decision Support Techniques
S34	SU Cost-Benefit Analysis
S35	SU Cost of Illness
S36	SU Cost Savings
S37	SU Hospital Costs
S38	TI economic OR AB economic
S39	SU Costs and Cost Analysis
S40	TI cost* OR AB cost*
S41	TI economic evaluation* OR AB economic evaluation*
S42	TI economic analy* OR AB economic analy*
S43	TI cost analy* OR AB cost analy*
S44	TI cost eff* OR AB cost eff*
S45	TI cost benefit* OR AB cost benefit*
S46	TI cost utilit* OR AB cost utilit*
S47	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46
S48	S19 OR S27
S49	S47 AND S48

Figure App5.1 Flow diagram of included studies



Appendix 6 Details of included cost-effectiveness studies

Study	Intervention	Population	Analysis Details • country • methodology • perspective • discount rate • time horizon • currency	Clinical & QALY Outcomes	Costs	Results
Aronsson 2016	Endovascular treatment compared with standard care (including IV t-PA).	Simulated cohort of patients with acute ischaemic stroke. Mean age 67.2 years.	• Sweden • Markov model • health care payer • 3% • Lifetime • converted to US$ at March 2015 exchange rates	Outcomes are based on mRS at 90 days, pooled from the ESCAPE, EXTEND-IA, MR CLEAN, REVASCAT and SWIFT PRIME studies.	The cost of added thrombectomy to standard care was $7,908 (€6,712).	Irrespective of which study data were used, there was a >85% probability that adding endovascular treatment to standard care would cost less than $10,000 (€8,488) per QALY gained.
Bouvy 2013	Intra-arterial treatment (IAT) with and without intravenous thrombolysis (IVT) compared with IVT. Conservative treatment also modelled.	Simulated cohort of patients with acute ischaemic stroke and who can be treated within 4.5 hours of symptoms onset.	• Netherlands • Markov model • payer • 3% • 6 months and lifetime • 2010 Dutch euro	Outcomes were based on expert opinion and published evidence.	Cost data were derived from two trials. No cost was stated specific to mechanical thrombectomy.	Based on a 6 months time horizon, IAT was dominated and the ICER for combined IV-IA thrombolysis was €31,687 (€41,137) per QALY. Based on a lifetime time horizon, the ICER for IV-IA thrombolysis relative to IAT was €1,922 (€2,495) per QALY.

Ganesalingam 2015	Mechanical thrombectomy in combination with IV t-PA compared with IV t-PA alone.	Patients presenting with acute ischaemic stroke.	• UK • Markov model • health service • 3.5% • 20 years (lifetime) • 2013/14 GBP converted to US$	Outcomes were estimated from a variety of sources including 5 RCTs and two UK stroke service reviews.	The cost of mechanical thrombectomy was $13,803 (€10,622).	The ICER for mechanical thrombectomy relative to IV t-PA alone was $11,651 (€8,966) per QALY.
Kim 2011	Mechanical thrombectomy in combination with IV t-PA compared with IV t-PA alone.	A 68 year old with acute large-vessel ischaemic stroke eligible for IV t-PA receiving thrombolysis within 3 hours of symptom onset.	• US • Markov model • societal • 3% • Lifetime • 2009 US$	Outcome data were derived from the Multi-MERCI trial.	The intervention was associated with an increase treatment cost of between $12,249 (€12,367) and $13,589 (€13,719).	The ICER for the intervention was $16,001 (€16,155) per QALY relative to IV t-PA alone.
Leppert 2015	Intra-arterial treatment (IAT – IA thrombolysis, mechanical thrombectomy, or both) with intravenous thrombolysis (IVT) compared with IVT alone.	A 65 year old with acute large-vessel ischaemic stroke eligible for IV t-PA receiving thrombolysis within 4.5 hours of symptom onset and IAT within 6 hours.	• US • Markov model • payer • 3% • 30 years • 2012 US$	Outcome data for mRS at 90 days were derived from the MR CLEAN trial.	The additional cost of IAT was $14,405 (€13,166) which could include arterial catheterisation with thrombolysis, mechanical thrombectomy, or both).	The ICER for the intervention was $14,137 (€12,921) per QALY relative to IV t-PA alone. In the one-way sensitivity analysis, the ICER remained below $50,000 (€45,698) per QALY in all cases.
Lobotesis 2016	Combined stent-retriever thrombectomy and IV t-PA compared with IV t-PA alone.	A 66 year old with confirmed occlusions in the proximal anterior intracranial circulation and an absence of large ischaemic-core lesions. Intervention	• UK • Markov model • healthcare provider • 3.5% • lifetime (and 1/2/5 years)	Clinical effectiveness (mRS at 90 days) and safety (symptomatic haemorrhage and vasospasm) data came from	The cost associated with the stent retriever was £7,283 (€9,247) per case.	At lifetime, two years and five years, the intervention dominates (i.e., is less costly and more effective than) IV t-PA alone. At one year, the ICER is £369 (€469) per QALY relative to

