Assessing the Clinical and Cost-Effective Resource Implications of Mechanical Thrombectomy for the treatment of Acute Ischaemic Stroke within the NHS

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Thesis submitted for the degree of

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Supervisors

Professor Alastair Buchan, Professor Gary Ford and Professor Alastair Gray

Abstract

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Stroke is a major health issue associated with severe disability and high mortality, particularly in acute ischaemic stroke (AIS) due to large artery occlusion (LAO). Early and complete recanlisation can lead to improved functional outcomes and reduced mortality. Mechanical thrombectomy (MT) with intravenous thrombolysis (IVT) is the most effective treatment for acute ischaemic stroke due to LAO. Yet the true cost of delivering the treatment within the National Health Service (NHS) has not been previously fully established. This study aims to fill that information gap and provide better estimates of the costs and drivers of costs of providing MT within the NHS.

The study begins with an evaluation of the evidence of the clinical benefit of MT with IVT by conducting a systematic review and meta-analysis of thrombectomy trials. Alternative treatment pathways are identified, and the resources used, for them, to determine the related unit costs along each identified treatment pathway using MT and IVT and various combinations. Through a comprehensive approach to measuring costs, the true cost of delivering MT and the main drivers of costs are also determined. The mean cost within 24 hours per patient treated with MT +/- IVT was £10,866 (standard deviation (SD) £2,801), with MT procedure accounting for 73% (£7,943/£10,866) of the 24-hour cost and devices, accounting for 65% (£5,176/ £7,943) of the procedure cost. The mean cost was £14,369 (SD £6,664) after 24 hours until discharge from MT centre (2018 prices). Next, the application of micro-costing data in an economic evaluation model provided health economic evidence and showed achievable cost-savings from health and social care; and societal perspectives.

The research carried out for this thesis has contributed to the literature for the treatment of AIS by: confirming the clinical benefits of MT; identifying variations in treatment of MT and IVT in different centres in the UK and other countries; and by establishing the comprehensive costs of delivering MT. It has demonstrated clear evidence of the benefits of MT for the treatment of AIS for restoring patients' functional independence to optimal levels and reducing avoidable morbidity. It concludes that MT with IVT is cost-effective when compared with standard care and associated cost-savings.

This thesis provides clinicians, researchers, hospital managers and policy makers with more accurate and comprehensive information than previously available on the community-based costs of delivering MT within the clinical setting of the United Kingdom's NHS.

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Statement of contributions

This doctoral thesis is independent and original work of which I am the sole author. Academic supervisors Professor Alastair Buchan, Professor Gary Ford and Professor Alastair Gray contributed supportive guidance on the overall research strategy, protocol, analyses, publications and presentation of results. Dr Paolo Candio provided guidance with the modelling method and analysis.

Other individuals and teams have made contributions in the following ways:

Neal Thurley: Outreach Librarian at the Bodleian Library, assisted in developing the search strategy for the Systematic Literature review in Chapters 3, 5 and 7

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Publications, presentations and award related to this thesis

Publications

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Balami JS, Coughlan D, McMeekin P, White PM, Flynn D, Roffe C, Wiggam I, Flynn P, Chembala J, Natarajan I, Dixit A, Hunter A, Foddy L, Hopkins E, Lumley H, Rice S, Burgess D, Craig D, Buchan AM, Ford GA, Gray A. Case costing of mechanical thrombectomy for acute ischaemic stroke in routine clinical setting: Cost differences between mothership vs drip and ship. Int J Stroke. 2018; 13:45 –6.

Balami JS, White PM, McMeekin P, Ford GA, Buchan AM. Complications of Endovascular Mechanical Thrombectomy for the Treatment of Acute Ischaemic Stroke: Prevention and Management. Int J Stroke. 2018 Jun;13(4):348-361.

Flynn D, Francis R, Halvorsrud K, Gonzalo-Almorox E, Craig D, Robalino S, McMeekin P, Cora A, **Balami J**, Ford GA, White P. Intra-arterial mechanical thrombectomy stent retrievers and aspiration devices in the treatment of acute ischaemic stroke: A systematic review and meta-analysis with trial sequential analysis. Eur Stroke J. 2017 Dec;2(4):308-318.

Sutherland BA, Ain A Neuhaus, Yvonne Couch, **Balami JS,** Gabriele C DeLuca, Gina Hadley, Scarlett L Harris, Adam N Grey, Alastair M Buchan. The transient intraluminal filament middle cerebral artery occlusion model as a model of endovascular thrombectomy in stroke. Journal of Cerebral Blood Flow & Metabolism. 2016 Feb;36(2):363-9.

Balami JS, Sutherland BA, Edmunds LD, Grunwald IQ, Neuhaus AA, Hadley G, Karbalai H, Metcalf KA, DeLuca GC, Buchan AM. A Systematic Review and Meta-analysis of Randomised Controlled Trials of Endovascular Thrombectomy Compared to Intravenous Thrombolysis for Acute Ischemic Stroke. Int J Stroke. 2015 Dec;10(8):1168-78 -
This formed basis of NICE IPG 545 (National Institute for Health and Care Excellence. Mechanical clot retrieval for treating acute ischaemic stroke IPG 548 (online) http://www.nice.org.uk/guidance/ipg548).

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List of Abbreviations

Abbreviation	Meaning
ADAPT	A Direct Aspiration First-Pass Technique
ADC	Apparent Diffusion Coefficient
AIS	Acute Ischaemic Stroke
ASPECTS	Alberta Stroke Program Early CT Score
ASU	Acute Stroke Unit
ANP	Assistant Nurse Practitioner
ATP	Adenosine Triphosphate
BASIS	Boston Acute Stroke Imaging Scale
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CCS	Causative Classification of Ischemic Stroke
CS	Conscious Sedation
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CMT	Core Medical Trainee
CPSS	Cincinnati Pre-hospital Stroke Severity Scale
CT	Computerised Tomography
CTA	Computerised Tomography Angiography
CTA-CS	Computerised Tomography Angiography Collateral Scoring
CTP	CT Perfusion (CTP)
CUA	Quality Adjusted Year
DAC	Direct Access Catheter
DALYs	Disability-Adjusted-Life-Years
DAM	Decision Analytical Modelling
DAWN	DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo
DEFUSE 3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3
DS	Drip-and- Ship
DSA	Digital Subtraction Angiography
DWI	Diffusion Weighted Imaging
DAWN	DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo
DEFUSE	Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution
EASI	Endovascular Acute Stroke Intervention
ECASS	European Cooperative Acute Stroke Study
ED	Emergency Department
EMS	Emergency Medical Service
*E*SCAPE	Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times

Abbreviation	Meaning
ESD	Early Supported Discharge
ER	Emergency Room
ESO	European Stroke Organisation
EVT	Endovascular Thrombectomy
EXTEND-IA,	Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial
FLAIR	Fluid-Attenuated Inversion Recovery
GA	General Anaesthesia
GBP	Great British Pounds
GCS	Glasgow Coma Scale
GDP	Gross Domestic Product
GRE	Gradient Recalled Echo
HASU	Hyper Acute Stroke Unit
HEMS	Helicopter Emergency Medical Service
HERMES	Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials
HDU	High Dependency Unit
HRG	Healthcare Resource Group
HRQol	Health Related Quality of Life
HTA	Health Technology Assessment
IA	Intra-Arterial
ICA	Internal Carotid Artery
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IPD	Individual Patient Data
IRS	Interventional Radiology Suit
ITT	Intention-To-Treat
IVT	Intravenous Thrombolysis
LA	Local Anaesthesia
LAO	Large Vessel Occlusion
LAMS	Los Angeles Motor Scales
LOS	Length of Stay
LY (S)	Life Year(s)
MDT	Multidisciplinary Team
mRS	Modified Rankin Score
MSU	Mobile Stroke Unit
MS	Mothership
MT	Mechanical Thrombectomy
MTT	Mean Transit Time
MSU	Mobile Stroke Unit
MA	Meta-Analysis
MCA	Middle Cerebral Artery
MCT	Multimodal Computed Tomography
mCTA	Multiphase CT Angiogram mCTA
MeSH	Medical Subject Headings
mRS	Modified Rankin score
MSU	Mobile Stroke Unit

Abbreviation	Meaning
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands
MR RESCUE	Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy
mTICI	Modified TICI
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NCCT	Non-Contrast Computed Tomography
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke trial of Tissue Plasminogen Activator for Acute Ischaemic Stroke
NNT	Number Needed to Treat
ODA	Operational Dependent Assistant
ODP	Operational Dependent Practitioner
oTICI	Original TICI
PBFC	Proximal Balloon Flow Arrest Guide Catheter
PISTE	Pragmatic Ischaemic Thrombectomy Evaluation
PICOS	Population, Intervention, Control, Outcomes, and Study Design
POCS	Posterior Circulation Stroke
PRISMA	Preferred Reporting Items for Systematic and Meta-Analysis
PROACT	Prolyse in Acute Cerebral Thromboembolism
PSSRU	Personal Social Services Unit
QALY	Quality Adjusted Year
QOF	Quality and Outcome Framework
RCT	Randomised Controlled Trials
RESILIENCE	Randomization of Endovascular Treatment With Stent-retriever and/or Thromboaspiration vs. Best Medical Therapy in Acute Ischemic Stroke Due to Large Vessel OcclusioN Trial
RACE	Rapid Arterial Occlusion Evaluation
RACECAT	Direct Transfer to an Endo-vascular Center Compared with Transfer to the Closest Stroke Center in Acute Stroke Patients with Suspected Large Vessel Occlusion
REVASCAT	Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 hours of Symptom Onset
rt-PA	Recombinant Tissue Plasminogen Activator
SD	Standard Deviation
SE	Standard Error
SICH	Symptomatic Intra-Cerebral Haemorrhage
(SITS-ISTR)	Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register Registrar

Abbreviation	Meaning
SITS-MOST	Safe Implementation of Thrombolysis in Stroke - Monitoring Study
SITS-TBY	Safe Implementation of Thrombolysis in Stroke-Thrombectomy
SN	Scrub Nurse
SR	Systematic Review
SR	Stent Retrievers
SRLA	Stent-Retrievers with Local Aspiration
SSNAP	Sentinel Stroke National Audit Programme
SSS-TOAST	Stop Stroke Study TOAST
SWI	Susceptibility Weighted Imaging
SWIFT PRIME	Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke
TA	Thrombo-Aspirators
TBEE	Trial-Based Economic Evaluation
THERAPY	The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke
THRACE	Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic
TIA	Transient Ischaemic Attack
TICI	Treatment in Cerebral Ischaemia (also termed the Thrombolysis in Cerebral Infarction) Thrombolysis in Cerebral Infarction Score
TPD	Total Patient Data
Tmax	Time-to-Maximum
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UK	United Kingdom
WTP	Willingness-To-Pay
WHO	World Health Organisation

CHAPTER ONE

1 INTRODUCTION

1.1 OVERVIEW OF THESIS

Stroke is a common clinical problem with high mortality and significant long-term disability among survivors. The treatment of acute ischaemic stroke (AIS) has evolved and mechanical thrombectomy (MT) has become part of standard care in routine clinical practice, but there are still evidence gaps concerning outcomes and costs. I intend to address these gaps in this thesis by exploring the clinical effectiveness and the costs to the National Health Service (NHS) of delivering MT in routine clinical practice in the United Kingdom (UK). I begin by establishing the existing evidence of the clinical benefit of MT in combination with intravenous thrombolysis (IVT) for the treatment of AIS through an overview of systematic review of MT randomised controlled trials (RCTs). This is followed by establishing whether outcomes and the safety of MT in real world practice matched those achieved in the RCTs, through analysis of clinical data and then comparing the results with those from the clinical trials. The results confirm the safety and efficacy of MT when used in combination with IVT for the treatment of large artery occlusion (LAO) strokes in regular community-based practice outside research settings and indicate that outcomes from MT in routine clinical practice in the UK are similar to those from the RCTs.

In response to these findings, the thesis then attempts to establish the actual cost of providing MT for AIS within the UK's NHS. Micro-costing methods were used

to enable a precise assessment of the costs of MT from an NHS perspective. Data were collected on patients treated, in line with routine clinical practice, in five experienced and active thrombectomy centres in England and Northern Ireland. The results provide detailed information of the current costs of providing MT in routine clinical settings.

1.2 AIM OF THESIS

This thesis aims to establish the clinical effectiveness of MT for AIS in routine clinical practice and to provide, by detailing contributory cost components and the total costs of delivering MT for stroke patients within the NHS in the UK.

1.3 RESEARCH OBJECTIVES

The research objectives of this thesis were:

1. To establish what is known in the existing literature on MT for large vessel occlusion strokes and identify research gaps.
2. To determine the effectiveness of MT in the clinical setting using established clinical metrics, to assess the current UK practice in the use of MT.
3. To identify the various treatment pathways for MT in routine clinical practice.
4. To evaluate the true costs of delivering MT in routine clinical practice to the NHS.
5. To determine how the introduction of a more detailed costing into an already developed model might affect the estimated incremental cost-effectiveness ratio (ICER) and the probability of the MT intervention being cost-effective.

1.4 STUDY METHODOLOGY

The evidence-based strategy to achieve these aims draws on the application of different methods for each of the chapters, including: a retrospective analysis of databases of stroke patients treated with MT and IVT in routine clinical practice; mapping the treatment pathways for patients treated with MT and IVT; cost analysis study and modelling using an existing cost-effectiveness model. The methods discussed in the various chapters are summarised in Table 1.1.

1.5 STRUCTURE OF THESIS

A brief description of all seven subsequent chapters of this thesis is provided in the following sections.

1.5.1 Chapter 2. Introduction to Acute Ischaemic Stroke

Chapter 2 introduces the clinical background of this thesis. The chapter begins with an introduction to the epidemiology and economic burden of stroke, the historical advances in stroke therapy and the current evidence-based treatment modalities.

1.5.2 Chapter 3. Systematic Review and Meta-analysis of Mechanical Thrombectomy for Treatment of Acute Ischaemic Stroke

Chapter 3 assesses the current evidence of MT for the treatment of AIS from the literature based on, a conducted systematic review and meta-analysis. These analyses demonstrate clear evidence of the benefits of MT when used alongside IVT compared with standard medical treatment (with or without IVT) for the treatment of AIS.

1.5.3 Chapter 4. Mechanical Thrombectomy for the Treatment of Acute Ischaemic Stroke in routine clinical practice in the UK

Chapter 4 examines the current UK experience with MT for AIS using prospective observational registry data of patients treated in routine clinical practice. The output from this process further confirms the evidence for the clinical effectiveness and safety of MT, both in research trials and routine clinical practice. Evidence gaps were, however, identified due to missing or incomplete data, particularly for recanalisation rates and the 90-day follow-up records.

1.5.4 Chapter 5. Treatment Pathways for Mechanical Thrombectomy and Intravenous Thrombolysis

Chapter 5 begins by exploring what is known from the existing literature about the range of treatment pathways for patients treated with MT and IVT. This is followed by identifying the treatment pathways from five neuroscience centres in the UK and five from other international centres (in Germany, Italy and Canada). Cohorts of patients following the selected pathways were tracked to establish the routes taken from the onset of stroke through to hospital admission and to discharge between January 2015 and December 2018. The variations across different treatment pathways were established and those from the UK were compared with those from Germany, Italy and Canada.

1.5.5 Chapter 6. Resource Use, Unit Costs and Cost of Mechanical Thrombectomy and Intravenous Thrombolysis for Treatment of Acute Ischaemic Stroke

Chapter 6 draws on from the identified treatment pathways identified in the previous chapter. Firstly, it identifies the detailed resources used, quantifying those resources and allocating unit costs for the resources used.

Secondly, the resources used are then quantified and unit costs apportioned. Finally, the total cost for all patients travelling through the pathway are calculated.

Based on a sample of comprehensive individual patient data (IPD), obtained from the participating hospitals in Chapter 5, the actual cost per patient going through the pathway was calculated to provide comparisons with all the admitted patients; to reveal the cost of the route variations adopted for some patients; and to provide opportunities for future studies to focus on selected details.

1.5.6 Chapter 7. Systematic Review of Economic Evaluation studies of Mechanical Thrombectomy for Treatment of Acute Ischaemic Stroke and Modelling using an existing Cost-Effectiveness Model

Chapter 7 begins with a systematic review (SR) of the published literature of cost-effectiveness analysis (CEA) studies of MT for acute ischaemic stroke. The second half of the chapter focuses on running a simulation using an existing cost-effectiveness model with more granular data from the micro-costing data in Chapter 6. From the analysis, it can be determined how widely the results from the new output might have differed or changed if the detailed micro-costing data had been used.

1.5.7 Chapter 8. Discussion and Conclusion

Chapter 8 summarises the findings of the thesis and the potential implications for future planning and expansion, re-structuring or re-organisation of thrombectomy services in the UK and in countries with limited MT services. The final discussion addresses the methodological strengths and limitations of the thesis and provides strategic directions for organising and delivering MT effectively and efficiently in routine clinical practice in the NHS.

1.5.8 Contribution to the Literature

This thesis contributes to the literature for the treatment of AIS by: confirming the clinical benefits of MT outside the research setting; identifying variations in treatment pathways of MT and IVT in different centres in the UK and other countries and; establishing the comprehensive costs of providing MT within the NHS in the UK.

1.5.9 Conclusion

This chapter has provided an introduction to the thesis, described the overall aims and objectives, summarised the methodology, outlined the chapters that follow and described the contribution made to the literature. The next chapter introduces the clinical and financial burden of stroke and discusses the evidence-based treatment using MT which is integral to each of the subsequent chapters.

Table 1.1. Summary of methods for the different chapters

Chapter	Methods
Chapter 2 Introduction to acute ischaemic stroke	A review of stroke epidemiology, economic burden and current evidence-based treatment modalities.
Chapter 3 Systematic review and meta-analysis of mechanical thrombectomy for treatment of acute ischaemic stroke	The Systematic review and meta-analysis of RCTs assessing the use of MT for the treatment of acute ischaemic stroke. It follows the Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA) Statement)(Moher et al., 2009) and the review protocols of the Cochrane Collaboration (Higgins and Green, 2009).
Chapter 4 Mechanical thrombectomy for the treatment of acute Ischaemic stroke in routine clinical practice in the UK	Data from the Safe Implementation of Thrombolysis in Stroke-Thrombectomy (SITS-TBY) register, an open, multicentre, prospective, observational registry of stroke patients treated with MT, is analysed. Main outcome measures of UK patients treated in the registry are compared with pooled data from five RCTs. Measures include: functional outcome determined by the modified Rankin score (mRS) at 90 days, recanalisation rate as measured by Thrombolysis in Cerebral Infarction (TICI) and symptomatic intracerebral haemorrhage (sICH).
Chapter 5 Treatment pathways for MT and IVT	The treatment pathways for patients treated with MT are established based on the current practices in routine clinical settings. Anonymised information from the local hospital stroke registries and the Sentinel Stroke National Audit Programme (SSNAP) database are used to populate the treatment pathways.
Chapter 6 Resource Use, Unit Costs and Cost of MT and IVT for treatment of acute ischaemic stroke	A cost analysis from the perspective of the UK National Health Service (NHS)[micro-costing using two costing methods - top-down (gross-costing) and bottom-up (micro-costing)] is adopted as a comprehensive approach to measure the actual cost of MT for the treatment of AIS in a non-research setting (Gold *et al*., 1996, Drummond et al., 2015, Jones et al., 2019).
Chapter 7 Economic evaluation of MT for treatment of acute Ischaemic stroke compared with IVT or standard care	In the first section, the systematic review follows the established review protocols of the Cochrane Collaboration (Higgins and Green, 2009) and Reviews and Dissemination's (CRD) guidance for undertaking reviews in health care (University of York, 2008). In the second section, the micro-costing information on the intervention cost of MT from Chapter 6 is applied to run a simulation using an existing cost-effectiveness model to determine how the ICER changes and if treatment with MT is cost-effective.

CHAPTER TWO

2 Introduction to Acute Ischaemic Stroke

2.1 Introduction

This chapter begins with the epidemiology and pathophysiology of acute ischaemic stroke (AIS). The chronology of the advances in stroke therapy are presented, followed by the economic burden of stroke.

2.1.1 Definition of stroke

The World Health Organisation's (WHO) definition of stroke is the most widely used: It describes stroke as "rapidly developed signs of focal (or global) disturbance of cerebral function lasting greater than 24 hours (unless interrupted by surgery or death), with no apparent non-vascular cause" (Thorvaldsen et al., 1995). An alternative definition by Warlow incorporates the aetiology and underlying associated risk factor, describing stroke as "a clinical syndrome characterised by an acute loss of focal cerebral function with symptoms lasting more than 24 hours or leading to death, and which is thought to be due to spontaneous haemorrhage into the brain substance or inadequate cerebral blood supply to part of the brain as a result of low blood flow, thrombosis, or embolism associated with diseases of the blood vessels" (Warlow et al., 2008, Jung and Mattle, 2019).

2.1.2 Epidemiology

2.1.2.1 International burden of stroke

Globally, stroke is the single largest cause of adult disability-adjusted-life-years (DALYs) lost and the third most common cause of death (Johnson et al., 2019, Wang et al., 2016). The incidence (crude rate) of stroke ranges from 185 to 199 per 100,000 population, with over 13.7 million new strokes, over 116 million DALYs and 5.5 million deaths per year, globally (World Stroke Organization, 2019, Johnson et al., 2019). There are over 80 million survivors of stroke globally, necessitating further secondary preventative strategies (World Stroke Organization, 2019, Feigin et al., 2018). The burden from stroke is estimated to double by 2030 as a result of population growth coupled with an aging population, placing additional demands on healthcare resources and long-term rehabilitation and care (Feigin et al., 2014, Feigin et al., 2017).

In Europe, there is a projected increase in stroke events from 613,148 in 2015 to 819,771 by 2035 (SAFE, 2015). Stroke is responsible for more than one million deaths each year and is the leading cause of long-term disability (Townsend et al., 2016, Wafa et al., 2020, Wilkins et al., 2017). Between 20% to 35% of stroke patients die within 30 days following their stroke, with about one third of survivors losing their independence (Feigin et al., 2009, Feigin et al., 2017, Heuschmann et al., 2011). The incidence and case fatality of stroke differs widely across Europe, with case fatality higher in central and eastern European countries than in northern, western and southern European countries (Feigin et al., 2017, Wafa et al., 2020, Wang et al., 2016, Wilkins et al., 2017).

2.1.2.2 Burden of stroke in the UK

Nationally, in the UK, stroke is the leading cause of DALYs (Newton et al., 2015). The incidence of strokes in the UK ranges from 115 to 150 per 100,000 population (Wang et al., 2013, King et al., 2020, Rothwell et al., 2004), with over 113,000 new strokes each year and an accumulated estimate of one million people living following a stroke (King et al., 2020, Patel et al., 2020, Rothwell et al., 2004). Although, a recent study has reported a continuing decline in stroke incidence, which fell by 32% in Oxfordshire and in other high-income settings over the last 30 years (Li et al., 2020), there is a predicted 13% increase of new cases by the year 2045, due to an ageing population (Li et al., 2020). Approximately half of all stroke survivors live with a disability that means they cannot perform activities of daily living unassisted (Stroke Association, 2018). An increase in incidences of stroke of 59% is projected over a 20-year period from 117,600 in 2015 to 148,700 in 2025 and up to 186,900 by 2035 (King et al., 2020). Similarly, a 123% increase in prevalence has been projected from 950,200 in 2015 to 1,424,100 in 2025 and up to 2,119,400 in 2035 (King et al., 2020). Overall, about 10-14% of patients die within a month of a first ischaemic stroke and 20% within 6 months; 15–30% are permanently disabled and dependent on others for activities of daily living (Luengo-Fernandez et al., 2013, NICEimpact, 2019) and 11-12% require institutional care (King's College London SSNAP, 2018, Clery et al., 2020).

2.1.3 Pathophysiology of acute ischaemic stroke

Cerebral infarction following a vessel occlusion of cerebral vasculature is a complex pathological process involving both cellular and molecular mechanisms that affect neuronal and glial function, that takes a few hours to complete. Brain function is reliant on a continuous supply of oxygen and glucose, and neuronal function within the brain is dependent on adenosine triphosphate (ATP). Following depletion of oxygen or glucose due to reduction in cerebral blood flow (CBF), the ATP production and other high-energy phosphate compounds diminishes, with subsequent failure of energy dependent processes, including ion pumping that is vital for tissue cell survival. The decrease in reperfusion sets a complex cascade of events including inflammation (Mitsios et al., 2006, Lakhan et al., 2009); release of excitatory neurotransmitters (Obrenovitch et al., 1993); disturbance of energy metabolism and oxidative/nitrative stress (Valko et al., 2007); excitotoxicity (Mitsios et al., 2006); apoptosis, and disruption of the blood brain barrier, leading to brain oedema due increased vascular permeability (Moskowitz et al., 2010). Figure 2.1 illustrates the complex cascade of biochemical and cellular pathophysiology events leading to neuronal death following cerebral ischaemia. The myriad of events can lead to permanent cerebral infarction if reperfusion is not promptly restored.

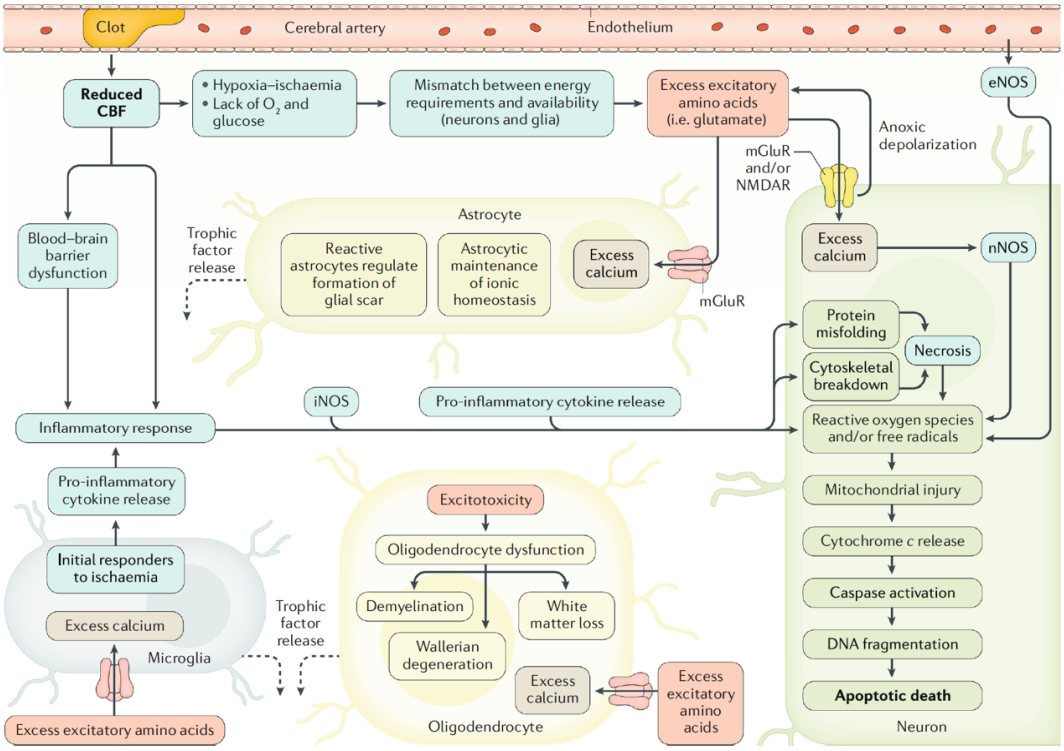


Figure 2.1. Ischaemia cascade

A series of responses are initiated by blockage of the cerebral artery by an embolus. Occlusion of the cerebral artery leads to reduced cerebral blood flow (CBF), consequently causing insufficient glucose and oxygen delivery to the neural cells and neuroglia (astrocytes, ependymal cells, microglial cells and oligodendrocytes) within the brain parenchyma. There is an increase of glutamate levels extracellularly, due to reduced glutamate uptake caused by anoxic depolarisation. This further leads to a calcium influx into the neurones via the N-methyl-d-aspartate (NMDA) ion receptor (NMDAR), in addition, to the release of calcium from intracellular stores in neurons and glia through the metabotropic glutamate receptors (mGluRs). An inflammatory response is initiated by the release of signalling molecules, such as cytokines, from the neuroglia, due to dysfunction of the blood–brain barrier. A cascade of responses causes necrosis and apoptosis of neurones. eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; nNOS, neuronal nitric oxide synthase. (Adapted from Campbell, 2019 (Campbell et al., 2019), with permission from Copyright Clearance Centre).

Following deprivation of oxygen and nutrients, some neurones die within minutes and irreversible brain injury occurs immediately, terminating the function of these cells permanently. It is estimated that about 1.9 million neurones, 14 billion synapses, and 12 km (7.5 miles) of myelinated fibres are lost each minute and 120 million neurones, 830 billion synapses and 714 km (447 miles) of myelinated fibres are destroyed each hour following an acute large vessel occlusive stroke without

treatment (Saver, 2006). The phrases "*time is brain",* and "*save a drop of brain, save a week of healthy life*" both coined by Saver (Saver, 2006, Saver, 2017) emphasise the need for timely recanalisation of an occluded vascular blood vessel for early restoration of cerebral perfusion to secure improved clinical outcomes (Khatri et al., 2014, Rha and Saver, 2007). Figure 2.2 illustrates how a one minute reduction in onset-to-treatment time led to a saving of 4.4 DALY-days post stroke (95% CI, 1.3–7.5 days, P = 0.006 (Kawano et al., 2017).

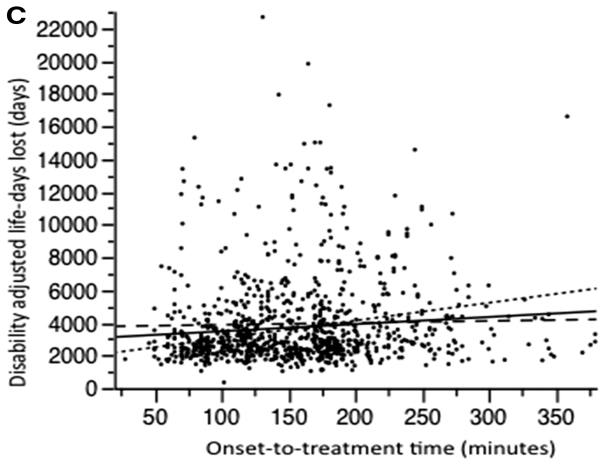


Figure 2.2. Relationship between stroke onset-to-treatment time and disability-adjusted life-days.

For every minute reduction in the time to treatment from the onset of stroke symptom, there is a saving of 4.4 DALY-days post-stroke (95% CI, 1.3–7.5, P = 0.006). Following recanalisation, each 1 min decrease in the treatment time from onset of stroke symptom resulted in 10.9 DALY-days (95% CI, 5.1–16.7 days, P < 0.001. (Adapted from Kawano, 2017 (Kawano et al., 2017) with permission from Copyright Clearance Centre).

While the time window is based on the time of symptom onset that can be easily measured (except for wake-up/unknown time of onset), the tissue window, based on biological timing, is a more reliable surrogate marker for brain physiology of evolving ischaemia (Wang and Wang, 2019, Xiang and Cao, 2019). The concept of "tissue window" was described as "penumbra or mismatch" by (Hacke, 2018).

The ischaemic penumbra is defined as the reversibly injured brain tissue with moderately reduced CBF (15-20ml/100 g/min) surrounding the area of necrosis or infarcted damaged tissues with drastically reduced CBF (<15ml/100 g/min), referred to as the ischaemic core (infarction). The penumbra, while at risk of further damage is by definition still viable and potentially salvageable (Astrup et al., 1981). However, in the absence of reperfusion, further injury progresses followed by irreversible time-related death (Mergenthaler *et al.,* 2004). The penumbra has lost its function but still has structural integrity and the blood supply is marginally sufficient to keep these cells alive (ischaemic penumbra)(Baron, 1999). This evolving dynamic area of bioenergetic agitation has been established in both animals and humans (Astrup et al., 1981, Hossmann, 1994) and is crucial for neurological and functional recovery. Figures 2.3 and 2.4 illustrate the relationship between DALYs gain, baseline penumbra volume and salvaged penumbra volume.

Saving the penumbra quickly is the goal of AIS treatment and the interventions that can be used to salvage the penumbra include restoring blood flow distal to the occlusion (recanalisation) and/or through the use of interventions that can protect and limit the further harmful effect of ischaemia on neurones, including neuroprotection (Neuhaus et al., 2017, Majid, 2014, Sutherland et al., 2012). Different neuroprotective agents have been developed to block specific points in the ischaemic cascade in animal studies, but there has been a lack of success of translation from animal studies into clinical practice (O'Collins et al., 2006). The development of neuroprotective agents continues to be a fundamental goal of preclinical research and translational medicine.

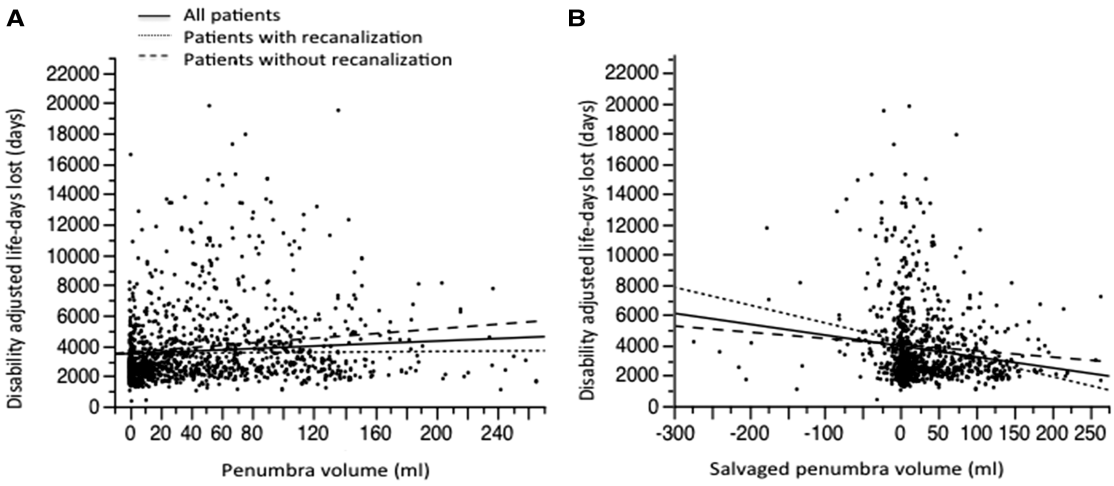


Figure 2.3. Relationship between, penumbra volume, salvaged penumbra volume and disability-adjusted life-days.

A: Each one ml baseline penumbra resulted in 4.1 DALY-days lost (95% CI, 0.8–7.5 days, P = 0.015). **B:** Each one ml of salvaged penumbra translated into a saving of 7.2 DALY-days (95% CI, −10.4 to −4.1, P < 0.001). (Adapted from Kawano, 2017 (Kawano et al., 2017) with permission from Copyright Clearance Centre).

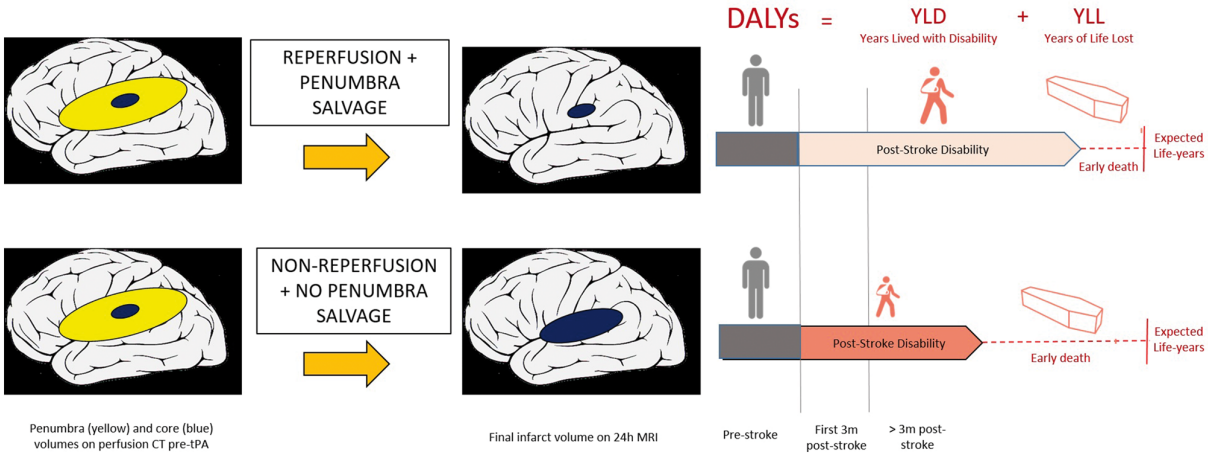


Figure 2.4. Relationship between Salvaged Penumbra and clinical outcome

A large, salvaged penumbra resulted in fewer years of optimal life lost to disability and fewer years of life lost to premature mortality. (Adapted from Saver,2017 (Saver, 2017) with permission from Copyright Clearance Centre). DALY= Disability- Adjusted Life Years.

2.1.4 Aetiology of Stroke

Stroke is a clinical syndrome with resultant loss of neurological function due to focal brain hypoxia caused by lack of blood supply or ischaemia (Thorvaldsen et al., 1995). The majority of strokes are ischaemic in nature (85%) resulting from arterial occlusion (Fieschi et al., 1989, del Zoppo et al., 1992), most commonly from clot formation blocking a blood vessel to the brain and 15% are haemorrhagic strokes from ruptured blood vessel (Broderick et al., 1993). From this point on, the use of the word ‘stroke’ in this thesis will refer only to acute ischaemic stroke.

Stroke is a heterogeneous condition that can result from multiple causes with complex mechanisms. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of stroke subtypes includes: large-artery atherosclerotic occlusion, the most common subtype; cardio-embolism; small-vessel occlusion; stroke of other determined aetiology; and stroke of undetermined cause (Adams et al., 1993). The classification has been modified due to advances in diagnostic tools, which has enabled the identification of more than one cause of stroke in a patient and with more stroke of undetermined cause identified. The limitations of the TOAST classification led to the development of the Stop Stroke Study TOAST (SSS-TOAST) (Ay et al., 2005) and subsequently the Causative Classification of Ischaemic Stroke (CCS) (Arsava et al., 2010). The CSS is a computerised, evidence-based classification system constructed upon the TOAST classification that provides both causative and phenotypic stroke subtypes with high reliability (Table 2.1).

Table 2.1. Causative Classification of Stroke System (CCS)*

Five Subtype CCS	Eight Subtype CCS	Sixteen Subtype CCS
Supra- aortic large-artery atherosclerosis	Supra- aortic large- artery atherosclerosis	Supra-aortic large-artery atherosclerosis
		Evident, probable, possible
Cardio aortic embolism	Cardio aortic embolism	Cardio aortic embolism
		Evident, probable, possible
Small- artery occlusion	Small- artery occlusion	Small- artery occlusion
		Evident, probable, possible
Other uncommon causes	Other uncommon causes	Other uncommon causes
		Evident, probable, possible
Undetermined	Undetermined	Undetermined
	Unknown-cryptogenic embolism	Unknown-cryptogenic embolism
	Unknown-other cryptogenic	Unknown-other cryptogenic
	Unclassified	Unclassified
	Incomplete evaluation	Incomplete evaluation

*CCS assigns causative stroke subtype in five main categories bases on the TOAST Classification (First column). The undetermined causes group are further divided into four categories including cryptogenic embolism, other cryptogenic strokes, incomplete evaluation, and unclassified groups (Middle column). This allows classification of stroke into eight aetiologic subtypes. For each aetiologic category in the CCS system it is further subdivided based on the weight of evidence as evident, probable, or possible, giving rise to a 16-subtype CCS (Last column). (Modified from Arsava, 2007)(Arsava et al., 2010).

Large artery occlusion (LAO) involves occlusion of the proximal middle cerebral artery (MCA), the terminal part of the internal carotid artery and basilar artery (Bhatia et al., 2010). Proximal occlusions of major intracranial vessels account for more than one-third of acute anterior circulation stroke (Heldner et al., 2013, Beumer D, 2013). About two-thirds of strokes occur in the anterior circulation, mainly involving the middle cerebral artery (MCA) territory (Adams et al., 1993, Feigin et al., 2018, Ng et al., 2007). Acute ischaemic stroke due to LAO is associated with severe disability and increased mortality (Saver, 2006, Khatri et al., 2012, Smith et al., 2011). Figure 2.5 illustrates different vascular territories.

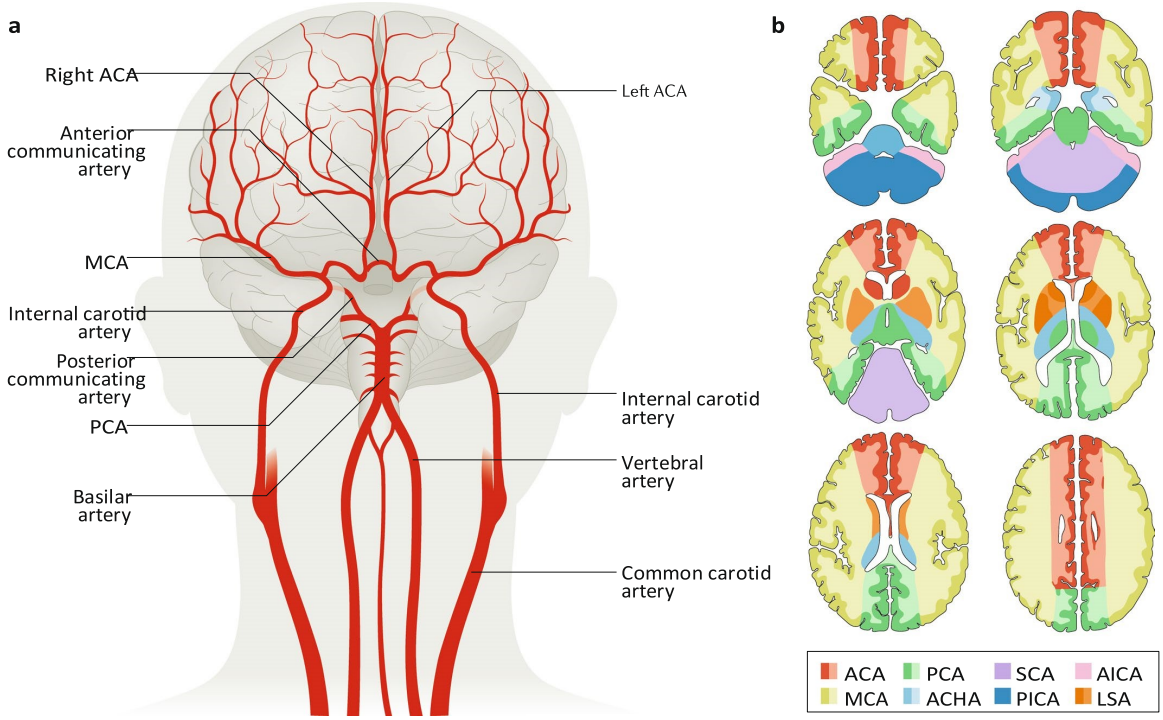


Figure 2.5 ***Cerebral vasculature***

The main arteries of the brain (part **a**) and their vascular territories (part **b**). ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; ACHA, anterior choroidal artery; SCA, superior cerebellar artery; PICA, posterior inferior cerebellar artery anterior choroidal artery; AICA, anterior inferior cerebellar artery; LSA, lenticulostriate artery (Adapted from Campbell,2019 (Campbell et al., 2019) with permission from Copyright Clearance Centre).

2.1.5 Stroke scales

2.1.5.1 Neurological deficit

Several stroke scales are used to measure acute neurological deficit, monitor progress, prognosis and inform further management and care needs. In research, they ensure homogeneity of patients recruited into larger trials and enable the understanding of the natural history of stroke. Despite the usefulness of the scales in clinical and research settings, limitations include high observer variability; relevance of individual modalities to the stroke patient at hand; complexity and practicality of use. Furthermore, they can be complicated and impractical to institute and difficult to analyse statistically. The National Institutes of Health Stroke Scale (NIHSS) is a commonly used scale for measuring stroke severity (Appendix 2.A), employing a 42-point scale that quantifies neurologic deficits assessed across 11 categories (Lyden et al., 1994). It has good correlation with subsequent measures of functional outcome, but it has been debated that its prognostic accuracy is not high and it has been criticised for its redundancy, complexity and for being relatively time consuming (Meyer and Lyden, 2009). Other commonly used stroke scales include the Scandinavian Stroke Scale (Scandinavian Stroke Study Group, 1985), the Canadian Neurological Scale (Côté et al., 1986) and the European Stroke Scale (Hantson et al., 1994).

2.1.5.2 Evaluation of Recanalisation

The Treatment in Cerebral Ischaemia (also termed the Thrombolysis in Cerebral Infarction [TICI]) classification (Appendix 2.B) is the scale currently used to assess the final revascularisation status on angiograms after MT (Zaidat et al., 2013) with a better correlation to clinical outcomes. The scores range from 0 (no perfusion) to 3 (full perfusion) and successful revascularisation is defined as TICI 2b to 3 (Shi et al., 2014). Recent variations in scoring include the original TICI scale (oTICI), the modified TICI (mTICI) and the modified TICI with 2c (mTICI 2c) (Goyal et al., 2014). While TICI 2b has been considered as the threshold for successful recanalisation (Jayaraman et al., 2013), some studies have found that patients with oTICI 3, mTICI 2c, or mTICI 3 reperfusion had significantly greater clinical outcomes compared with patients with oTICI 2b and mTICI 2b reperfusion (Dargazanli et al., 2017, Kleine et al., 2017, Almekhlafi et al., 2014).