		arm had to undergo mechanical thrombectomy within 6 hours of symptom onset.	• 2013/14 GBP	the SWIFT PRIME study.		IV t-PA alone.
Mangla 2016	Mechanical thrombectomy compared with IV t-PA alone.	Patients that had an acute stroke secondary to large vessel occlusion and considered eligible for medical or interventional treatment.	• US • cost-benefit analysis • payer • not applied • lifetime • 2015 US$	Outcome data were based on mRS at 90 days as reported in the MR CLEAN study.	Based on Medicare Severity DRG, the intervention cost $20,371 (€17,291) and standard care cost $5,788 (€4,913). Remaining QALYs were valued at $129,090 (€109,574) per annum.	The direct benefit of mechanical thrombectomy was valued at $1,788 (€1,518) per patient, and the indirect benefit was valued at $161,836 (€137,370) per patient.
Nguyen-Huynh 2011	Endovascular treatment with mechanical clot removal or clot disruption in comparison with best medical therapy outside the 3 hour window for IV t-PA.	Patients aged 65 year with acute ischaemic stroke who present 3 to 8 hours after symptom onset.	• US • Markov model • societal • 3% • Lifetime • 2009 US$	Recanalisation and mRS outcomes for the intervention were taken from the Multi MERCI trial. Outcomes for best medical care were taken from a meta-analysis.	Using Medicare Severity DRGs, the intervention cost $28,087 (€28,357) with and $19,210 (€19,394) without ICH complications. Standard care cost $10,245 (€10,343) with and $4,686 (€4,731) without ICH complications.	The ICER for the intervention was $9,386 (€9,476) per QALY relative to best medical therapy.

Ontario 2016	Mechanical thrombectomy (with or without IVT) compared with IVT alone.	Patients aged 65 to 70 years with an acute large-artery ischaemic stroke, occlusion confirmed by imaging, and functioning independently prior to the stroke.	• Canada • Markov model • payer and societal • 5% • 5 years • 2015 Canadian dollars	Outcome data on mortality, mRS and QoL were derived from pooled data from 5 RCTs (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE).	The additional cost of mechanical thrombectomy (compared to IVT alone) was $15,000 (€10,440).	From a payer perspective, the ICER for combined mechanical thrombectomy and IVT was $11,990 (€8,345) per QALY relative to IVT alone. From a societal perspective, the intervention dominated standard care.
Patil 2009	Mechanical thrombectomy with the MERCI device compared with standard medical therapy (including antiplatelet agents but no thrombolytics).	A 67 year old patient with large-vessel ischaemic stroke who could receive treatment within 8 hours of symptom onset.	• US • Markov model • societal • 3% • 20 years • 2008 US$	Outcomes (recanalisation, SICH, recurrent stroke, functional independence) were derived from the MERCI, NINDS tPA and PROACT II trials.	Procedural costs were estimated as $24,154 (€25,159) for mechanical thrombectomy and $6,749 (€7,030) for standard therapy.	The ICER for mechanical thrombectomy compared with standard therapy was $12,120 (€12,624) per QALY.
Thurman 2015	Thrombectomy (primarily with stent retrievers) in addition to IVT compared with IVT alone.	A 67 year old patient with newly detected acute severe ischaemic stroke.	• Sweden • Markov • societal • not reported/not applied • 20 years • 2015 Swedish kroner	Outcomes are based on mRS at 90 days, pooled from the MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME and REVASCAT studies.	The intervention was estimated to cost 78,400 kroner (€7,372) more than standard care.	The ICER for mechanical thrombectomy with IVT compared with IVT alone was SEK45,000 (€4,231) per QALY.

Key: GBP, British pounds; IAT, intra-arterial thrombolysis; ICER, incremental cost-effectiveness ratio; IV t-PA, ; QALY, quality-adjusted life year; SEK, Swedish kroner; US$, US dollars.

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