2.1.5.3 Functional outcome

The Modified Rankin score (mRS) is the most commonly used scale for measuring pre-stroke functional status and functional disability after stroke (Rankin, 1957, Sulter et al., 1999, van Swieten et al., 1988). The mRS score is also used as a primary endpoint in most RCTs (64%) and is a valuable tool for assessing the impact of new stroke treatments (Banks and Marotta, 2007, Quinn et al., 2009). It is a 6-point scale where 0 indicates the absence of disability and 5 indicates severe disability. Excellent outcome is defined by dichotomisation, either mRS ≤1, or mRS 0-2 for good outcome and poor clinical outcome as mRS >3 (Appendix 2.C). Its performance through a structured interview has been shown to improve its quality and bias between different assessors (Wilson et al., 2005). Benefits of mRS

include its straightforward application, which makes randomisation into stroke trials easy and quick to perform (van Swieten et al., 1988); its ability to discriminate levels of stroke disability, and a moderate and acceptable inter-rater reliability (Banks and Marotta, 2007, Quinn et al., 2009, Kwon et al., 2004).

Limitations include factors such as multiple co-morbidities, prior disability, cognitive abilities, socioeconomic factors and overall health status that may have a negative impact on mRS. Furthermore, it combines measures of impairment and disability, and is heavily dependent on mobility measures, which lowers its sensitivity (Banks and Marotta, 2007, Nichols-Larsen et al., 2005). The Barthel Index is another scale for the assessment of activities of daily living (ADL) following stroke disability (Mahoney and Barthel, 1965). It is commonly used in RCTs (40.5%) (Quinn et al., 2009).

2.1.6 Imaging of acute ischaemic stroke

There have been significant advances in neuroimaging, which is an integral component of acute stroke management. Although stroke is a clinical diagnosis, its treatment requires accurate detection and interpretation of ischaemic changes or infarct measurement using brain imaging. Neuroimaging techniques have changed from providing solely anatomical information to providing physiological information that could help identify which patients might benefit from reperfusion therapy (Byrne et al., 2020, Heit et al., 2018). The goal of neuroimaging for acute stroke is to establish a diagnosis as early and fast as possible, since time is of the essence when it comes to the management of acute ischaemic stroke (Byrne et al., 2020, Lin and Liebeskind, 2016).

Broadly, imaging modalities include multimodal computed tomography (MCT) and Magnetic Resonance Imaging (MRI) (Lin and Liebeskind, 2016, Byrne et al., 2020). Due to the widespread availability, easy accessibility and shorter scanning durations and the ability to easily monitor the acutely unwell patients on the scanner, MCT remains the most utilised imaging modality in the acute stroke setting (Byrne et al., 2020). Magnetic Resonance Imaging is increasingly being used in dedicated and major stroke centres (Lin and Liebeskind, 2016). Multimodal CT evaluation that combines non-contrast computed tomography (NCCT), CT angiography (CTA), and perfusion CT (PCT) has transformed the delivery of stroke care (Byrne et al., 2020, Leiva-Salinas et al., 2018, Wintermark et al., 2006) (Figure 2.6). Multimodal MRI includes sequences such as diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps, magnetic resonance angiography (MRA), perfusion-weighted MRI, gradient recalled echo (GRE), susceptibility weighted imaging (SWI) and fluid-attenuated inversion recovery (FLAIR) (Lin and Liebeskind, 2016).

2.1.6.1 Computed Tomography (CT)

Non-contrast computed tomography (NCCT) is usually the first line imaging modality which aids with the detection and quantification of ischaemic changes or measurement of infarct size and for exclusion of intracerebral haemorrhage (a contraindication to reperfusion therapy) and other stroke mimics (Figure 2.7A) (Leiva-Salinas et al., 2018, Byrne et al., 2020). The main shortcoming of CT is the failure to detect acute infarct in the first few hours after stroke onset due to subtle changes (Gao et al., 2017). An earlier study reported a specificity of 56% to 100%

and poor sensitivity (20% to 75%) for detecting early ischaemic changes, particularly in patients with posterior fossa ischaemia (Lansberg et al., 2000).

2.1.6.2 Computed Tomography Angiography (CTA)

Computed tomography angiography (CTA) is an advanced form of imaging that provides information regarding thrombus location and characteristics, large artery occlusion, intracranial and cervical vasculature, stenosis or dissection of large vessels (Leiva-Salinas et al., 2018, Byrne et al., 2020). Computed tomography angiography is used to evaluate the collateral blood flow for treatment triage (Byrne et al., 2020, Elijovich et al., 2016, Ravindran et al., 2021) (Figure 2.7B). The collateral status at initial presentation may determine the potential to expand eligibility for reperfusion therapy beyond the time window-based selection criteria and has also been shown to predict clinical outcome (Ravindran et al., 2021, Elijovich et al., 2016). A post hoc analysis of the Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE) trial demonstrated how measuring collateral status beyond target occlusion is capable of selecting patients with LAO who could potentially benefit from MT (Evans et al., 2018). A good collateral status has been shown to predict a decreased final infarct volume, higher recanalisation rate and favourable clinical outcome in patients with LAO treated with MT (Elijovich et al., 2016). Conversely, poor collateral status is associated with fast infarct growth and poor clinical outcomes despite recanalisation in patients with LAO (Elijovich et al., 2016, Wufuer et al., 2018). Patients with poor collaterals were excluded from the ESCAPE thrombectomy trial (Goyal et al., 2015).

Collateral status can be assessed using either a single-phase CTA (sCTA) or multiphase CTA (mCTA). Both single phase CT (Santos et al., 2019, DiBiasio et al., 2019) and mCTA (Motyer et al., 2018, Uransilp et al., 2019) have shown to be valuable tools for selecting patients for MT beyond the treatment window. However, mCTA has an advantage over sCTA for detection of distal intracranial occlusion (Yu et al., 2016, Byrne et al., 2017). Additionally, Multiphase CT angiogram (mCTA) which includes the various phases of time-resolved images allows even better delineation of collateral supply as it provides progressive, temporal information on the blood flow and on the degree and extent of pial arterial filling in the whole of the brain (Elijovich et al., 2016, Menon et al., 2015, Havenon et al., 2019).

Collateral status can be assessed using either a single-phase CTA (sCTA) or multiphase CTA (mCTA). Both single phase CT (Santos et al., 2019, DiBiasio et al., 2019) and mCTA (Motyer et al., 2018, Uransilp et al., 2019) have shown to be valuable tools for selecting patients for MT beyond the treatment window. However, mCTA has an advantage over sCTA for detection of distal intracranial.

The mCTA collateral-based imaging has emerged as an important tool for determining collateral status and has been shown to compare well with CTP in selecting patients that could benefit from reperfusion therapy in the extended time window (Almekhlafi et al., 2020).

There are shortcomings to the use of both the single phase and multiple phase CTA scans. The single-phase CTA carries the risk of mislabelling pial arterial due to lack of temporal resolution (Menon et al., 2015). Likewise, the interpretation of

mCTA scans can also be impaired; as a result of a delay in contrast material filling of the pial arteries due to pathology, such as the existence of flow-limiting proximal stenosis and winding at base-of-skull collaterals(Menon et al., 2015).

2.1.6.3 Computed Tomography Perfusion (CTP)

Computed tomography perfusion (CTP) is another valuable tool that has transformed stroke care, particularly in patients with unknown time of symptom onset or 'wake-up' stroke (Thomalla et al., 2020). Perfusion imaging was used in the MT trials to triage and treat patients with a limited-size-predicted infarct core or substantial salvageable brain tissue (target mismatch) up to 16 hours and 24 hours from onset of stroke (Albers et al., 2018, Nogueira et al., 2018). Perfusion imaging is increasingly being used along with NNCT to identify patients with penumbra tissue that could benefit from therapy (Figure 2. 7C). It provides information about the tissue that is at risk for progression to infarction if reperfusion is not achieved (penumbra), the irreversibly damaged tissue (the infarct core) and the normally perfused tissue (benignly hypoperfused or hyperaemic) (Astrup et al., 1981, Hossmann, 1994, Wintermark et al., 2006, Wintermark et al., 2001). CT perfusion imaging uses sequential brain imaging to evaluate three parameters: the flow of contrast through cerebral vessels (mean transit time) or time to peak (TPP); the total cerebral blood volume (CBV) and the cerebral blood flow (CBF) to a region (Wintermark et al., 2006, Wintermark et al., 2001, Byrne et al., 2020). The information from the CTP parameters is used to demarcate the ischaemic penumbra (prolonged MTT or Tmax, moderately reduced CBF and near-normal or even increased CBV) and the core infarction (prolonged MTT or Time-to-Maximum (Tmax), markedly decreased CBF and markedly reduced CBV (Wintermark et al.,

2006, Wintermark et al., 2001). A mismatch between the two areas predicts the most likely benefit from reperfusion therapy (Wintermark et al., 2006). The most common set of thresholds defining penumbra and core are time to peak of the residual function (Tmax) > 6 s and relative cerebral blood flow (rCBF) <30% or delay time (DT) >3s and rCBF <30% (Vagal et al., 2019). The ischaemic tissue can be estimated using a time to peak of greater than 6 seconds (Vagal et al., 2019, Bivard et al., 2013) and the irreversible ischaemic tissue a cerebral blood flow of less than 30% compared with the normal brain parenchyma (Vagal et al., 2019, Campbell et al., 2011). Ischaemic core volume greater than 70 ml at presentation is associated with low probability of a favourable outcome, notwithstanding reperfusion therapy with recanalisation (Yoo et al., 2010). However, the interpretation of CT perfusion scans can be impaired by confounding pathology, such as cardiac arrhythmias, low cardiac output or aortic valvular disease and technical issues, such as the bolus's timing, larger radiation dose, additional contrast and patient motion during the scan. Another drawback of CT perfusion is the post-processing methods (smoothing of the data) variability, which can lead to considerable differences in the CBV or CBF thresholds used to measure the acute infarct core or penumbra volumetrically (Almekhlafi et al., 2019, Bivard et al., 2013).

2.1.6.4 Magnetic Resonance Imaging (MRI)

With MRI techniques such as perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) are being used to select patients for thrombolytic therapy (Schellinger et al., 2003). DWI is a more sensitive imaging modality for detection of early ischaemic brain changes with sensitivity of 91% to 100% and specificity

of 86% to 100% within less than 6 hours from onset (González et al., 1999) (Figure 2.7D). Similar to CTA, MRA is used to evaluate collateral status to provide information on collateral flow (Lin and Liebeskind, 2016). MRI is much more limited by patient contraindications (e.g. metals) or intolerance (e.g. claustrophobia), (Dill, 2008).

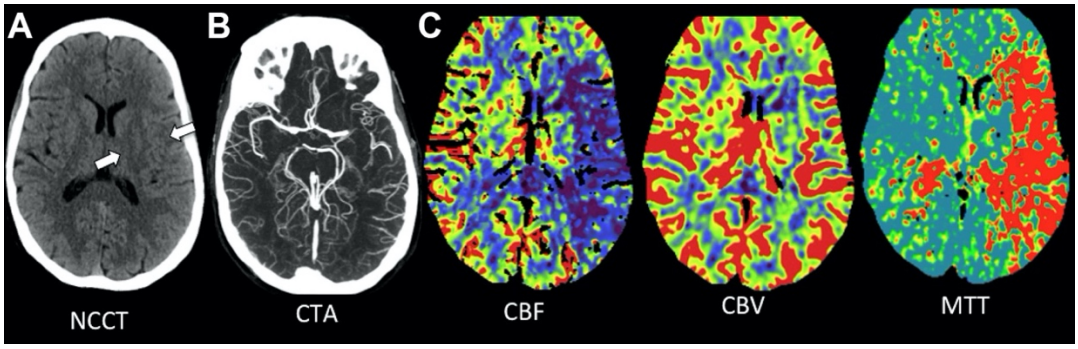


Figure 2.6. Multimodal CT

A: NCCT demonstrates a small acute left MCA territory infarct involving the left basal ganglia and frontal operculum (white arrows). **B:** CTA shows a left M1 occlusion with good collaterals.
C: CT perfusion shows a small infarct core (small area of reduced CBV or CBF <30% = 8 mL) and large penumbra, that is, area of reduced CBF, prolonged MTT and Tmax >6 seconds with a mismatch volume (penumbra) of 77 mL) (NNCT= Non-contrast computed tomography; CTA= CT angiography; CBF= cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; MC= middle cerebral artery.(Adapted from Byrne,2020 (Byrne et al., 2020) *with permission from Copyright Clearance Centre).*

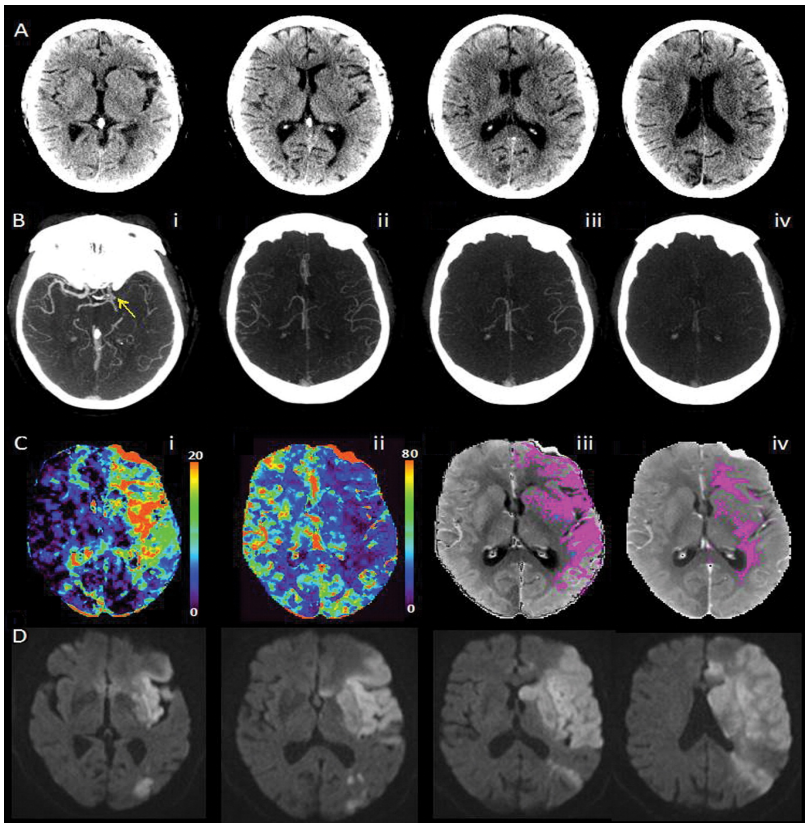


Figure 2.7. Imaging modalities

A= Non-contrast CT (NNCT). ***B*** = Multiphase CT angiography (three phases) showing MI occlusion. ***C*** = CT perfusion (Tmax and CBF maps *(i, ii)*, (CBF-defined infarct core is 1 mL(*iii*) and (mismatch ratio and a small infarct core (iv). ***D*** =MR diffusion images at 26 hours after admission (Adapted from Menon,2015 (Menon et al., 2015) with permission from the Radiological Society of North America (RSNA®).

2.1.6.5 Neuroimaging scales

Neuroimaging scales in addition to other clinical parameters help guide timely therapeutic decisions for acute stroke treatment.

2.1.6.5.1 Alberta Stroke Program Early CT Score (ASPECTS)

The Alberta Stroke Program Early CT Score (ASPECTS) is a standardised, systematic and validated 10-point scoring scale designed for the quantitative evaluation of early ischaemic changes in the middle cerebral artery (MCA) territory on NNCT (Barber et al., 2000). The cerebrum is divided into 10 topographic regions and a single point is deducted from the score for evidence of early ischaemic change in each of the 10 ASPECTS regions. A score of 10 reflects a normal CT scan, while a score of 0 indicates substantial ischaemic involvement throughout the complete MCA territory (Figure 2.8). ASPECTS score of less than seven correlates with stroke severity and is an indicator of an increased risk of symptomatic intracranial haemorrhage and of a worse outcome following intravenous thrombolysis (Barber et al., 2000). Similarly, the posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) is a predictive scale for quantifying ischaemic changes in the posterior circulation (Puetz et al., 2008). Although ASPECTS score was based on Non-Contrast CT (NCCT), it has been calculated through CT perfusion (CTP) (Aviv et al., 2007) and MR-DWI (McTaggart et al., 2015, Rangaraju et al., 2015). Cerebral blood volume ASPECTS can predict both radiological outcome and major neurological improvement (Aviv et al., 2007) with a better interrater reliability over NCCT ASPECTS. ASPECTS score was originally designed as an imaging selection tool to predict outcome in treatment with intravenous thrombolysis (Barber et al., 2000), it has also been used as an

independent predictor of outcome for patients with large vessel occlusive stroke undergoing treatment with MT (Werner et al., 2019, Olive-Gadea et al., 2019). ASPECTS was applied also in three of the five initial thrombectomy trials, used primarily as an imaging selection tool alongside other clinical inclusion criteria (ESCAPE, SWIFT PRIME and REVASCAT)(Goyal et al., 2015, Saver et al., 2015, Jovin et al., 2015). The MT trials used baseline ASPECTS <6 as an exclusion criteria for their trials. Furthermore, in one of the trials (REVASCAT) (Jovin et al., 2015), patients with symptoms beyond 4.5 hours, had to be evaluated for favourable ASPECTS by CT perfusion or DWI-MRI before MT. However, a meta-analysis of the trials using individual patient data suggests clear benefit for patients with ASPECTS score of >5 (Goyal et al., 2016).

The limitations of the score include modest inter-rater variability (Farzin et al., 2016) an inequitable weighing of brain regions with the striatocapsular region accounting for 21% and the total 10 regions for 51% of the maximum MCA infarct territory volume (Phan et al., 2006) and failure to correlate with infarct volume depending on the lesion position (Schröder and Thomalla, 2016).

Automated ASPECTS has the potential to reduce interobserver variability in the determination of early ischaemic changes (Nagel et al., 2017, Sundaram et al., 2019) and has been validated (Kuang et al., 2020).

Other neuroimaging scores have been developed to improve detection and guide treatment decisions and prognostic predictions include the one-third middle cerebral artery territory method (hypoattenuation in less than one-third of the

middle cerebral artery territory) (von Kummer et al., 1996, Silver et al., 2001) and the Boston Acute Stroke Imaging Scale (BASIS)(Torres-Mozqueda et al., 2008).

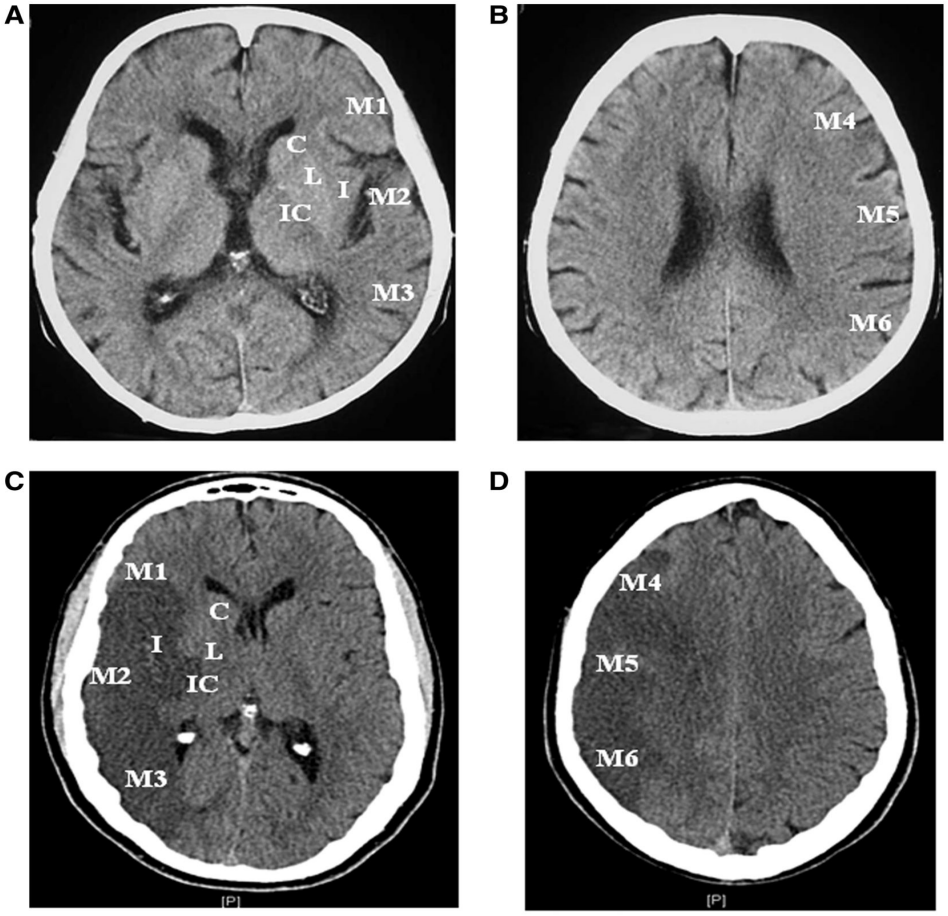


Figure 2.6. ASPECTS images showing the MCA territory

Subcortical region: C = caudate; L = lentiform; IC = internal capsule; I = insular.
Cortical regions: M1, M2, M3, M4, M5, M6 = cortical regions.
(**A** and **B**) ASPECTS = 10 (no ischaemic changes identified): Potential for favourable outcome with reperfusion therapy.
(**C** and **D**) ASPECTS = 3 (severe tissue damage). Potential for a poor outcome from reperfusion
An ASPECTS of >7 predicts a favourable outcome and ASPECTS <7 a poor outcome.
(M1= Anterior MCA cortex;M2 =MCA cortex lateral to the insular ribbon; M3 = Posterior MCA cortex; M4, M5, and M6= the anterior, lateral and posterior MCA territories immediately superior to M1, M2 and M3) (adapted from Balami, 2013 (Balami et al., 2013), with permission from Copyright Clearance Centre).

2.1.6.5.2 Imaging based Collateral Grading scores

Similar to the ischaemic penumbra, the collateral status is also an important imaging finding in the hyperacute stroke setting that can predict outcome and guide AIS treatment decisions.

The collateral circulation provides blood flow to conserve the ischaemic penumbra following a LAO and can prolong the time window for penumbral salvage with reperfusion therapy (Miteff et al., 2009). Several collateral-based imaging scoring scales have been devised (Menon et al., 2015, Miteff et al., 2009, Tan et al., 2009, Parthasarathy et al., 2015, Zaidat et al., 2013, Souza et al., 2012) to provide information on the collateral status so as to facilitate decisions for correct patient treatment triage and prognosis prediction.

The mCTA collateral score (Menon et al., 2015) is a 6-point score (score of 3 or less = poor prognosis) designed to evaluate the degree and extent collateral filling in AIS in a time-resolved manner and is a reliable and well-validated tool for measuring collateral status beyond the target LAO (Uransilp et al., 2019, d'Esterre et al., 2017).

Another simple and commonly used scoring system is a scale of 0-3, where 0 equal no collateral filling, 1 assigned to collateral filling less than 50%, 2 to collateral filling greater than 50% and less than 100%, and 3 to 100% collateral filling (Tan et al., 2009, Angermaier et al., 2011).

There is no consensus on the optimal scoring scale. Nevertheless, the collateral scoring scales aim to provide detailed information on the collateral status to enhance reperfusion decisions and prediction of prognosis.

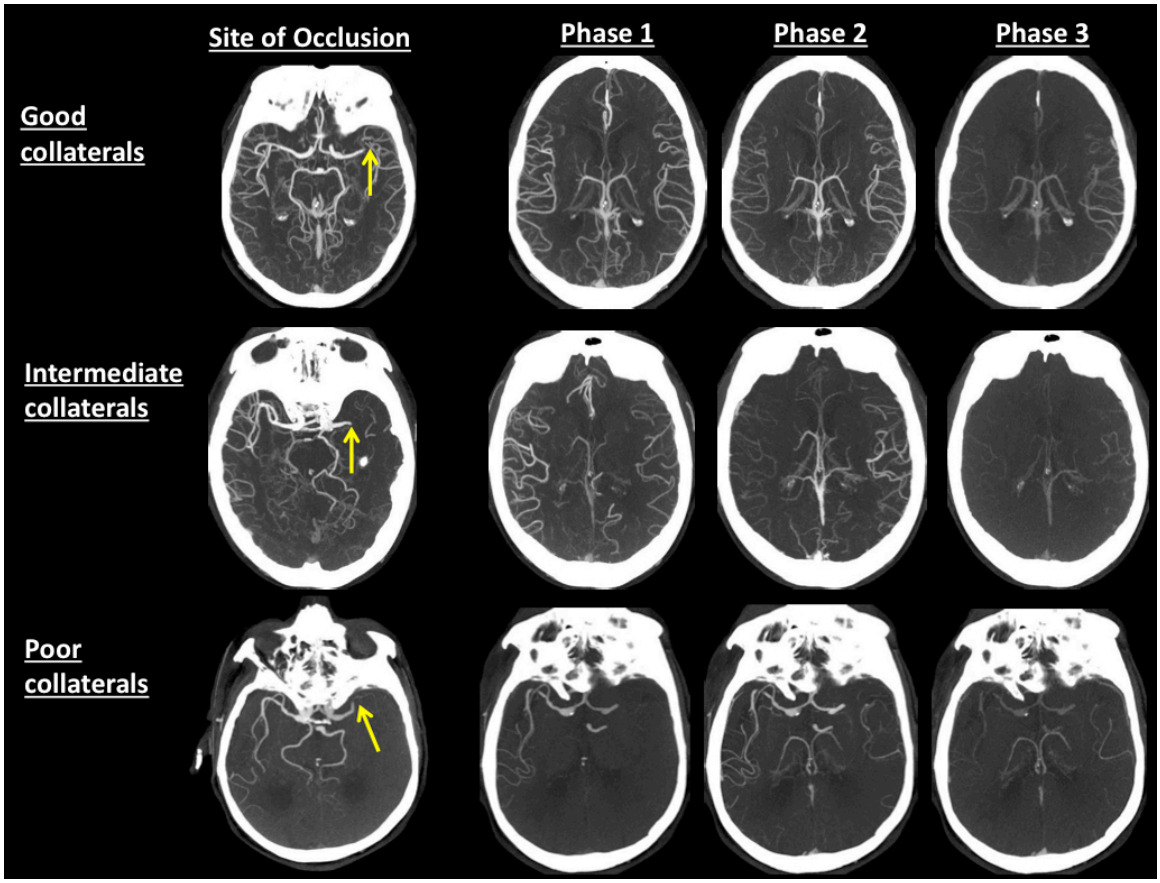


Figure 2.7. mCTA Collateral Score

Collateral status evaluated on 3-phase CTA and multiphase CTA demonstrates site of occlusion (left M1 MCA occlusion (arrow).
Pial arterial filling, scored into 5 categories: Good collateral= backfilling arteries, Intermediate collateral= Moderate backfilling arteries, Poor collateral= minimal backfilling arteries. With permission from the Calgary Stroke Program (Calgary Stroke Program, 2021).

2.1.7 Treatment of acute ischaemic stroke

Acute ischaemic stroke (AIS) treatment has evolved significantly over the last two decades. The key to ischaemic stroke treatment is early and complete recanalisation (restoration of blood flow) of the occluded blood vessels to allow reperfusion (Rha and Saver, 2007). This is a major predictor of improved functional outcome among other factors, such as time to recanalisation and the degree of already infarcted tissue. Recanalisation can be achieved through the use of thrombolytic agents, mainly recombinant tissue plasminogen activator (rt-PA, alteplase) administered intravenously (NINDS, 1995, Hacke et al., 2008, Emberson et al., 2014) or recently with tenecteplase (Burgos and Saver, 2019, Berge et al., 2021) and MT using thrombectomy devices (Goyal et al., 2016).

2.1.7.1 History of Advances in Acute Ischaemic Stroke Treatment

2.1.7.1.1 Intravenous Thrombolysis

In 1995, the landmark National Institute of Neurological Disorders and Stroke (NINDS) trial changed the management of AIS from a non-treatable condition to an acute emergency. This is despite the initial nihilism regarding the management of AIS. The trial demonstrated the functional benefit of intravenous (IV) rt-PA compared with placebo (OR 1.7, 95% CI: 1.2-2.6; p=0.008) for the treatment of AIS within three hours of the onset of stroke symptoms. Although there was a significant difference in the incidence of symptomatic intracranial haemorrhage (sICH) in the first 36 hours in patients treated with IV rt-PA compared with placebo (p=0.001), there was no significant difference in mortality at 90 days (p=0.30) between the two groups. There was an improved functional outcome at 90 days in

the IVT treated group (NINDS, 1995). Based on the NINDS trial, intravenous thrombolysis with alteplase was approved and widely accepted as the first line standard treatment for AIS within 3 hours of stroke onset. The National Institute for Health and Care Excellence (NICE) first approved rt-PA for use in the UK in 2007 (NICE, 2007).

The European Cooperative Acute Stroke Study III (ECASS III), which treated stroke patients with alteplase up to 4.5 hours after symptom onset, demonstrated a reduced risk of dependency and mortality at 3 months (47.6% vs 54.8%, *p*=0.04. NNT 14). There was, however, a significant increase in sICH (7.9% vs. 3.5%, *p*=0.006. NNH 22) and in any intracranial haemorrhage (27% versus 17.6%, *p*=0.001, NNH to harm 10) (Hacke et al., 2008). Following the publication of the ECASS III, the treatment window for AIS using IV rt-PA was extended from 3 hours to 4.5 hours post symptom onset and guidelines were updated (European Stroke Organisation, 2009, Jauch et al., 2013). It was also updated by NICE in the UK (NICE, 2012).

Pooled analyses of major IVT trials showed that treatment with alteplase within 4.5 hours of stroke onset can significantly reduce the risk of a poor outcome (Emberson et al., 2014, Lees et al., 2010, Wardlaw et al., 2012). The pooled analysis of individual patient data of nine RCTs involving 6,756 stroke patients treated with alteplase compared with placebo, demonstrated a higher benefit (OR 1·75, 95% CI 1·35–2·27), in favour of treatment within 3 hours compared with greater than 3 hours up to 4.5hrs (OR 1.26, 95% CI 1·05–1·51) and decreasing efficacy over 4.5hrs (OR 1.15, 95% CI 0·95–1.40) of stroke onset, suggestive of the benefits of early treatment (Emberson et al., 2014).

Despite the established evidence of the benefits of IV rt-PA for the treatment of AIS, there are several limitations to the use of alteplase. Firstly, there is a low recanalisation rate: only about 50% of the patients achieve recanalisation (Rha and Saver, 2007, Mazighi et al., 2009). Factors such as the location (Menon et al., 2018, Hirano et al., 2010, Saarinen et al., 2012), length (Mishra et al., 2014, Elofuke et al., 2016, Kamalian et al., 2013), size (Riedel et al., 2011) and thrombus characteristics such as permeability (Menon et al., 2018) of the arterial thrombus, might lead to IVT rt-PA resistance in about 50% of patients (Balami et al., 2013). Even if recanalisation is achieved, re-occlusion with neurological deterioration has been reported to occur in more than 30% of these patients (Alexandrov and Grotta, 2002, Rubiera et al., 2005, Grotta et al., 2001). Additionally, the rate of recanalisation for large vessel occlusion (basilar artery, internal carotid artery and middle cerebral artery) is relatively low due to the larger volume of the clot (del Zoppo et al., 1992, Wolpert et al., 1993). The rate of recanalisation for the main middle cerebral artery (MCA- M1) has been reported as 33%, compared to 66% in smaller MCA branches (M2 or distal); (del Zoppo et al., 1992). Similarly, in an internal carotid artery occlusion, it has been shown to be as low as 6%-14% (Mazighi et al., 2009, Saqqur et al., 2007).

Secondly, there is a limited time window, with only a minority of patients treated within the 4.5 hours of symptom onset, due to late hospital presentation or other related contraindications. There is also a wide variation in the provision of thrombolysis both within the UK and between countries (Aguiar de Sousa et al., 2019). The reported thrombolysis rates varied from 5.7 to 24% (Aguiar de Sousa et al., 2019, Wijngaarden et al., 2009, Watkins et al., 2019, Liu et al., 2017, Scherf

et al., 2016, Bandettini di Poggio et al., 2019). From the recent Sentinel Stroke National Audit Programme (SSNAP) report, the thrombolysis rate in the UK has remained static at 11-12% over seven years (SSNAP Report, 2021), but some well organised centres in the UK treat up to 20% (SSNAP, 2016, Thames Valley Clinical Senate, 2020) and recently up to 24% from the SNAPP data between October and December 2020(SSNAP, 2021) of patients are treated within the time window of 4.5 hours. The Helsinki Stroke Thrombolysis reported rates of up to 35% (Meretoja et al., 2012) after implementation of interventions to reduce treatment delays.

However, trials have shown the benefit of IVT for patients outside the known 4.5hour window, for example; 'WAKE UP' strokes using advanced imaging (Meretoja and Tatlisumak, 2006, Thomalla et al., 2020).

Thirdly, there is a risk of developing ICH, which is one of the major complications of alteplase (NINDS, 1995). In a meta-analysis the absolute risk of sICH increased from 2% in patients with mild stroke to 5% in those with severe stroke (Whiteley et al., 2016).

The limitations of IVT, particularly the low recanalisation rate, have led to the exploration of other treatment strategies with higher recanalisation rates. This has been through intra-arterial catheter techniques, using thrombolytics and later mechanical endovascular therapy, particularly for large vessel occlusions.

2.1.7.1.2 Intra-arterial Thrombolysis

The Prolyse in Acute Cerebral Thromboembolism (PROACT II) trial compared intra-arterial thrombolysis (with pro-urokinase) to heparin-only controls in AIS

patients. The trial recruited 180 patients with confirmed middle cerebral artery (MCA) occlusion. The IA group had significantly higher recanalisation rates and more favourable outcomes (modified Rankin Score 0–2) at 3 months: 40% compared with 25% in the heparin alone group. There was similar mortality, higher risk of intracerebral haemorrhage within 24 h of stroke onset (Furlan et al., 1999), which was attributed to the longer (six hour) time window, as well as greater baseline stroke severity. The Alberta Stroke Program Early CT Score (ASPECTS) allowed for stratification of patients that benefited from the intra-arterial thrombolysis (Hill et al., 2003). Regardless of the encouraging results (adjusted RR 15%, NNT = 7), the Food and Drug Agency (FDA) did not approve intra-arterial pro-urokinase for AIS. It requested a further confirmatory trial that has never been performed. Nevertheless, the success of PROACT II using endovascular therapy has led to a new era in the development of MT for AIS treatment.

2.1.7.1.3 Mechanical thrombectomy

Mechanical thrombectomy is an endovascular procedure that involves intra-arterial clot retrieval using thrombectomy devices to remove the blood clot in a large artery, thereby restoring reperfusion. The devices include: first-generation devices (Smith et al., 2005, Smith et al., 2008); aspiration-based embolectomy procedures (Bose et al., 2008, Penumbra Pivotal Stroke Trial Investigators, 2009); and stent-retriever based procedures (Saver et al., 2012, Nogueira et al., 2012).

Endovascular thrombectomy (EVT) includes rt-PA delivered directly into the artery or retracting a clot using a stent-retriever device. From this point on, the use of the word ‘mechanical thrombectomy’ will refer to the use of thrombectomy devices, except where EVT was referred to in the trials or in the referenced literature.

In 2012, three randomised controlled trials (RCTs) using first or early generation thrombectomy devices failed to show any superiority of intra-arterial thrombectomy over best standard treatment, which may or may not include the use of IVT (IMS III, SYNTHESIS, MR RESCUE) (Kidwell et al., 2013, Ciccone et al., 2013, Broderick et al., 2013). The reasons for the negative results included: poor patient selection; lack of documented vessel occlusion before treatment; not stratifying by ASPECTS or using tissue window; time delay from stroke onset to treatment; and the use of first generation thrombectomy devices with lower recanalisation rates. The earlier devices could lead to minor trauma from increased traction of the vascular tree, unlike the new generation devices. The lessons learned from these failed trials such as the need for effective advanced imaging for proof of proximal vessel occlusion, collateral blood flow, integrity of brain tissue, and the use of new generation devices and faster treatment workflows, helped to shape subsequent thrombectomy trials.

At the end of 2014, the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN), became the first RCT to demonstrate the efficacy of MT for the treatment of AIS due to LAO. MR CLEAN reported early treatment with MT leads to functional recovery in about 33% of patients with AIS treated within 6 hours (MR CLEAN 2015) (Berkhemer et al., 2015). There was an OR of 1.67 (95% CI 1.21 to 2.30) for improved functional outcome (mRS) 0–2 at 90 days in the intervention arm compared with the control arm. There were similar ICH rates (7.7% vs 6.4%) and 90-day mortality (18.9% vs 18.4%). Following the results from the MR CLEAN trial, which demonstrated the efficacy of MT, other ongoing major trials (ESCAPE, EXTEND-IA, SWIFT

PRIME and REVASCAT)(Goyal et al., 2015, Campbell et al., 2015a, Saver et al., 2015, Jovin et al., 2015) were terminated early once a predefined efficacy stopping point had been reached in favour of MT from the already collected data. There is, however, the risk of overestimation of the treatment effect size due to a reduced sample size from the prematurely stopped trials based on the efficacy signal (Bassler et al., 2010).

The year 2015 saw ground-breaking advances with a greater number of positive MT trials than in previous years. The success of the recent MT trials was based on the lessons learnt from previously failed trials. The main requirement for the new trials was the documentation of large vessel occlusion using CTA or MR angiography before randomisation. Also, new generation thrombectomy devices, predominantly stent-retrievers with a higher rate of successful reperfusion, were used as well as the strict time constraints. All the new trials used second-generation devices, predominantly stent-retrievers. The latest five MT trials have been hugely successful as the investigators had the benefit of learning from past failures.

There have been five more trials (THERAPY, THRACE, PISTE, EASI, RESILIENCE) (Mocco et al., 2016, Bracard et al., 2016, Muir et al., 2017, Khoury et al., 2017, Martins et al., 2020) since the initial five trials confirming the benefits of MT up to 6 hours, as well as some studies showing some benefit to even more delayed treatment (DAWN, DEFUSE) (Nogueira et al., 2018, Albers et al., 2018). Similar to the pooled analysis of the IVT trials (Emberson et al., 2014) the MT trials also demonstrated the benefits of timely and early intervention for AIS (Saver et al., 2016). In the setting of MT, there was a 12–15% relative reduction

in the likelihood of a good clinical outcome for every 30-minute delay in the time to reperfusion (Khatri et al., 2014). Additionally, for every hour delay to reperfusion, the absolute risk difference for a favourable clinical outcome is reduced by 6% (Fransen et al., 2016). Overall, these studies suggest that MT is an effective and safe treatment option for AIS due to LAO.

2.1.8 Economic Impact of Stroke

2.1.8.1 International economic burden of stroke

Stroke remains the third most costly health condition in the Western World (Rajsic et al., 2019, Stroke Foundation, 2020). Although the short-term costs are widely expected to rise with advances in imaging, new treatments and stroke care, it is anticipated that the long-term costs will reduce due to improved clinical outcomes and reduced disability.

In Europe, the annual total cost of stroke across 32 countries was estimated at €60 billion, of which €27 billion (45%) was incurred by healthcare systems, representing 1.65% of these countries' healthcare budgets. Out of the €27 billion healthcare costs due to stroke, €16 billion (62%) accounted for inpatient hospital care; €4.7 billion (18%) for outpatient care; €3.3 billion (13%) for primary care; €1.3 billion (5%) due to pharmaceuticals and €919 million (3%) for emergency care. An additional €5 billion (8%) cost was for social care systems, representing an annual stroke care spend of €59 per capita in Europe.

Furthermore, non-health or social care accounted for 47% (€29 billion); informal care for €16 billion and 27% (€13 billion) from productivity loss due to early death

or absence from work (Luengo-Fernandez et al., 2020). The economic burden is projected to increase to €90 billion, due to an ageing population (Luengo-Fernandez et al., 2020).

2.1.8.2 Economic burden of stroke in the UK

In 2009, the UK cost for treatment and productivity loss arising from stroke was estimated at £8.9 billion per year, accounting for about 5% of the total NHS cost (Saka et al., 2009). The cost has been increasing due to increasing age, increase in stroke events, and advances in imaging with improvement in treatments leading to increasing survival from stroke.

In the Oxford Vascular Study (OXVASC), that evaluated the Hospital Care Costs during five years post stroke, the mean 5-year total hospital costs after stroke according to stroke severity were: $23,031 (95% CI, 19,616–26,448) for minor stroke (NIHSS score <4); $31,953 (95% CI, 25,784–38,120) for moderate stroke (NIHSS score 4–10) and $27,348 (95% CI, 21,085–33,617) for patients with severe stroke (NIHSS score >10) with mean survival time of 1.45 years (Luengo-Fernandez et al., 2012). Another more recent UK study evaluated the average care costs associated with different stroke severities (Patel et al., 2017). Patel and colleagues estimated that patients with moderate/severe stroke or severe stroke (NIHSS scores 16-42) incurred NHS costs of £18,012 in their first year after stroke, and that those with minor stroke (NIHSS scores 1-4; incurred NHS costs of £9,261. This represents a cost differential of £8,751 between minor strokes and moderate/severe strokes. The costs of moderate to severe strokes could apply to LAO strokes, the group that would benefit from MT.

In more recent studies, the total cost of 84,184 stroke patients from SNAPP between April 2015 and March 2016 in England, Wales and Northern Ireland was estimated at £1.74 billion at one year after admission and £3.6 billion after five years post stroke (Xu et al., 2018). The total healthcare and societal costs of stroke to the National Health Service (NHS) are estimated to vary widely due to patient characteristics and ranges from £7,322 to £44,854 at one year and £19,101 to £107,336 at five years post stroke. The mean per-patient cost of healthcare due to stroke was £13,452 in the first year and £17,963 at five years post stroke. The mean per-patient social care cost was £8,977 in the first year and £28,076 at five years post stroke. Whilst healthcare cost was higher for the first year of stroke, the mean social care cost contributed to higher cost at five years post stroke (Xu et al., 2018).The total mean per-patient cost attributable to both healthcare and social care was £22,429 at one year and £46,039 at five years. Furthermore, while the total healthcare cost was higher in the first year of stroke, the total social care cost contributed to higher cost at five years post stroke (Xu et al., 2018).

A recent discrete event simulation modelling updated the cost of stroke for patients aged 40 years and above in the UK (Patel et al., 2020). The modelling captured the costs along the whole stroke pathway, which started with admission to a hospital acute stroke unit, through to other settings such as community rehabilitation and early supported discharge to discharge to different destinations (care home or own home) or death. The costs of imaging, thrombolysis and other treatments were also captured. However, the cost of treatment with mechanical thrombectomy was not included in the modelling. The total mean cost of new strokes (incident stroke) for NHS, social care, unpaid care and productivity loss are

£45,409 (95% CI 42,054-48,763) and £24,778 (20,234–29,322) in the first and subsequent years (prevalent stroke) after stroke. Out of the total cost, this study estimated the first year mean annual cost per-patient from an NHS and social care perspective at £18,081 (95% CI 17,621–18,542) and £27,328 (24,434–30,221) for unpaid care and lost productivity. Similarly, for subsequent years the mean costs were estimated at £7,759 (95% CI 7,200–8,318) for NHS and social care and £17,019 (13,034–21,005) for unpaid care and lost productivity. The higher mean annual cost per-patient from an NHS perspective of £13,269 (95% CI 13,058–13,480) compared with £4,812 (95% CI 4,434–5,190) for social care in the first year, and the higher social care of £5,544 compared with NHS cost of £2,215 in subsequent years were similar to the findings by Xu and colleagues (Xu et al., 2018).

For unpaid care, the costs were £25,897 (95% CI 23,621–28,173) and £15,354 (95% CI 12,501–18,656) for the first and subsequent years respectively. The mean annual cost of productivity loss is £1,431 (95% CI 813–2,049) in the first year and £1,666 (95% CI 983–2,349) in subsequent years after stroke. Relatedly, the aggregate cost of both incident and prevalent stroke is estimated at £26 billion per year. Out of the total cost, NHS cost accounts for 13% (£3.4 billion); social care 20% (£5.2 billion); unpaid care 61% (£15.8 billion); and 6% (£1.6 billion) for productivity loss (Patel et al., 2020).

The overall costs of stroke in the UK are projected to increase from £26 billion in 2015 to £75 billion in 2035. The societal costs are projected to represent 1.4% of GDP in 2015 to 2.0% in 2025 and 2.9% in 2035 (King et al., 2020). Table 2.2

Illustrates the breakdown of the projected future costs of stroke in the UK, after adjusting for inflation.

Table 2.2. Projections of the overall future costs of stroke, age 45 and over in the UK

Cost (£ billions)	**2015**	**2025**	**2035**	**% change**
Health Care	£3,400	£6,900	£10,200	**200%**
Social care	£5,200	£10,100	£19,300	**270%**
Unpaid care	£15,600	£24,400	£42,200	**170%**
Lost productivity	£1,500	£2,300	£3,500	**135%**
Total Cost	£25,700	£42,600	£75,200	**193%**

Data obtained from King,2020 (King et al., 2020).

The projected breakdown of the total cost for the different regions in the UK are from £22,515 in 2015 to £66,487 by 2035 in England; £1,008 to £2,776 in Wales; £484 to £1,510 in Northern Ireland and £1,620 to £4.572 in Scotland (Patel et al., 2020). Notably, the cost of MT was not included in both the current and projected costs of stroke for the next 20 years, although it is the impact of MT on costs, not just the cost of MT, as it reduces disability and saves costs.

From the breakdown of costs associated with stroke, social care costs including both public and private, are projected to account for the greatest increase due to increased ageing population at risk of stroke and the large number of stroke survivors (no improvement in treatment of AIS that reduces disability).

The higher rate of disability associated with LAO can lead to higher health and social care costs compared to the non-LAO stroke population.

Despite the projected increase in the expected cost of stroke in the next 20 years measures can be taken to alleviate costs and reduce the economic burden of stroke. Immediate access to early diagnosis, timely treatment with evidence-based interventions including IVT, MT, admission to a stroke unit, multidisciplinary approach and rehabilitation will improve clinical outcome and reduce disability. Stroke survivors with improved functional outcome will be less reliant on the healthcare system, care needs or informal care. Primary and secondary interventions aimed at control of hypertension and cholesterol, anticoagulation for atrial fibrillation, smoking cessation strategies, and lifestyle modifications can reduce the incidence of stroke and stroke recurrence.

2.2 Conclusions

Stroke is a major clinical problem with a high morbidity. This chapter has provided the clinical background for the thesis in terms of the clinical burden of stroke, the treatment modalities including IVT and MT and the economic burden.

The next chapter aims to provide the evidence of efficacy and safety of MT alongside IVT, compared with standard medical treatment with or without IVT for the treatment of AIS. Accordingly, a systematic review and meta-analysis of MT trials was conducted and is presented in the following chapter.

CHAPTER THREE

3 Systematic Review of Endovascular Mechanical Thrombectomy for Treatment of Acute Ischaemic Stroke

3.1 INTRODUCTION

Until recently, thrombolysis with intravenous recombinant human tissue-type plasminogen activator (rt-PA, formulated as alteplase) was the only approved acute drug treatment for AIS (NINDS, ECASS III, ESO 2009) (NINDS, 1995, Hacke et al., 2008, European Stroke Organisation, 2009). Treatment with intravenous thrombolysis (IVT) for LAO is, however, associated with low recanalisation rates as only 10–55% of patients with LAO achieve complete recanalisation with good outcomes (Smith et al., 2009, Rha and Saver, 2007, Mokin et al., 2012, Lima et al., 2014). Treatment with IVT is also limited by a narrow treatment time window of 4.5 hours (ECASS III) (Hacke et al., 2008). The limitations of IVT, particularly the low recanalisation rate, have led to the development and study of endovascular strategies with higher recanalisation rates.

Initial endovascular therapy (EVT), including rt-PA delivered directly into the artery (intra-arterial thrombolysis) or retracting a clot using a thrombectomy device failed to show a significant benefit of MT compared with IVT (the Interventional Management of Stroke (IMS III) (Broderick et al., 2013), the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) (Kidwell et al., 2013) and the Intra-arterial Versus Systematic

Thrombolysis for Acute Ischemic Stroke SYNTHESIS Expansion) (Ciccone et al., 2013).

The clinical benefits of endovascular intervention with mechanical thrombectomy (MT) for LAO were first convincingly demonstrated by the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) (Berkhemer et al., 2015).

Subsequently, other Randomised Controlled Trials (RCTs) also confirmed the benefits of MT for LAO. These included the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) (Goyal et al., 2015); Extending the Time for Thrombolysis in Emergency Neurological Deficits –Intra-Arterial (EXTEND-IA) (Campbell et al., 2015a); Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment Trial (SWIFT PRIME) (Saver et al., 2015) and Randomized Trial of Revascularization With the Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion (REVASCAT) (Jovin et al., 2015). The trials demonstrated the superiority of MT in combination with medical therapy over the best medical treatment for AIS (best medical treatment was with or without the use of intravenous thrombolysis). The overwhelming benefit demonstrated in recent thrombectomy RCTs has led to a paradigm shift in the management of AIS.

The early systematic reviews (SRs) and MA of EVT studies did not show any superiority or benefit of EVT over IV thrombolysis for AIS (Nam et al., 2015, Osanai et al., 2015, Singh et al., 2013). However, subsequent SRs and MAs including all previous prospective studies in addition to MR CLEAN, the positive MT trial, have demonstrated superiority of MT over best medical treatment alone for treatment of AIS (Fargen et al., 2015). Another SR and MA that included five positive trials also demonstrated superiority of MT over standard treatment (Badhiwala et al., 2015).

While earlier SRs and MAs were limited by trials using older techniques, poor patient selection, the inclusion of pilot studies, observational studies and results from large phase 2 and 3 trials; subsequent ones were limited by the variability in reporting individual studies and not differentiating where more new generation thrombectomy devices were utilised. There is, therefore, a need to examine RCTs, where at least one-third of cases in the intervention were treated with thrombectomy devices.

The aim of this part of the thesis is to systematically examine the efficacy and safety of MT for the treatment of AIS where thrombectomy devices were utilised in at least one-third of EVT cases. A systematic review of the literature will amalgamate what is already known about MT and identify key research gaps in the literature.

3.2 METHODS

Focused questions and definitions

The approach taken to determine the quality of the current evidence of MT for the treatment of AIS was to conduct a systematic review of the literature in 2015* (*since then, other trials have been published). The focused question was “What is the current evidence of the clinical effectiveness and safety of MT for the treatment of patients with AIS due to large artery occlusion?”

Endovascular therapy may include chemical clot dissolution with rt-PA delivered directly into the artery, or mechanical clot disruption or retraction using a thrombectomy device, or a mixture of both. Mechanical thrombectomy can be defined as a process of clot retraction, or aspiration in an artery, using mechanical devices such as aspiration catheters or stent retrievers. Standard medical treatment may or may not include the use of IVT (some patients receive direct mechanical thrombectomy without prior IV thrombolysis).

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA) Statement (Moher et al., 2009) and the review protocols of the Cochrane Collaboration (Cochrane Handbook) (Higgins and Green, 2009).

3.2.1 Inclusion criteria

The final selection of full-text articles was based on the Population, Intervention, Control, Outcomes, and Study Design (PICOS) protocol (Table 3.1).

Table 3.1. Selection Criteria

PICO Protocol	
Population	Patients ages ≥18 years with documented blood vessel occlusion using either computed tomography angiography (CTA) or Magnetic resonance angiography (MRA)
Intervention	Endovascular therapy using thrombectomy devices with or without intra-arterial alteplase
Comparator	Standard medical treatment or care with or without intravenous thrombolysis (alteplase)
Outcomes	Functional outcome as measured by modified Rankin Score (mRS) of 0-2 at 90 days, mortality and symptomatic intracerebral haemorrhage (sICH)
Study Designs	Randomised control trials of Endovascular mechanical thrombectomy (EVT)

3.2.2 Exclusion criteria

Studies were excluded if they did not meet the PICO criteria; had a population of less than 20; a thrombectomy device was utilised in less than one-third of cases; were pilot studies, post-hoc analyses of trials or unpublished trials.

Studies that did not report a risk estimate [relative risk or odds ratio (OR)] or did not have available data for the calculation of a risk estimate, were also excluded.

3.2.3 Search strategy

A literature search was performed using electronic databases (Medline; EMBASE; Cochrane Database of Systematic Reviews and the Cochrane Central Registry of Controlled Trials; Stroke Trials Registry; Clinicaltrials.gov and Current Controlled Trials); cross-referencing and hand-searching reference lists of relevant journals. The review identified studies published in English between January 1995 and May 2015* (*since completing and publishing this work, I have updated it and the results of the updated search are discussed in Section 3.4.2).

The key search terms included ‘brain isch(a)emia’, ‘acute isch(a)emic stroke’, ‘cerebral infarction’, ‘cerebrovascular accident’, ‘CVA’, AND ‘mechanical thrombolysis’, ‘endovascular treatment’, ‘endovascular therapy’, “endovascular thrombectomy”, “endovascular embolectomy”, “intra(-)arterial treatment”, “intra(-)arterial therapy”, “intra(-)arterial thrombolysis”, “intra(-)arterial intervention”, “neuro(-)thrombectomy”, AND “randomized controlled trial”, “randomised controlled trial”. Search Strategy in Appendix 3.A.

3.2.4 Study selection

The titles and abstracts were screened initially for relevant studies by one reviewer (JB) with random assessment of the selection process provided by the second reviewer (AB). This was then followed by scrutiny of the full text to determine eligibility. Once eligibility had been assessed, data from each study were extracted by (JB) and entered into a spreadsheet using a standard format designed specifically for the review. The second reviewer independently assessed the accuracy of the extracted data (AB). Discrepancies were resolved via discussion. The PRISMA flow chart of study selection is shown in Figure 3.1.

3.2.5 Data extraction

The following information was extracted from each of the eligible studies:

1) Study characteristics (trial name and first author, trial period, location, number of centres, number of patients, devices used and percentage treated with MT devices) (Table 3.1).

2) Main characteristics (age, sex, stroke severity on admission as measured with NIHSS); time from symptom onset to treatment; recanalisation as measured by TICI Score; primary outcome (mRS at 90 days); secondary outcome (mortality and sICH) (Table 3.2).

3) Study secondary characteristics (onset to groin puncture, imaging to groin puncture, onset to randomisation, baseline Alberta Stroke Program Early CT Score (ASPECTS) and NIHSS score post treatment) (Table 3.3).

4) Outcome measure data (primary and secondary) as described below.

5) Adverse effect/complications related to MT.

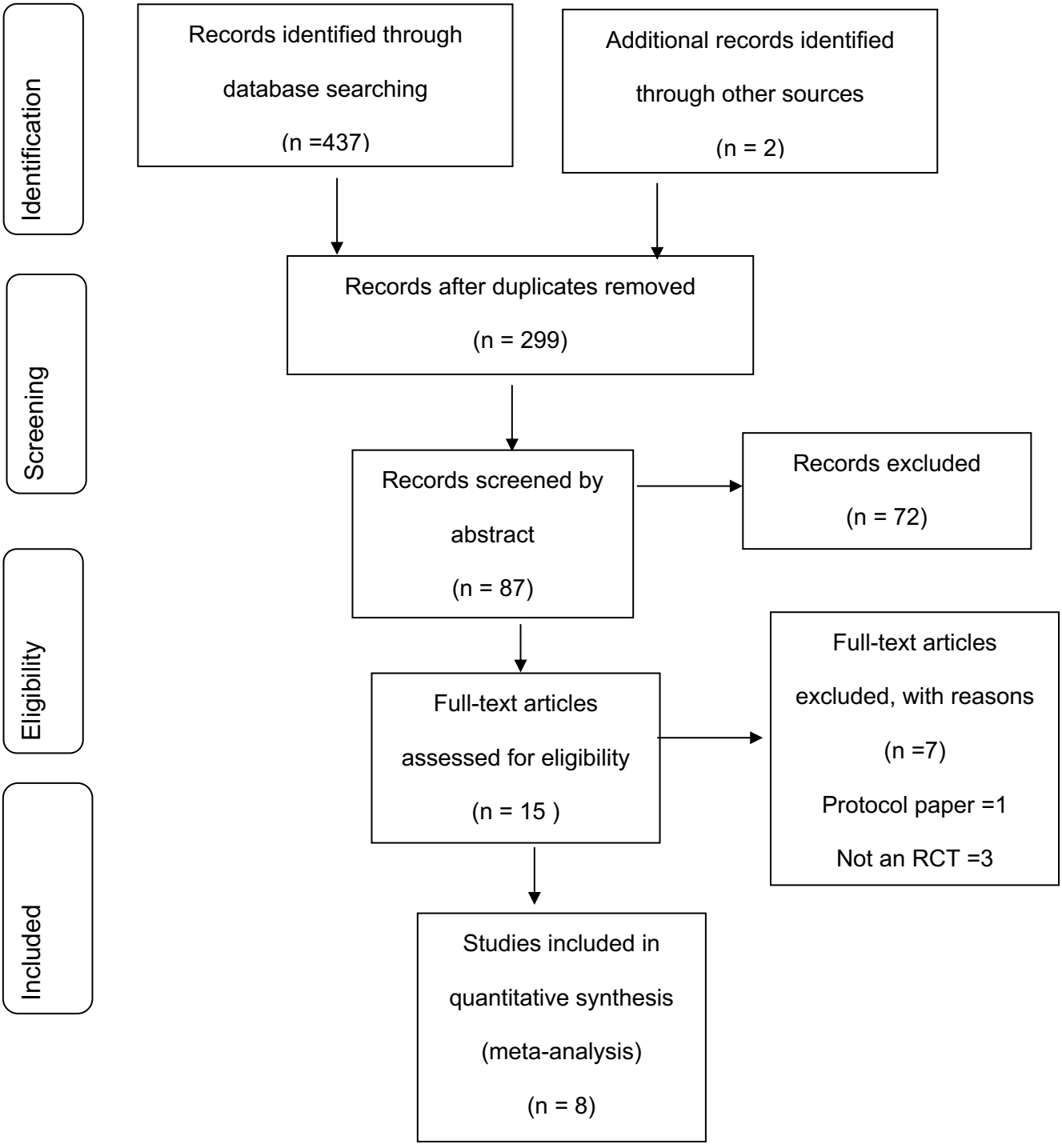


Figure 3.1. PRISMA flow chart of study selection

Adapted from Moher, 2009 (Moher et al., 2009).

3.2.6 Assessment of quality

The quality of included RCTs was assessed using the Critical Appraisal Skills Programme (CASP) Randomised Controlled Trials Checklist (CASP, 2014) and the risk of bias within studies using the methodological quality assessment framework for RCTs developed by the Cochrane Collaboration (Higgins et al., 2011).

3.2.7 Outcome measures

The primary outcome is about clinical effectiveness and the secondary outcome, is about the safety of MT. The primary outcome measure of functional independence, as measured by the modified Rankin Scale (mRS), a measure of disability as described in Chapter 2 (Appendix 2.A). A score of 0-2 at 90 days was defined as a good outcome. Secondary outcomes were symptomatic intracerebral haemorrhage (sICH) as defined by the individual trials and all-cause mortality at 90 days. Other outcomes of interest included procedural- and/ or device-related adverse events.

3.2.8 Data Analysis

The MA was performed using RevMan Manager version 5. 3. The Mantel-Haenszel method was used to calculate the odds ratios (ORs) and 95% confidence intervals. Statistical heterogeneity between studies was tested using inconsistency index (I^2) statistics. Values less than 25% were considered low, between 25-75% as moderate, and above 75% as highly heterogeneous (Higgins et al., 2011). When heterogeneity was present, the DerSimonian and Laird's random effects synthesis was used because it is the most robust statistically. A p-value of <0.05 was considered statistically significant.

3.3 RESULTS

3.3.1 Included Studies

3.3.1 1 Study characteristics

A total of 437 studies were identified from the search, but only eight fulfilled the eligibility criteria and were used for the meta-analysis. The eight retained RCTs comparing MT with IVT or Standard medical treatment meeting the eligibility criteria, included: MR CLEAN; ESCAPE; EXTEND-IA; SWIFT PRIME; REVASCAT; IMS III; MR RESCUE and SYNTHESIS (Kidwell et al., 2013, Ciccone et al., 2013, Broderick et al., 2013, Goyal et al., 2015, Saver et al., 2015, Jovin et al., 2015, Berkhemer et al., 2015, Campbell et al., 2015a). Most of the studies were multi-centre trials based in several countries. The studies' origins were: The Netherlands (MR CLEAN) (Berkhemer et al., 2015); Canada, USA, Ireland, UK, South Korea (ESCAPE) (Goyal et al., 2015); Australia and New Zealand (EXTEND-IA) (Campbell et al., 2015a); USA, Germany, France, Spain, Switzerland, Austria (SWIFT PRIME) (Saver et al., 2015) and Spain (REVASCAT) (Jovin et al., 2015). The studies comprised a total of 2,423 patients and populations per centre ranged from 70 to 656 patients. There were 1,110 patients randomised to IVT and 1,313 to MT. All the trials performed MT within 6 hours of stroke onset, but a small proportion of patients were treated up to 8 hours in REVASCAT(Jovin et al., 2015) and up to 12 hours in ESCAPE (Goyal et al., 2015). Different thrombectomy devices were used in the RCTs, but new-generation devices were predominantly used in more recent trials (Table 3. 2). Characteristics of included studies are summarised in Tables 3.2, 3.3, and 3.4.

3.3.1 2 Pre-stroke functional state

The proportion of patients with pre-stroke mRS of 0 range from 81.5 to 87.3% in the MT group and 80.1 to 88.7% in the control group from four trials (IMS III, MR CLEAN, REVASCAT, SWIFT PRIME) and in SWIFT PRIME ≤1(intervention group 99%, control group 98%). The trials required different pre-stroke functional status as part of their inclusion criteria. SWIFT PRIME and REVASCAT required a pre-stroke mRS of ≤1 and EXTEND IA, IMS III and MR RESCUE mRS of ≤2 as inclusion criteria. The ESCAPE trial required a pre-stroke functional state based on the Barthel Index of ≥90 (another measure of disability as described in Chapter 2).

3.3.1.3 Age distribution

The mean age range was 65.8 to 71 years for the IVT treated group and 65-71 years for the EVT group. All trials required patients to be aged ≥18 years as the lower limit for inclusion, but five trials had an upper age limit for inclusion. REVASCAT, SWIFT PRIME and SYNTHESIS Expansion excluded patients aged greater than 80 years; IMS III excluded patients aged greater than 82 years; MR RESCUE excluded those aged greater than 85 years and MR CLEAN, ESCAPE and EXTEND-IA trials had no upper age limit.

3.3.1.4 Stroke severity

The median baseline NIHSS ranged from 13 to 18 for the IVT treated group and 13 to 19 for the MT treated group. The EXTEND-IA trial had a difference of greater than one point in the median baseline NIHSS scores of control and intervention arms (control median baseline NIHSS, 13; intervention, 17).

The trials had different minimum NIHSS baseline levels for inclusion. MR CLEAN required a baseline NIHSS of ≥2, MR RESCUE and REVASCAT required a baseline NIHSS ≥6 and SWIFT PRIME required a baseline NIHSS of ≥8. IMS III required a baseline NIHSS of ≥10 at the time of commencing treatment with IV rt-PA or an NIHSS of >7 and <10.

3.3.1.5 Imaging selection

All eight trials required the basic initial non-contrast CT (NCCT) of the brain to exclude intracerebral haemorrhage. Additionally, five trials required CT angiogram (CTA) or magnetic resonance angiography (MRA) to demonstrate proximal large vessel occlusion prior to selection. Furthermore, ESCAPE, REVASCAT and SWIFT PRIME also required the Alberta Stroke Program Early CT Score (ASPECTS)(Barber et al., 2000) to quantify the extent of early ischaemic changes on the NCCT and excluded patients with baseline ASPECTS <6. In REVASCAT, patients with symptoms beyond 4.5 hours had to be evaluated for favourable ASPECTS by CT perfusion or DWI-MRI before MT (Table 3.3).

3.3.1.6 Location of stroke

The trials predominately included patients with anterior circulation large artery occlusion. Based on advanced imaging the occlusions were confined to MCA (MI and /or M2), intracranial internal carotid artery and /or ACA [AI and /or A2] in the new trials (MR CLEAN, EXTEND-IA, SWIFT PRIME, ESCAPE and REVASCAT). A small number of patients with posterior circulation stroke were recruited in SYNTHESIS Expansion (25/362) and IMS III (4/434). Following clinical

assessment on day seven, five additional patients (30/362) were found to have posterior circulation in SYNTHESIS Expansion.

3.3.1.7 Time from symptom onset to treatment

The median time from stroke onset to thrombolysis ranged from 87 to 153 mins in the control group and from 85 to 150 mins in the MT group (MR CLEAN, EXTEND-IA, SWIFT PRIME, ESCAPE and REVASCAT). In the SYNTHESIS Expansion trial, the median time from onset of symptoms to thrombolysis in the control arm of those who received IV t-PA only, was 165 minutes. While the median time to thrombolysis was shorter in the MT group than in the control group in four of the trials (MR CLEAN, EXTEND-IA, SWIFT PRIME and ESCAPE), it was longer in the REVASCAT trial. The median time from stroke onset to groin puncture for MT ranged from 210 (EXTEND-IA) to 269 minutes (REVASCAT). MR RESCUE reported a mean time from onset of stroke 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.

Table 3.2. Background characteristics of the included studies

Trial, Author, Year	Trial period	Location of trial	Number of centres	Total number of patients	Type of devices	Percentage treated with a thrombectomy device
MR CLEAN (Berkhemer et al., 2015)	2010–2014	Europe	30	500 (233/267)	Retrievable stents used in 81.5% cases, other devices (not specified)	82%
ESCAPE (Goyal et al., 2015)	2013-2014	North America, Europe, South Korea	22	315 (165/150)	Solitaire™ FR + unspecified others	79%
EXTEND-1A (Campbell et al., 2015a)	2012-2014	Australia & New Zealand	14	70 (35/35)	Solitaire™ FR Device	77%
SWIFT PRIME (Saver et al., 2015)	2013 - 2014	North America, Europe	39	196 (98/98)	Solitaire™ FR Device Solitaire™2	89%
REVASCAT (Jovin et al., 2015)	2012-2014	Spain	4	206 (103/103)	Solitaire™ FR Device	95%
IMS III (Broderick et al., 2013)	2006–2012	North America, Europe, Australia	58	656 (434/222)	Merci Retriever, Penumbra System®, Solitaire™ FR Device, Micro Sonic	39%
MR RESCUE (Kidwell et al., 2013)	2004–2011	North America	22	118 (64/54)	Merci Retriever, Penumbra System®	95%
SYNTHESIS (Ciccone et al., 2013)	2008–2012	Europe	24	362 (181/181)	Solitaire™ FR Device, Penumbra System®, Trevo®, Merci	31%

Table 3.3. Summary of included studies: main characteristics

Trial, year	No. patients (male %)	Age(y) [mean ±] or median (IQR)	Admission NIHSS score, mean/median (IQR)	Occlusion sites (ICA, ICA + M1, M1, M1 + M2, M2, A1 or A2)	Time from stroke onset to treatment(min) mean ± SD/ Median (IQR)	Recanalisation (TICI Score) 2b/3	Primary outcome (mRS 0-2) at 90 days; or mean, (CI)	Secondary outcomes Mortality, sICH
MR CLEAN, (Berkhemer et al., 2015)								
IV	267(58.8)	65.7 (55.5–76.4)	18 (14-22)	CA=3, ICA + M1=75, M1=165, M2=21, A1 or A2=2; ExCr=70	N/A		19.1%	22%, 6.4%
EVT	233 (57.9)	65.8 (54.5–76.0)	17 (14-21)	ICA=1, ICA + M1=59, M1=154, M2=18, A1 or A2=1; ExCr 75	260 (210–313) *	58.7%	32.6%	21%, 7.7%
ESCAPE, (Goyal et al., 2015)								
IV	150 (47.3)	70 (60-81)	17(12-20)	ICA + M1=39, M1 + M2=105, M2=3	N/A	31.2% (AOL score)	29.3%	19.0%, 2.7%
EVT	165 (47.9)	71 (60-81)	16 (13-20)	ICA + M1=45, M1 +, M2=111, M2=6	200	72.4% (TICI 2b/3)	53.0%	10.4%, 3.6%
EXTEND-IA, (Campbell et al., 2015a)								
IV	35 (49)	70.2±11.8	13 (9-19)	ICA=11, M1=18, M2=6	N/A		40.0%	20%, 6.0%
ET	35 (49)	68.6±12.3	17 (13-20)	ICA=11, M1=20, M2=4	210 (166-251)*	86.0% (25/29 pts)	71.0%	9.0%, 0%
SWIFT PRIME, (Saver et al., 2015)								
IV	98 (47)	66.3±11.3	17 (13-19)	ICA=15, M1=76, M2=62			36.0%	12.0%, 3.0%
EVT	98 (55)	65.0±12.5	17 (13-20)	ICA=17, M1=6, M2=13	224*	88.0%	60.0%	9.0%, 0%
REVASCAT, (Jovin et al., 2015)								
IV	103 (52.4)	67.2±9.5	17.0 (12–19) 17.0 (14–20)	ICA=1, ICA + M1=27, M1=65, M2=8			28.0%	16.0%, 1.9%

EVT	103 (53.4)	65.7±11.3		ICA + M1=26, M1=66, M2=10	269 (201–340)*	66.0%	44.0%	18.0%, 1.9%
IMS III, (Broderick et al., 2013)								
IV	222 (55.0%)	68 (23- 84)	16 (8-30)	LH: 106 (47.7); RH: 109 (49.1); BS: 4 (1.8); UnK: 3 (1.4)	122.4±33.7	38.0% (ICA), 44.0% (M1), 44.0% (single M2), 23.0% (multiple M2)	40.2%	21.6%,5.9%
EVT	434 (50.2%)	69 (23-89)ǂ	17 (7-40)	LH: 224 (51.6); RH: 197 (45.4); BS: 10 (2.3); UnK: 3 (0.7)	249.4±50.6		42.7%	19.1%,6.2%
MR RESCUE, (Kidwell et al., 2013)								
IV	34 (44)	65.8±16.9	16 (11–18)	ICA=5, M1=23, M2=6	348±60●	52.0%	26.0%	21.0%,
Penumbral	20 (60)	69.4±15.9	20.5 (17–23)	ICA=2, M1=16, M2=2	342±84●	20.0%	10.0%	30.0%,
Non-penumbral	34 (50)	66.4±13.2	16 (12–18)	ICA=6, M1=18, M2=10	318±96●	57.0%	21.0%	18.0%,
EVT	30 (43)	61.6±12.0	19 (17–22)	ICA=7, M1=21, M2=2	312±84●	37.0%	17.0%	20.0%,
Penumbral								
Non-penumbral								
SYNTHESIS, (Ciccone et al., 2013)								
IV	181 (57)	67±11	13 (9–18)	N/A	165 (140-200)	N/A	46.4%	6.0%,6.0%
EVT	181 (59)	66±11	13 (9–17)	N/A	225 (194-440)		42.0%	8.0%,6.0%

* = Onset to groin puncture; ●Time to enrolment

Table 3.4. Summary of included studies: secondary characteristics

Author, Year published	Imaging prior to intervention	Imaging exclusion criteria	Onset to groin puncture (min)	CT to groin puncture	Onset to randomisation	ASPECT interquartile range	NIHSS score, mean/median Post treatment
MR CLEAN (Berkhemer et al., 2015) **IV** **EVT**	NNCT, CTA/MRA	None	260 (210-313)	Not given	196 (149-266) 204 (152-251)	9 (8-10) 9 (7-10)	24 hr: 16 (12-21) 13 (6-20)
ESCAPE(Goyal et al., 2015) **IV** **EVT**	NNCT, CTA	NCCT ASPECTS <6, CTA with no collateral filing	200	51 (39-68)	172 (119-284) 169 (117-285)	9 (8-10) 9 (8-10)	24 hr: 13 (6-18) 6 (3-14)
EXTEND-1A (Campbell et al., 2015a) **IV** **EVT**	NNCT, CTA/MRA, CTP/MRA	Ischaemic core <70mL on CTP or MRI	210 (166-251)	93 (71-138)	Not given	Not given	Only given as reduction from baseline
SWIFT PRIME (Saver et al., 2015) **IV** **EVT**	CT/MRA	CT or MRI mismatch for first 71 ASPECTS ≥6 for remaining 125	224	58 (41-83)	N/A	9 (8-10) 9 (7-10)	At 27h: −8.5±7.1 −3.9±6.2
REVASCAT, (Jovin et al., 2015) **IV** **ET**	CTA, MRA, DSA	NCCT ASPECTS ≥7 ≥6 (MRI-DWI)	269 (201–340)	NA	226 (168–308) 223 (170–312)	8 (6.0–9.0) 7.0 (6.0–9.0)	At 90 days: 6.0 (2.0 to 11.0) 2.0 (0.0 to 8.0)
IMS III (Broderick et al., 2013) **IV** **EVT**	N0	>1/3 MCA excluded	208 (SD 46.7)	N/A	N/A	Not given	Used for stratification for mRS; full data not presented
MR RESCUE(Kidwell et al., 2013) **IV** **Penumbral** **Non-penumbral** **EVT** **Penumbral (Non-penumbral)**			330	NA	NA	Not given	Not given
SYNTHESIS, (Ciccone et al., 2013) **IV** **EVT**			N/A N/A	N/A N/A	2:25 (1:59–2:59) 2:28 (2:04–3:10)	Not given	Day7 (or at discharge): 13 (9-18) 13 (9-17)

3.3.2 Quality assessment

The overall risk of bias for each included study, as assessed using the Cochrane Collaboration's tool, was rated as low (Table 3.4).

The quality of the evidence of the included RCTs, as assessed with the CASP RCTs checklists, was rated as low for mRS of the five trials (MR CLEAN, ESCAPE and EXTEND IA, SWIFT PRIME and REVASCAT) and moderate for the earlier trials (MR RESCUE SYNTHESIS Expansion and IMS III); it was moderate for other outcomes of effectiveness. The treatment effect was significant for all of the trials except for IMS III (Appendix 3.B).

However, some methodological issues were identified that may have affected the outcome of the included studies. While the other trials used an intention-to-treat (ITT) analysis, MR RESCUE carried out a per-protocol analysis. The effectiveness outcomes may have been affected by the per-protocol analysis as 9 of the127 patients were excluded from the final analysis in MR RESCUE. Only three trials were completed as per planned protocols (MR CLEAN, MR RESCUE and SYNTHESIS Expansion). The treatment effect could have been over or under-estimated in following the interim analyses of three trials (ESCAPE, EXTEND IA and SWIFT PRIME) that were stopped early. One trial (REVASCAT) was also stopped early due to a claimed loss of equipoise because of the results from MR CLEAN, ESCAPE and EXTEND IA.

Table 3.5. Methodological Quality and Risk of Bias Assessment

Primary Author; Study Name	Power calculation	Sample size achieved (reason for stopping early)	Attrition (n/%)	Adequate sequence generation	Allocation concealment	Blinding of participants / personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Free of other problems	Overall Risk of Bias
MR CLEAN (Berkhemer et al., 2015)	Yes	Yes	2/0.4%	Low risk	Low risk	High risk**	Low risk	Low risk	Low risk	Low risk	Low
ESCAPE (Goyal et al., 2015)	Yes	No (Efficacy)	N/A	Low risk	Low risk	High risk**	Low risk	N/A	Low risk	Low risk	Low
EXTEND-IA (Campbell et al., 2015a)	Yes	No (Efficacy)	N/A	Low risk	Low risk	High risk**	Low risk	N/A	Low risk	Low risk	Low
SWIFT PRIME (Saver et al., 2015)	Yes	No (Efficacy)	N/A	Low risk	Low risk	High risk**	Low risk	N/A	Low risk	Low risk	Low
REVASCAT (Jovin et al., 2015)	Yes	No (Efficacy)	N/A	Low risk	Low risk	High risk**	Low risk	N/A	Low risk	Low risk	Low
IMS III (Broderick et al., 2013)	Yes	No (Futility)	N/A	Low risk	Low risk	High risk**	Low risk	N/A	Low risk	Low risk	Unclear
MR RESCUE (Kidwell et al., 2013)	Yes	Yes	9/7%	Low risk	Low risk	High risk**	Low risk	Low risk	Low risk	Low risk	Low
SYNTHESIS (Ciccone et al., 2013)			Low risk	Low risk	Low/high risk	Low risk	Low risk	Low risk	Low risk		Low

** Not feasible to blind interventionists and was unlikely to have biased outcome in these trials.

3.3.3 Meta-analysis of outcome measures

Meta-analyses were performed for two groups: the first set included the eight identified studies (Table 1) and the second showed the six published studies that had >50% of patients in the MT group treated with MERCI and new generation devices (ESCAPE; EXTEND-IA; MR CLEAN; MR RESCUE; REVASCAT and SWIFT PRIME) (Goyal et al., 2015, Campbell et al., 2015a, Berkhemer et al., 2015, Kidwell et al., 2013, Jovin et al., 2015, Saver et al., 2015).

3.3.3. 1 Primary outcome

Treatment with MT was associated with a significantly higher chance of a favourable functional independence (mRS 0–2) at 90 days (OR 1.56 (95% CI, 1.32-1.85), p<0.00001) compared with standard medical treatment alone (Figure 3. 2a). Despite the moderate heterogeneity among studies (I^2=75%, p=0.0002), a random effect analysis (Figure 3b) still confirmed the improved functional outcome (OR 1.71 (1.18-2.48), p=0.005) with MT. Based on the symmetrical funnel, there was limited evidence of publication bias (mRS 0-2 at 90 days (Appendix Figure 3.C).

3.3.3. 2 Secondary outcomes

Treatment with MT compared with standard medical treatment alone did not significantly reduce mortality at 90 days (OR 0.87 (0.70-1.08), p=0.21) (Figure 3.3a). Similarly, compared with standard medical treatment alone, MT did not increase the incidence of sICH (OR 1.03 (0.71-1.49), p=0.88) (Figure 3.3b). No heterogeneity was noted between studies for the secondary outcomes (I^2=0% for both mortality and sICH), contrary to the primary outcome.

3.3.3. 3 Subgroup analysis

3.3.3 3.1 Published RCTs with >50% of patients who underwent MT with a thrombectomy device in the intervention arm

The subgroup analysis of the six RCTs (Berkhemer et al., 2015, Goyal et al., 2015, Campbell et al., 2015a, Saver et al., 2015, Jovin et al., 2015), where >50% of patients underwent MT with a thrombectomy device, demonstrated an increase in the OR (2.23, 1.77-2.81, p<0.00001; Figure 3.4a) for a favourable outcome in the MT group compared with standard medical treatment alone. However, treatment with MT did not significantly reduce the 90-day mortality, OR 0.79 (0.60-1.05, p=0.10); Figure 3.4b). Equally, MT did not increase sICH compared to standard medical treatment alone (OR 1.02, 0.61-1.70, p=0.95; Figure 3.4c). No heterogeneity was noted between studies for these outcomes (I^2=20% for mRS score 0-2, 4% for mortality, and 0% for sICH) in the subgroup analysis.

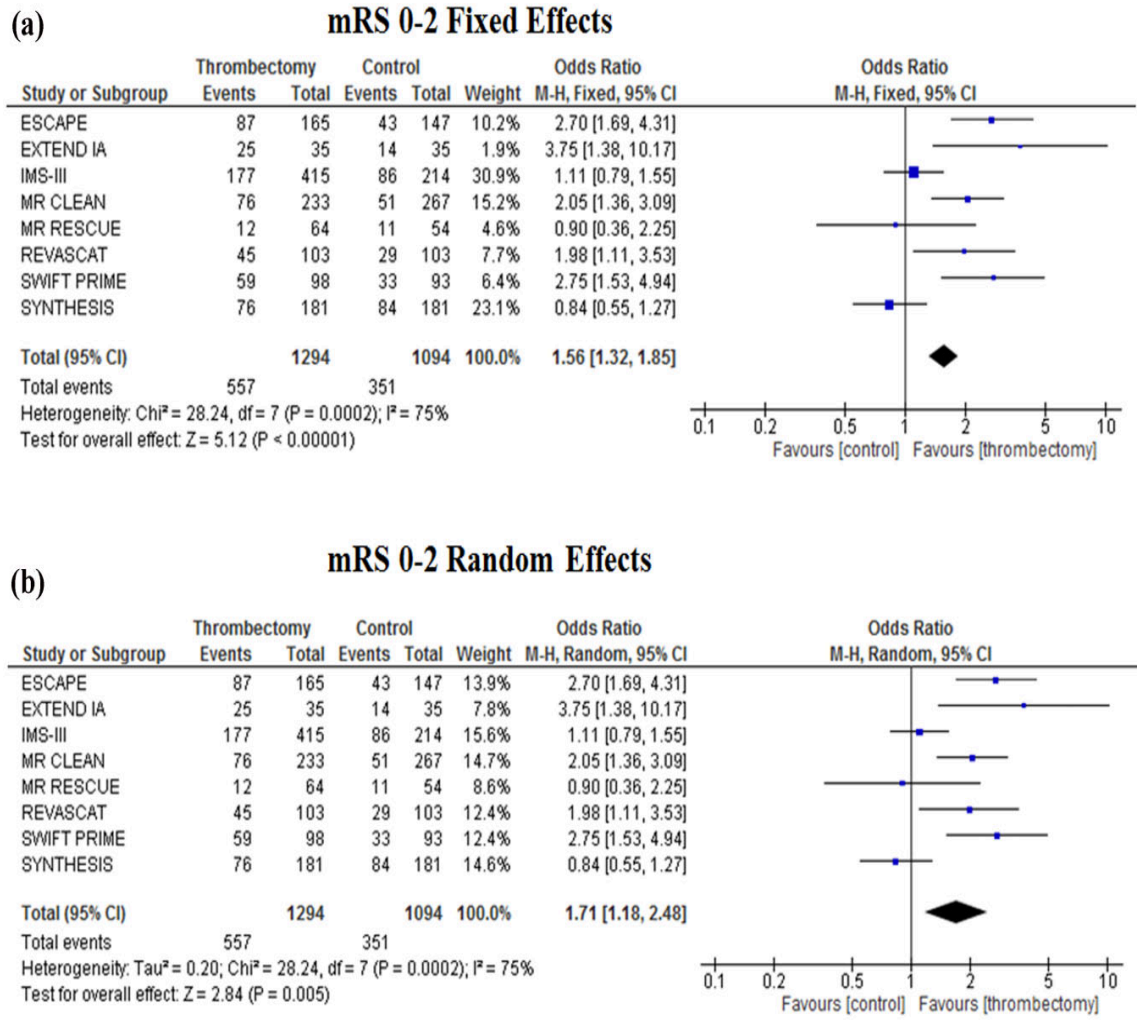
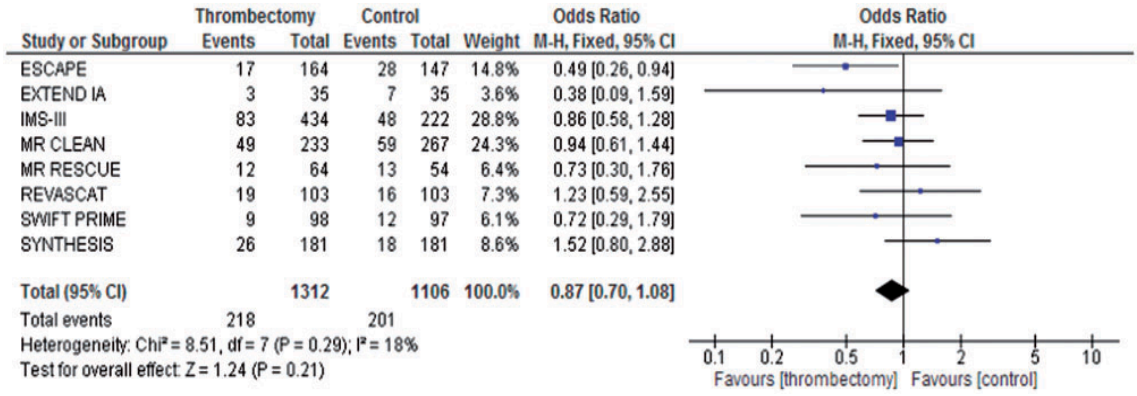


Figure 3.2. Forest plot of functional outcome

Functional outcome (mRS 0-2) of the group treated with MT compared with the control group using (a) Fixed effect model and (b) Random effect model (adapted from Balami, 2015) (Balami et al., 2015).

(a) Mortality



(b) Symptomatic intracerebral haemorrhage

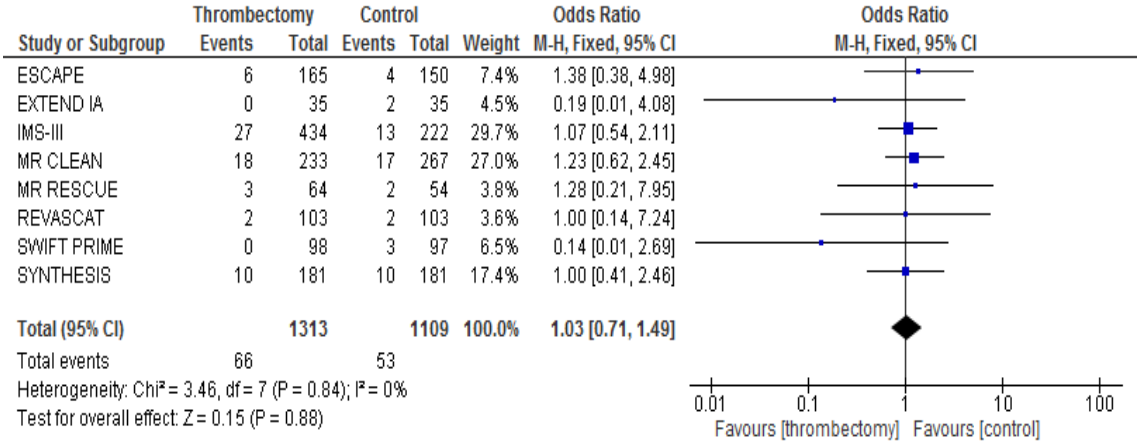


Figure 3.3. Forest plot of mortality and intracerebral haemorrhage

(a) mortality and (b) symptomatic intracerebral haemorrhage of the group of patients treated with MT compared with the control group (adapted from Balami, 2015) (Balami et al., 2015)).

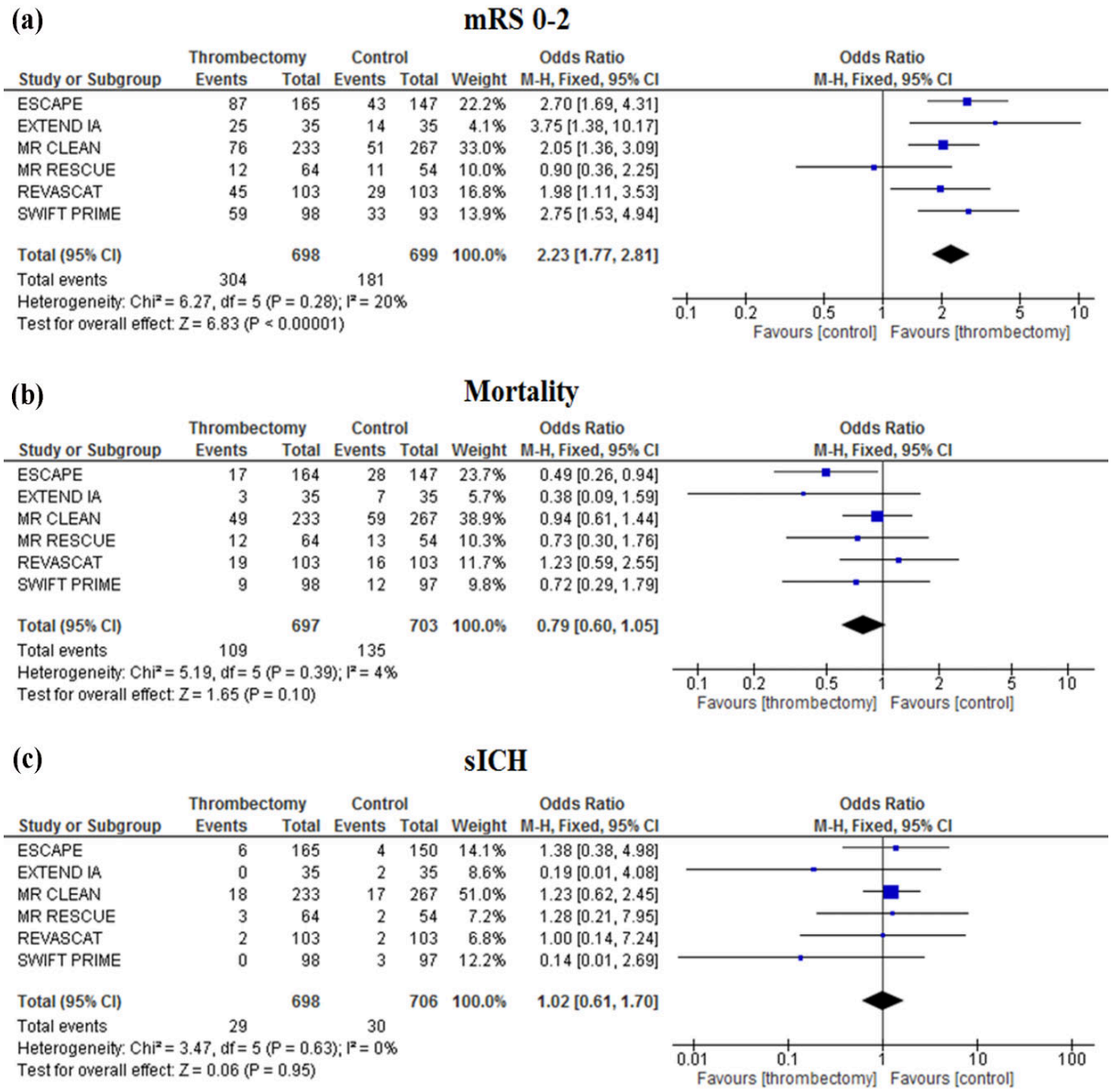


Figure 3.4. Subgroup meta-analysis

Trials with greater than >50% patients who underwent mechanical thrombectomy with a device in the treatment group. Outcome measures analysed include mRS 0–2 at 90 days (a), mortality at 90 days (b) and symptomatic intracerebral haemorrhage (c), (adapted from Balami, 2015) (Balami et al., 2015).

3.3.3.4 Adverse events /Complications

The complications associated with MT intervention could be procedural- and or device-related adverse events. Procedural complications include: access site problems (difficulty gaining access, vessel injury and access site haematoma) and device-related complications (vasospasm, arterial perforation and dissection, device detachment/misplacement); others include symptomatic intracerebral haemorrhage; subarachnoid haemorrhage; embolisation to new or target vessel territory. All the trials, except SYNTHESIS Expansion, reported procedure-related device-related adverse events in the intervention group. Five trials (MR RESCUE, IMS III, EXTEND-IA, REVASCAT and ESCAPE) did not differentiate between procedure-related and device-related adverse events. ESCAPE further reported serious and non-serious adverse events and SWIFT PRIME classified the reported complications as non-serious adverse events, all of which were device-related. IMS III reported 70 patients had a device- or procedure-related adverse event, including groin haematoma, emboli to previously uninvolved territories and vessel perforation or dissection, but did not specify the numbers for each of the noted complications. MR RESCUE, however, reported on the type and number of the adverse events of the 10 individual patients in the intervention arm. These comprised one device fracture, seven vessel perforations, one vessel dissection and one embolus to a previously uninvolved territory (Appendix 3.D). Overall, the risk of complications with actual/probable sequelae from MT occurred in 15% of patients (Balami et al., 2018b).

3.4 Discussion

These SR and MA evaluated RCTs wherein >50% of cases in the intervention arm were treated with a thrombectomy device, demonstrate more pronounced effects compared with other studies (Fargen et al., 2015, Badhiwala et al., 2015). They included eight trials with a total of 2,423 patients with AIS treated with MT, compared with standard medical treatment alone, which were included in the analysis. MT showed improved functional outcomes (mRS 0-2) [odds ratio (OR) 1·56 (1·32-1·85), $p < 0·00001$]. There was marginal evidence for reduced mortality at 90 days by MT [OR 0.87 (0.70-1.08), p=0.21] and MT did not increase the rate of sICH [OR 1·03 (0·71-1·49), P = 0·88] compared with standard medical treatment alone. The benefit of MT was found to be higher in the trials where new generation devices were used in greater than 50% of cases [OR 2·23 (1·77-2·81), $p < 0·00001$]. The quality of the pooled data for the outcomes from the included studies was rated as low or moderate and the risk of bias was rated as low.

Treatment with MT demonstrated improved clinical functional outcome but there was moderate heterogeneity between the eight studies combined in the meta-analysis. The heterogeneity could be accounted for by different study designs, imaging methodologies and the use in recent trials of new -generation devices with higher recanalisation rates. There was a tendency towards decreased mortality with MT compared with IVT, signifying the benefit of intervention with MT. Furthermore, there was an increase in the risk of haemorrhage, suggesting the safety of MT alongside IVT compared with standard medical treatment alone for treatment of AIS.

The earlier two trials predominantly used intra-arterial rt-PA with less use of MT devices (IMS III: 39.2%, SYNTHESIS Expansion: 30.9%) (Broderick et al., 2013, Ciccone et al., 2013). In contrast, the remaining seven trials had more substantial use of thrombectomy devices in each trial with more than 50% of cases using a device in the intervention group. From the new trials, the proportion of patients treated with MT devices in the intervention group ranged between 71.1% and 100%. The results from the separate meta-analysis of the RCTs with the greater use of MT, showed that in these trials, the chance of a better outcome was superior to those revealed in the primary meta-analysis, and there was greater homogeneity between studies, which could be attributed to the use of similar study design and more consistent use of MT with thrombectomy devices in the intervention arm.

There was a significant reduction in the 90-day mortality, further supporting the benefit of MT with new generation devices. However, similar to the primary analysis, there was no difference in sICH rate between MT and standard medical treatment alone in the trials with substantial endovascular thrombectomy, compared with standard medical treatment (IV rt-PA), but with less certainty, as shown by confidence intervals with a wide range.

The TICI or mTICI scores, which are measures of restoration of cerebral blood flow on final angiography, varied across the studies between 78% and 67% in the recent and earlier trials respectively. The trials reported markedly improved rates of reperfusion in the MT groups compared with the standard medical treatment alone group.

The success of recent MT trials was based on the lessons learned from previously failed trials. The main requirement for the new trials was the documentation of vessel occlusion using CTA or MR angiography or ASPECTS for tissue stratification before randomisation, which helped with the identification of eligible patients or those who could potentially benefit from MT. New generation thrombectomy devices, predominantly stent-retrievers with a higher rate of successful reperfusion, were used as well as the strict time constraints of some trials. All the trials that used stent-retrievers showed positive results for the primary endpoint. MR RESCUE used the Merci retriever (first generation devices) alone, unlike IMS III and SYNTHESIS Expansion which both used a mixture of first- and second-generation devices. Later trials all used newer generation devices - mainly stent retrievers - (EXTEND-IA, SWIFT PRIME REVASCAT) or in most of cases (MR CLEAN, ESCAPE). The newer thrombectomy devices were associated with earlier and faster reperfusion with higher recanalisation rates, reduced ICH and reduced disability at 90 days (Saver et al., 2015, Zaidat et al., 2014, Zaidat et al., 2018).

3.4.1 Limitations and strengths

The limitations of this SR and MA are the heterogeneous study design, methodology and reporting. The studies had different patient selection criteria: two of the studies (EXTEND-IA and SWIFT PRIME) mandated IV rt-PA in the inclusion criteria, while three other studies (MR CLEAN, ESCAPE and REVASCAT) compared MT against “best standard care” that may or may not have included treatment with IVT rt-PA. In MR CLEAN for example,10% of patients were treated with MT alone. Furthermore, IMS-III and SYNTHESIS had

a much greater proportion of patients treated endovascularly by intra-arterial rt-PA than with MT using thrombectomy device.

Since the restoration of cerebral blood is gradual with rt-PA and instant with thrombectomy, as well as higher recanalisation rate with MT than with local infused lytic drugs, the difference between the two modalities of therapy could have an effect on the clinical outcome. Similarly, the studies used different thrombectomy devices, with stent-retrievers predominantly used by the five new trials. The inclusion criteria required that at least one-third of patients in the intervention arm were treated with thrombectomy devices. Hence the sub-group MA of the trials that used thrombectomy devices in greater than 50% of patients in the intervention arm showed a stronger positive effect on functional outcome and greater homogeneity between studies. Consequently, the meta-analysis population was not perfectly homogeneous for the primary outcome when assessing all eight eligible studies for the MA.

There was heterogeneity in reporting some of the outcome measures or scales. Firstly, the different time points of reporting of the NIHSS: seven of the trials, for example, reported better outcomes in the MT using the NIHSS at different time points and in different ways. Secondly, outcome measures such as the mTICI and TICI were used interchangeably as measures of recanalisation (EXTEND-IA), reperfusion (ESCAPE, MR CLEAN) or revascularisation (MR RESCUE, REVASCAT). Similarly, while MR RESCUE reported TICI, the rest of the studies, reported mTICI and the scores varied markedly across studies. MR RESCUE reported 71.4% TICI score of 2A-3 and for the other studies reported mTICI 2b-3

ranging from 58.7% (MR CLEAN) to 88% (SWIFT PRIME). Although IMS III used mTICI and reported two final mTICI scores of 2b-3 (23% and 44%) for multiple M2 and MI or Single M2 occlusions, respectively. Thirdly, the time points of reporting reperfusion varied across studies. While EXTEND-IA reported on reperfusion at 24 hours, SWIFT PRIME reported at 27 hours and MR RESCUE reported on reperfusion at seven days.

Lastly, aggregate data were used in this MA, as opposed to pooled individual patient data (IPD), which has the scope for further analysis. Factors contributing to clinical outcomes would have been assessed if it had been possible to undertake IPD in this analysis.

Notwithstanding the limitations identified, the evidence from the SR and MA confirms the safety and clinical effectiveness of MT alongside IVT, compared with IVT or standard medical treatment alone, thereby demonstrating the positive impact of MT on outcomes in AIS due to LAO. The pooled data from the eight trials allowed for both primary and secondary outcomes and some sub-group analyses, where consistencies between studies were attained.

The main SR and MA were not updated with the identified studies from the updated search because they have been published. Most importantly, they did not add further evidence to the clinical outcomes from the main SR and MA. The results from the updated search are instead described in section 3.4.2.

3.4.2 Results of an updated search

Since the completion of this meta-analysis, which was published in 2015, an updated search (31 August 2020) identified 4809 additional titles using the title-search strategy. Of the publications issued after May 2015 and before September 2020, six articles were relevant to the clinical effectiveness and safety of MT.

The pooled individual patient data (IPD) from the five initial big trials (HERMES) – the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials collaborative (Goyal et al., 2016) has also been published. Additionally, new multi-centre RCTs of MT in several countries have been published. These studies included: The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (THERAPY); Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke (THRACE); Pragmatic Ischaemic Thrombectomy Evaluation (PISTE); Endovascular Acute Stroke Intervention Trial (EASI); EndoVascular Treatment with Stent-retriever and/or Thromboaspiration vs. Best Medical Therapy in Acute Ischemic Stroke (RESILIENT); Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE 3) and DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) (Mocco et al., 2016, Bracard et al., 2016, Muir et al., 2017, Khoury et al., 2017, Albers et al., 2018, Nogueira et al., 2018, Martins et al., 2020). Similarly, a SR & MA using the additional new studies (Flynn et al., 2017) has also been published.

The additional evidence from the updated SR & MA including additional new trials (THERAPY, THRACE and PISTE), revealed a slightly decreased effect size, but with increased certainty, as indicated by the confidence internal with a narrower range (mRS 0 to 2; OR 2.07, 95% CI.1.70 to 2.51). This is similar to findings in the present study of OR 2·23 (1·77-2·81, P < 0·00001) when newer generation thrombectomy devices were used in greater than 50% of the cases in each trial. However, the most robust of the additional evidence was from the HERMES MA of 1287 patients (634 MT and 653 standard care), which showed a significant reduction in disability at 90 day (adjusted common odds ratios (cOR) 2.49, 95% CI 1.76–3.53; p<0.0001) (Goyal et al., 2016). While the earlier five trials predominantly used stent retrievers, subsequent trials used both stent retrievers and aspiration devices. All the studies, including the HERMES MA, further confirmed the safety and clinical effectiveness of MT and have shown consistent benefit of MT for the treatment of AIS, caused by occlusion of the proximal anterior circulation closely endorsing my current analysis.

While my SR and MA and other subsequent trials had similar outcomes for patients treated within 6 hours of symptom onset, two more recent studies demonstrated the benefits of MT at 6 to 16 hours (endovascular therapy following imaging evaluation for ischaemic stroke 3 [DEFUSE 3] and 6 to 24 hours (DAWN) from symptom onset, albeit these are highly selected patients.

Notably, two of the earlier trials in my SR and MA had suggested further benefits of treatment with MT up to 8 h (REVASCAT) and 12 h (ESCAPE) from symptom onset. Similarly, HERMES MA suggested a clinical benefit up to 7 hours from

stroke onset, although they also noted that the effects became nonsignificant after 7.3 hours from onset (Saver et al., 2016).

The DEFUSE-3 and DAWN trials late window treatments were based on strict imaging-based selection, with advanced CTP/magnetic resonance (MR) DWI-PWI imaging and MT offered based on salvageable penumbra.

The DEFUSE 3 and DAWN late window treatments, however, contradicts the HERMES MA suggestion of non-significant effect of treatment with MT after 7.3 hours of stroke onset and most importantly, the time-dependency notion that each hour delay to reaching reperfusion diminishes the likelihood of favourable outcomes. Conversely, the DEFUSE 3 and DAWN trials introduced the concept of “collateral flow” which together with elapsed time, contribute to duration of tissue viability during AIS. Hence, surrogate assessment of collaterals rather than tissue only viability, now represents an important variable for imaging selection of patients for MT, based on strict imaging criteria in DEFUSE 3 and DAWN time-based treatment window and extended time window (Details of the new studies are in Appendix 3 E).

3.4.3 Conclusion

This review has demonstrated clear evidence of the benefits of MT for the treatment of AIS for restoring patients’ functional independence. Further corroboration can be found in my aggregate data meta-analysis, HERMES meta-analysis, recent RCTs and SRs and MAs of recent trials.

3.4.4 Implications for future research

Further research is needed to see how this evidence translates into clinical practice and how it compares with the data from routine clinical practice as the trials were conducted in high volume centres with efficient stroke pathways and workflow, as well as MT being performed by highly experienced interventionists.

The next chapter will examine the current UK experience with MT for AIS using prospective observational registry data of patients treated in routine clinical practice. Furthermore, the outcomes from routine practice will be compared with those from the published RCTs.

CHAPTER FOUR

4 Mechanical Thrombectomy in Routine Clinical Practice in the UK

4. 1 Introduction

Until 2015, thrombolysis with Intravenous recombinant tissue-type plasminogen activator (rt-PA) was the only approved and recommended medical treatment for AIS. There has been a paradigm shift in the management of AIS following the publication of five positive RCTs of MT (Berkhemer et al., 2015, Goyal et al., 2015, Campbell et al., 2015a, Saver et al., 2015, Jovin et al., 2015).

The evidence of the benefits of MT for the treatment of AIS for restoring patients' functional independence was established in Chapter 3. Since completion of the SR and MA, the evidence has been supported by subsequent trials (Bracard et al., 2016, Muir et al., 2017, Khoury et al., 2017). The individual patient data (IPD) "HERMES" meta-analysis summarised the benefits of MT using predominantly stent retrievers for the treatment of AIS caused by occlusion of the proximal anterior circulation (adjusted common odds ratios (cOR) 2.49, 95% CI 1.76–3.53; $p<0.0001$) and showed complete recovery (mRS 0-1) in 27% and good functional outcome (mRS 0-2) in 46% of MT treated patients, compared with best medical treatment including IV thrombolysis. Overall, the number needed to treat (NNT) to achieve a good functional outcome (mRS 0 -2) was between three and four patients and the NNT for reduced disability was 2.6 (Goyal et al., 2016).

In light of the evidence from these trials, MT in combination with IVT for LAO stroke, has been recommended by several guidelines (Wahlgren et al., 2016,

Casaubon et al., 2016, Powers et al., 2015). In UK, the National Institute for Health and Care Excellence (NICE) and Health Care Improvement Scotland also published guidance for MT (NICE, 2016, Health Improvement Scotland, 2016). This is in addition to the published guidelines by the Royal College of Physicians (RCP) London (National Clinical Guideline for Stroke, 5th Edition 2016) (RCP, 2016).

However, despite the overwhelming evidence from the recent positive trials, it is still unknown to what extent trial outcomes are achieved in routine clinical practice. This is in addition to issues related to service delivery of the new interventions, such as the requirement for further resources and staff training.

Having established by means of SR and MA overwhelming evidence of the safety and clinical effectiveness of MT for AIS due to LAO, particularly from the recent positive trials discussed in Chapter 3, this chapter sets out to examine the extent to which these findings are transferable to routine clinical practice. Prospective observational registry data of stroke patients treated with MT alongside IVT in routine clinical settings, is used to determine the safety and effectiveness of MT in the UK.

This chapter begins by analysing data of stroke patients treated with MT with or without IVT in routine clinical practice from the Safe Implementation of Thrombolysis in Stroke (SITS) Thrombectomy registry (UK SITS-TBY)(SITS-TBY). The outcomes of the UK SITS-TBY cohort treated with MT with or without IVT are compared with the pooled analysis of the five trials (HERMES) (Goyal et al., 2016).

The UK and Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) network registries have previously reported outcomes from IVT in routine clinical practice compared to RCT (Wahlgren et al., 2007, Lees et al., 2008).

Research hypothesis:
The clinical outcomes from MT in clinical practice in the UK will match those seen in the RCTs.

The aims and objectives of the chapter can therefore be summarised as follows:

1 To assess current UK practice concerning the use of MT in patients with AIS treated outside the research setting. This is in respect to characteristics of patients treated and not the geographical distribution of treatment.
2 To compare outcomes from patients treated with MT with and without IVT in the UK, with that in the HERMES meta-analysis.

4.2 Method

The SITS-thrombectomy registry (SITS-TBY) (SITS-TBY) is an open, multicentre, prospective, observational registry of stroke patients treated with MT within the European Union and countries affiliated to the European Evaluation of Medicines Agency. The SITS network (SITS-TBY, SITS-ISTR) collects data on patients treated with both IVT and MT. The SITS-TBY collects data from 24 participating countries on patients treated with both IVT and/or MT. Nineteen of the 21 thrombectomy centres in the UK have been contributing their clinical data on

interventional thrombectomy to SITS-TBY. In this study, I draw on the data from the 19 centres in the UK who contributed data on interventional thrombectomy to SITS-TBY and on intravenous thrombolysis to SITS- IVT, between 2012 and 2016.

Baseline demographics, risk factors, time intervals and outcome data were extracted from the SITS registry for patients registered between January 2012 and March 2016. Additional information was extracted on time to treatment with both intravenous thrombolysis and interventional thrombectomy (onset–to-groin puncture and onset to thrombectomy). Good functional outcome was defined as a modified Rankin Scale (mRS) score of 0–2 at 90 days and surrogate for safety outcomes were symptomatic intracerebral haemorrhage and mortality at 90-days. Symptomatic Intracerebral Haemorrhage (sICH) as defined by the SITS-MOST criteria was used: local parenchymatous haemorrhage type 2 (PH2) (haemorrhage in >30% of the infarcted area with significant space-occupying effect) or remote parenchymal haemorrhage at 22-36 hours post-treatment combined with neurological deterioration of ≥4 points from the lowest NIHSS within 24 hours (Wahlgren et al., 2008). The pooled RCTs' definition of sICH was based on the individual trial definition. The used definitions include The European Cooperative Acute Stroke Study (ECASS) II (Larrue et al., 1997), The National Institute of Neurological Disorders and Stroke (NINDS) study group (NINDS t-PA Stroke Study Group, 1997) and The Safe Implementation of Thrombolysis in Stroke (SITS-MOST) (Wahlgren et al., 2007). The degree of vessel recanalisation was classified using the TICI score (Higashida et al., 2003) with successful

revascularisation defined as TICI 2b to 3 (Shi et al., 2014). The TICI scores in UK SITS-TBY are done by local teams, unlike the RCTs which are core lab based.

4.2.1 Statistical analysis

The statistical analysis used R (https://www.R-project.org) (R Core Team, 2016). The baseline characteristics were summarised using simple descriptive statistics. Baseline characteristics and outcomes between groups were compared using Pearson X^2 or Fisher's exact test for categorical variables and Student t-test or Mann Whitney U test for continuous variables. Efficacy and safety outcomes between groups were unadjusted. A p-value of <0.05 was considered statistically significant. The UK SITS-TBY results were compared with those of pooled outcome data for five RCTs (Goyal et al., 2016). The outcomes of patients treated with MT, both with and without IVT, were examined.

4.3 Results

4.3.1 Baseline data

Nineteen thrombectomy centres within the UK contributed data to the SITS-TBY between January 2012 and March 2016. There were 491 UK patients in the UK SITS-TBY registry, of whom 339 received combined MT with IVT and 152 had MT-alone. The number of patients per centre who were included into the SITS-TBY subset ranged from one to 172. Ten patients were part of the PISTE trial. Outcome data at 90 days were available in 362 (74%) of SITS-TBY patients. Out of the 491 patients, 129 were missing 90-day outcomes and 224 were missing recanalisation assessment (TICI scores) following MT. Of the 129 missing 90-day outcomes, 79 patients had information about recanalisation recorded. Out of the 224 patients missing information about recanalisation, 174 patients had their 90-day outcomes recorded. Fifty patients had neither 90-day outcomes nor recanalisation information recorded. A higher proportion of patients treated with combined MT with IVT had a more severe stroke, with median baseline NIHSS of 18 (13 to 22) compared with the IVT-alone treated patients with median NIHSS of 11 (7 to 11).

I will now compare the results of UK SITS-TB cohort with those from the pooled RCTs, beginning with the intervention arm (MT+ IVT) followed by comparison of the interventional arm (MT-alone) treated subgroup.

4.3.2 Comparison with pooled RCTs (intervention group- MT+ IVT)

4.3.2.1 Baseline data

Baseline and demographic characteristics of the UK SITS-TB cohort and pooled RCTs are shown in Table 4.1. The UK SITS-TBY cohort were slightly younger at 66 years than participants in the pooled RCTs at 68 years. Baseline stroke severity was similar in both the intervention groups with NIHSS score of 18 in the UK SITS-TBY cohort compared with 17 in the pooled RCTs.

Table 4.1. Baseline demographic and characteristics of patients in UK SITS-TBY and pooled RCTs

	UK SITS -TBY	**Pooled RCT**
Clinical Parameters	**Intervention (MT+ IVT) (n=491)**	**Intervention (MT+ IVT) (n=634)**
Age (median, IQR)	66 (51 to 75)	68 (57-77)
Sex, Male [n (%)]	286 (58%)	330 (52%)
Hypertension [n (%)]	198 (40%)	352 (56%)
Diabetes mellitus [n (%)]	52 (11%)	82 (13%)
Atrial fibrillation [n (%)]	82 (17%)	209 (33%)
Baseline NIHSS (median, IQR)	18 (13 to 22)	17 (14-20)
Blood glucose (mmol/L) (mean SD)	7 (2.18)	6.6 (5.9-7.8)

Intervention = Mechanical thrombectomy with or without IVT/BMT, BMT = Best Medical Therapy (may include IVT), NIHSS = National Institute of Health Stroke Scale Score, mRS= Modified Rankin Score, SD=standard deviation, IQR=interquartile range.

4.3.2.2 Clinical Outcomes

The UK SITS-TBY cohort had a shorter onset-to-groin puncture time at 226 min than in the pooled RCTs (238 min). In the UK SITS-TBY cohort, thrombectomy was performed with a variety of devices: Solitaire FR (47%); Penumbra system (9%); Trevo (11%); Revive (1%); and others (32%). There was limited information on 32% of the other devices used. Stent-retrievers were the predominant devices used in the pooled RCTs. In three of the trials from the pooled RCTs (EXTEND-IA, SWIFT PRIME and REVASCAT) (Campbell et al., 2015a, Saver et al., 2015, Jovin et al., 2015), stent retrievers were used in all patients and in the majority (86%) of the patients in ESCAPE (Goyal et al., 2015) and MR CLEAN (82%) (Berkhemer et al., 2015).

The UK SITS-TBY patients had a much lower recanalisation (TICI 2b/3) rate in comparison with the pooled RCTs (58% vs 71% p<0.001). Nevertheless, there was no significant difference between the UK SITS-TBY and the pooled RCTs in the overall distribution of the mRS at 90 days (OR 1.08, 95% CI 0.887- 0.782, P=0.823) [Figure 4.1]. Good functional outcome (mRS ≤2) at 90 days was similar (48% vs 46% p=0.6) between the two cohorts. The mean NIHSS score at 24hrs was higher for the UK SITS-TBY cohort compared with the pooled RCTs (12.2 vs 10.4, p= 0.002), but change in the NIHSS score from baseline to 24hrs was similar (Table 2). The efficiency outcomes of the UK SITS-TBY cohort and pooled RCTs are shown in Table 4.2.

4.3.2.3 Safety Outcomes

The reported rate of sICH in the UK SITS-TBY cohort according to the SITS-MOST criteria, was 1.0%, which was appreciably lower than 4.4% (95% CI -73.7

to -66.1, p <0.001) for the pooled RCTs, as defined by the trials' definitions of sICH (SITS-MOST, ECASS and NINDS) (Wahlgren et al., 2007, Larrue et al., 1997, NINDS t-PA Stroke Study Group, 1997). The rate of reported parenchymal haematoma type 2 (PH2) was also lower in the UK SITS-TBY (2.0% vs 5%), p= <0.001). There was a non-significant trend to higher 90-day mortality in the UK group (20% vs 15.3%: 95% CI -0.9 to 9.5, p=0.099). The rate of hemicraniectomy for the UK SITS-TBY and the pooled RCTs was similar (3% vs 2.8%, p=1). The safety outcomes of the UK SITS-TBY cohort and pooled RCTs are shown in Table 4.2.

4.3.3 Comparison with pooled RCTs (Intervention group (MT-alone))

In the UK-SITS-TBY cohort, 152 of 491 (31%) of patients were treated with MT-alone and 108 of 633 (17%) in the pooled RCTS. These were patients that were ineligible for treatment with IVT. Outcome data at 90 days were available in 110 (72%) of SITS-TBY MT-alone treated patients. There was no significant difference between the UK SITS-TBY MTS - alone cohort and the pooled RCTs MT- alone cohort in the overall distribution of the mRS at 90 days (OR 0.93, 95% CI 0.53 -1.62; p=0.428) [Figure 4. 2]. The UK SITS-TBY MT-alone treated cohort had similar 90-day functional outcome (mRS 0-2) (48% vs 41% p=0.219), sICH (1.0% vs 0.7%, p=1.000), but statistically higher 90-day mortality [20% vs 27%, p=0.002) over the combined MT with IVT group. Similarly, in the pooled RCTs there was no difference in the treatment effect size in the MT-alone treated group over the combined MT with IVT common OR 2.43(95% CI 1·30–4·55).

Table 4.2. Efficacy and safety outcomes of patients in UK SITS-TBY compared with pooled RCTS

	UK SITS -TBY	**Pooled RCT**	
Clinical Outcomes	**Intervention (n=491)**	**Intervention (n=634)**	**95% CI, P-value**
Median (IQR) NIHSS at 24 hours	10 (3 to 19)	8 (3 to 16)	
Mean (SD) NIHSS at 24 hours	12.2 (9.8)	10.4(8.7)	(0.8 to 3.6), p=0.002
Mean (SD) change in NIHSS from baseline to 24 hours	-5.3 (9.1)	-6.4 (8.2)	(-2.4 to 0.2), p=0.100
Median Time (IQR) door -to- imaging (mins)	23 (14 to 39)	19 (12 to 33)	
Median Time (IQR) from onset -to-arterial puncture (mins)	226 (183 to 295)	238(180 to 302)	
mRS score 0-1 at 90 days [n (%)]	30.4% (110/362)	26.9% (170/633)	(-2.5 to 9.6), p=0.263
mRS score 0-2 at 90 days [n (%)]	47.8% (173/362)	291/633 (46.0%)	(-4.8 to 8.5), p=0.626
0 [n (%)]	9% (34/362)	10%	(-4.6 to 3.5), p=0.861
1 [n (%)]	21% (76/362)	17%	(-1.2 to 9.4), p=0.129
2 [n (%)]	17% (63/362)	19%	(-6.7 to 3.6), p=0.600
3 [n (%)]	13% (48/362)	17%	(-8.4 to 1.1), p=0.152
4 [n (%)]	9% (34/362)	16%	(-10.9 to -2.2), p=0.005
5 [n (%)]	9% (33/362)	6%	(-0.4 to 7.0), p=0.070
6 [n (%)]	20% (71/362)	15%	(-0.9 to 9.5), p=0.099
Recanalisation 2b/3 (%)	58% (154/267)	71%	(-27.0 to -13.3), p=0.000
Symptomatic intracranial haemorrhage [n (%)]	1% (5/491) ¶	4.4% (28/634) §	(-73.7 to -66.1), p=0.000
Parenchymal haematoma type 2 [n (%)]	2% (9/491)	5% (32/629)	(-73.0 to -65.2), p=0.000
Mortality at 90 days from onset [n (%)]	20% (71/362)	15.3% (97/633)	(-0.9 to 9.5), p=0.099
Hemicraniectomy [n (%)]	3% (15/491)	2.8% (18/634)	(-2 to -2), p=1

¶ = SITS-MOST definition, § =Trials' definition (ECASS AND NINDS), mins=minutes.

NIHSS=National Institute of Health Stroke Scale, OR= odd ratio, CI =Confidence interval, OTTT= onset to treatment time

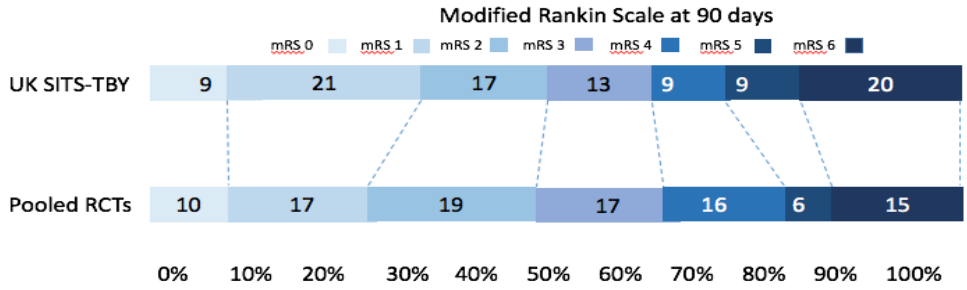


Figure 4.1. Distribution of modified Rankin Scale score at 90-day

Distribution of modified Rankin Scale score at 90-day in the UK SITS-TBY and pooled RCT cohorts following MT. Shown are the percentages of the UK SITS-TBY and the pooled RCTs patients with mRS scores of 0-6. A modified Rankin score of 0 to 2 indicates good functional independence and 6 indicates mortality. There was no significant difference between the UK SITS-TBY and the pooled RCTs in the overall distribution of the mRS at 90 days (OR 1.08, 95% CI 0.8868- 0.7824, P=0.823).

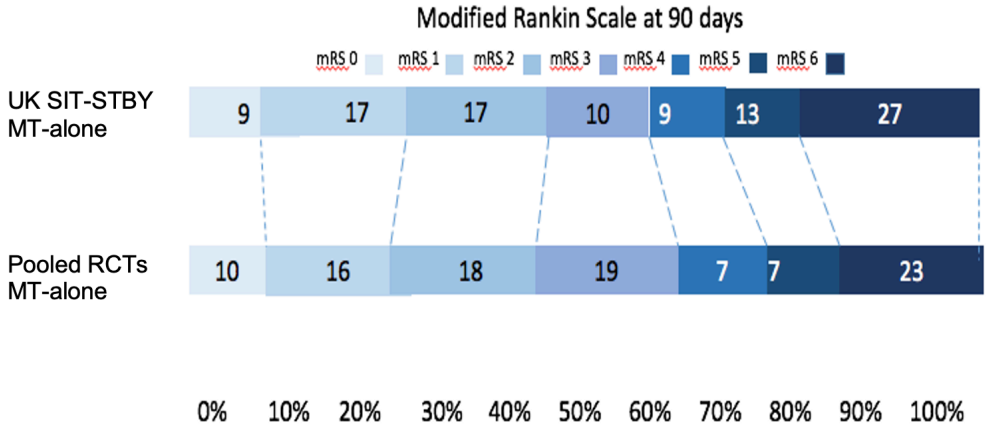


Figure 4.2. Distribution of modified Rankin Scale score at 90-day (MT -alone)

Distribution of modified Rankin Scale score at 90-day in the UK SITS-TBY intervention (MT-alone) treated group and the Pooled RCT intervention (MT-alone treated group.
Shown are the percentages of the UK SITS-TBY(MT-alone) and the pooled RCT (MT-alone patients with mRS scores of 0-6. A modified Rankin score of 0 to 2 indicates good functional independence and 6 indicates mortality. There was no significant difference between the UK SITS-TBY intervention- alone and the pooled RCT intervention-alone cohorts in the overall distribution of the mRS at 90 days (OR 0.93, 95% CI 0.53 -1.62; p=0.428).

4.4 Discussion

This multicentre, prospective, non-randomised registry which provides data for a cohort of patients treated with MT in the UK with clinical outcomes represents the real-world experience of the use of MT for the treatment of AIS in the UK. The Sentinel Stroke National Audit Programme (SSNAP, 2016) is another UK registry data of stroke patients treated with IVT and MT, but only started collecting MT data in April 2016 and with limited clinical outcomes.

The median onset-to-groin puncture time was 10 minutes shorter in UK SITS-TBY than the pooled RCTs. Another IPD analysis of the five trials showed how the odds of better outcome at 90 days decreases with longer time from symptom onset to arterial puncture (Saver et al., 2016). The efficacy of thrombectomy with respect to clinical outcomes is highly time dependent. Early series of endovascular stroke therapy often treated patients later than in HERMES trials (Goyal et al., 2016, Saver et al., 2016). It is reassuring that treatment in routine clinical practice is delivered at least as rapidly as in the trials.

The lower recanalisation (TICI 2b/3) rate in the UK SITS-TBY cohort, compared with the pooled RCTs may relate to missing data which was uniform across most centres. Higher recanalisation rates in the pooled RCTs compared with the rate in the UK SITS-TBY register have been attributed to the use of Solitaire stents (Campbell et al., 2016). The ASTER trial, however, suggests no difference in successful recanalisation rates (TICI 2b/3) between contact aspiration vs stent retriever arms (85.4% [n = 164] vs 83.1% [n = 157]; OR, 1.20; 95% CI, 0.68-2.10; *P* = .53), with a risk difference of 2.4% (95% CI −5.4% to 9.7%) (Lapergue et al., 2017).

The lower recanalisations rates could also be due to the fact that the UK's Interventional Neuroradiologists (INRs) were on a learning curve as opposed to the pooled RCTs where the procedures were performed by experienced INRs at high output comprehensive centres.

The recanalisation rates published in other non-randomised studies (Kuntze-Söderqvist et al., 2014, Nikoubashman et al., 2016, Urra et al., 2015, Weber et al., 2017, Abilleira et al., 2014, McCusker et al., 2015, Mueller-Kronast et al., 2017, Minnerup et al., 2016), ranged between 72% and 92%, clearly higher than the UK SITS-TBY rate. Despite the higher rate of recanalisation in the pooled trial data, the SITS-TBY cohort had similar functional outcomes to the pooled RCTs. This recanalisation/functional outcome discrepancy could be due to lack of expert independent consistent reporting of TICI (as used in RCTs and some Registries) in SITS-TBY by Neuro-interventional operators, along with the under-reporting of 90-day outcomes and potential follow up bias in the UK dataset.

The safety measures and clinical outcomes from the UK SITS-TBY cohort are not comparable with those from pooled RCTs due to under reporting of sICH, because scans were not independently assessed, although the hemicraniectomy rates were similar or compared well with those from pooled RCTs. The findings from the UK SITS-TBY cohort are, however, comparable with the results of other smaller prospective studies and registries (Mueller-Kronast et al., 2017, Nikoubashman et al., 2016, Urra et al., 2015, Weber et al., 2017, Abilleira et al., 2014, McCusker et al., 2015, Minnerup et al., 2016). The real-world data, however, are limited by incomplete data acquisition and ascertainment bias, as well as probably less stringent inclusion criteria compared with the RCTs.

Other non-trial cohorts reported similar functional outcomes at 90 days (mRS score of 0-2) to the UK SITS-TBY rates: 50% (Kuntze-Söderqvist et al., 2014) and up to 56.5% (Mueller-Kronast et al., 2017). The rates were, however, slightly higher than those obtained in MR CLEAN (32.6%) and THERAPY (30.4%). MR CLEAN was a pragmatic trial which recruited patients similar to those treated in routine clinical settings. Some trials had a higher 90-day functional outcome, which ranged between 53% and 70% (ESCAPE, EXTEND-IA and SWIFT PRIME). Overall, the other registries showed a good outcome in around 40% (Serles et al., 2016, Abilleira et al., 2014, Nikoubashman et al., 2016, Weber et al., 2017). Similarly, the 90-day functional outcome of some trials was higher, ranging between 53% and 70% (ESCAPE, EXTEND-IA and SWIFT PRIME).

The UK SITS-TBY reported sICH rate of 1%, which is lower than that of the pooled RCTs and other non-observational studies; this is likely to be mainly due to local underreporting of the 24-hour CT and NIHSS score post thrombectomy. The rates for the individual trials were 7.7% for MR CLEAN, 4.9% for REVASCAT, 3.6% for ESCAPE while EXTEND-IA and SWIFT PRIME did not observe any sICH. These trials had independent reading of scans, more consistent assessment of 24 hr NIHSS and adjudication of sICH. The STRATIS and Spanish registries also reported lower than expected sICH rates of 1.4% and 1.9%, respectively (Mueller-Kronast et al., 2017, Urra et al., 2015). This is almost certainly because ascertainment of sICH in routine clinical practice is less rigorous than in trials. The lack of ownership of data collection between the interventional team and the physicians or between hospitals, when patients are repatriated following thrombectomy, particularly in a hub and spoke tertiary referral model, may have contributed systematically to such underreporting.

The rates in the other studies varied: 3.1% (Rebello et al., 2016); 5.6% (Abilleira et al., 2014); 5.7% (Kuntze-Söderqvist et al., 2014); 5.9% (Weber et al., 2017); 7% (Serles et al., 2016); 15.8% (Minnerup et al., 2016).

The 90-day mortality rate of 20% for the UK SITS-TBY is comparable with other registries and trials with simple CT/CTA selection - MR CLEAN (18.4%) and PISTE (21% on ITT). In contrast, the mortality rates in studies with more stringent imaging selection were 12% for SWIFT PRIME, 10% for ESCAPE and 9% for EXTEND-IA.

It is not possible from the register to estimate the treatment rate in the UK. However, based on the rigorously completed Sentinel Stroke National Audit Programme (SSNAP), across all stroke services in England, Wales & N Ireland, 580 of 85,122 patients (<1%) who presented between April 2016 and March 2017 with AIS were treated with MT in 25 thrombectomy centres (Thrombectomy Report for April 2016 - March 2017) (SSNAP, 2017a). The number treated with MT is expected to rise due to the requirement from National Policy and commissioning drivers for reorganisation and expansion of thrombectomy services. It has been estimated that 7-10% of patients with AIS could be eligible for MT (Chia et al., 2016, McMeekin et al., 2017, Campbell et al., 2015b), but so far this is proving to be difficult to achieve in practice across large populations. Even more established multi-site services such as Catalonia are achieving only 3.3 % (Urra et al., 2015), suggesting that there is still much to be done to improve public awareness, diagnosis, service efficiency and provision through research and reorganisation.

Furthermore, 10 patients in the SITS registry were recruited into the PISTE trial, although they were not included in the HERMES IPD, which included only the initial five positive trials. It is arguable whether patients in trials should be included in observation registry datasets as this can lead to heterogeneity of the data due to different treatment protocols and potential double counting of patients, particularly between a comparison of a study and any registry those patients are in already.

The UK SITS-TBY findings of MT-alone treated patients are in keeping with the MT-alone patients treated in the pooled RCTs. So are the findings from other non-randomised studies (Weber et al., 2017, Rebello et al., 2016). These studies found no statistical difference in the rates of functional outcome (mRS 0-2) between the combined MT with IVT and the MT-alone treated patients (35.2% vs 40%, p=0.444) and 45% vs 38%; p=0.21) respectively (Rebello et al., 2016, Weber et al., 2017). Whilst the findings indicate that treatment with MT-alone may be as effective as combined MT with IVT therapy, the studies had a small number of patients treated with MT-alone. This is because the standard of care for LAO is combined treatment of IVT plus MT, except where IVT is contraindicated.

The Direct Intra-arterial thrombectomy in order to Revascularize AIS patients with large vessel occlusion Efficiently in Chinese Tertiary hospitals: A Multicentre randomized clinical Trial *(*DIRECT-MT)*;* reported how therapy with MT alone was noninferior to combination therapy (Yang et al., 2020). There is a need for further research into the use of rapidly delivered MT-alone therapy with a larger population of patients. It is anticipated that the results from the Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke

(SWIFT DIRECT) (NCT03192332) (DIRECT-NCT03192332); DIRECT SAFE: A Randomised Controlled Trial of Direct Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval (NCT03494920)(DIRECT-SAFE); MR CLEAN-NO IV: intravenous treatment followed by endovascular treatment versus direct endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion (SRCTN80619088) (Treurniet et al., 2021) when completed could provide further evidence on the possible superiority of MT alone without initial use of alteplase.

4.4.1 Limitations and Strengths

Most studies on the introduction of new treatment innovations from RCT level into routine clinical practice suffer from significant limitations. This study is no exception because it also encountered challenges arising from incomplete data acquisition and some ascertainment bias; it also employed less stringent inclusion criteria than those in the RCTs. Arguably, in the early days of SITS reporting completeness was high.

The main limitation of the database was its missing and incomplete data, particularly for recanalisation rate and the 90-day follow-up record. Information on CT imaging, ASPECTS scores, site of occlusion and use of general anaesthesia versus conscious sedation were limited or not available. The unusually low rate of sICH in the UK SITS-TBY Registry, cannot be a true assessment and indicates the challenges with sites independently reporting outcomes. This could be due to under-reporting of 24-hr neurological deterioration and CT haemorrhages in clinical practice compared with RCTs.

This is similar to earlier work in carotid endarterectomy where independent neurologists found much higher rates of stroke than reported by surgeons.
The incomplete data in the UK SITS-TBY database probably arose from local inability to collect and record the details required and the unavoidable repatriation of patients to other centres, preventing further data collection. That is a common outcome from the relocation of patients to other geographical locations part-way through their treatment pathway. Complete follow-up data on 90-day mRS were available for only three quarters of cases treated with MT in combination with IVT in the registry.

The SITS network database is of value in confirming the effectiveness of thrombolysis in real-life practice compared with the trials. This is because the database was substantially complete and incorporates good follow-up data. However, the MT SITS Database, as used in the UK, is not robust enough to answer the questions regarding the utilisation of MT in the UK. The limitations of the UK SITS-TBY database has very important implications for the use of all clinical practice databases. For them to be reliable and usable there is a clear need to institute robust measures of quality; currently, the UK SITS-TBY Database, is not adequate to answer all of the questions addressed in this study. The potential solutions to ensure that good quality data are collected outside the research setting, include more responsibility by all stroke networks and payment for reporting, for example a Quality and Outcomes Framework (QOF) type mechanism, in secondary care.

The data was collected from observations taken from many stroke centres. The effect of this is to introduce the variability of protocols used among those hospital

into the dataset, particularly in terms of criteria for patient selection. It is, therefore, possible that some selections were less stringent than those applied in the published RCTs. Similarly, the variation in imaging and the usage of different thrombectomy devices may have resulted in increased heterogeneity of data.

Lastly, a limitation unrelated to the database arose from the statistical analyses used for comparing the differences between the SITS data to the pooled RCTs' data. The analyses were performed using aggregated summary data from the published RCTs, not from IPD.

Despite these limitations, the study, has a number of strengths. The SITS-TBY Registry is the first, large, observational dataset of patients treated in the UK with MT and is representative of the use of MT in routine practice. Representing real-world practice, it has considerable potential for informing clinicians and researchers across the UK and indeed, more widely. Although the data is drawn from an observational registry, the majority of the patients who were treated with IVT-alone constitute a concurrent control group.

4.4.2 Conclusions

The findings from the multicentre observational data of UK patients treated in routine clinical practice have further confirmed the safety and efficacy of MT when used in combination with IVT for the treatment of LAO stroke outside randomised trials. However, awareness of the high rate of missing data in this registry requires that any interpretations drawn must be duly qualified. Future studies must include proper data collection.

4.4.3 Implications for future research

This study examined the current UK experience of MT for AIS using prospective observational registry data of patients treated in routine clinical practice. There is a need for a larger study using a robust database to establish the utilisation of MT in clinical settings in the UK. Further research into the use of MT-alone therapy and technical issues concerning optimum devices to use, is urgently required.

Furthermore, there is a need to map out the different treatment pathways: this is done in the next chapter which focuses on undertaking a mapping and data collection exercise to describe the treatment pathways currently being used in a range of different treatment centres, both nationally and internationally.

CHAPTER FIVE

5 Treatment Pathways for Mechanical Thrombectomy and Intravenous Thrombolysis

5.1 INTRODUCTION

The management of acute ischaemic stroke (AIS) has continued to evolve with improvements in imaging techniques and treatment such as intravenous thrombolysis (IVT) and recently, mechanical thrombectomy (MT) using thrombectomy devices. Early and rapid reperfusion to recanalise occluded blood vessels is the key to ischaemic stroke treatment to improve functional outcome and reduce disability and mortality (Rha and Saver, 2007). Recanalisation can be achieved with intravenous recombinant tissue-type plasminogen activator (rt-PA, NNT 5-9), or in large artery occlusion (LAO), with MT using thrombectomy devices (NNT 3). Recent randomised controlled trials (RCTs) have demonstrated the clinical benefit of MT in conjunction with IVT in reducing disability compared with IVT alone or in conjunction with supportive care for the treatment of AIS (Goyal et al., 2016). In consequence, MT is now the standard of care for LAO stroke and is recommended by several guidelines (NICE, 2016, Wahlgren et al., 2016, Powers et al., 2015, Powers et al., 2018, Boulanger et al., 2018).

The proportion of patients with AIS who could be eligible for MT has been estimated in a number of studies. The PEARS (Promoting effective and rapid stroke care) group from Newcastle upon Tyne in the UK, estimated that approximately 10% of patients with AIS could be eligible for MT (McMeekin et al.,

2017), as have studies by (Campbell et al., 2015b, Rai et al., 2017). A Scottish study estimated that up to 15% (Tawil et al., 2016) of patients with AIS might be eligible for treatment with MT.

It is crucial to understand the treatment pathways undertaken by patients presenting with stroke, particularly severe LAO stroke, for a timely intervention to achieve a favourable functional outcome and to prevent disability.

There has also been considerable discussion about the best way of delivering MT. A recent systematic review identified four main models: the ‘‘mothership,’’ ‘‘drip-and-ship,’’ ‘‘mobile interventionist,’’ and ‘‘mobile stroke unit’’ model (Ciccone et al., 2019). In the mothership model, patients are transferred directly to a thrombectomy centre, usually a neuroscience centre or a comprehensive stroke centre with neuro-interventional capability, while in the drip-and-ship model patients are transported initially to the nearest primary hospital/stroke centre before a second transfer to a thrombectomy centre (Ismail et al., 2019). In the mobile interventionist model, sometimes referred to as the drip-and-drive, or ‘drive the doctor’ model, the interventionist is transported to the primary hospital to perform MT with the local team (Brekenfeld et al., 2018, Seker et al., 2018, Wei et al., 2017). In the Mobile Stroke Unit (MSU), the patient is initially managed in the equipped mobile unit with thrombolysis commenced quickly and is then transported to the nearest MT centre (Yamal et al., 2018).

There is some evidence that the mothership model has been the predominant delivery method in the randomised trials which have been conducted in this area: for example, the MR CLEAN (Berkhemer et al., 2015), ESCAPE (Goyal et al.,

2015), EXTEND-IA (Campbell et al., 2015a), SWIFT PRIME (Saver et al., 2015), REVASCAT (Jovin et al., 2015), THRACE (Bracard et al., 2016), THERAPY (Mocco et al., 2016), PITSE (Muir et al., 2017), EASI (Khoury et al., 2017), DAWN (Nogueira et al., 2018) and DIFFUSE 3 (Albers et al., 2018) trials have all published treatment protocols and pathways for eligible stroke patients using variants of the mothership model, in some cases comparing this with other delivery methods. Meanwhile, a combination of mothership and drip-and-ship appears to be more widely used in the clinical setting.

However, there is very little reliable evidence on the effectiveness of different treatment pathways being used in the delivery of mechanical thrombectomy and intravenous thrombolysis, their costs and associated outcomes.

The RACECAT (Direct Transfer to an Endo-vascular Center Compared with Transfer to the Closest Stroke Center in Acute Stroke Patients with Suspected Large Vessel Occlusion) trial compared functional outcomes at 90 days between pre-hospital triage directly to an MT centre (Mothership), with transfer to local stroke hospital (drip -and- ship) alongside IVT (Abilleira et al., 2019). The recently published RECECAT (Desai et al., 2021) after this study was conducted, failed to show any superiority of mothership transfer protocol for suspected LAO compared with drip and ship.

This chapter begins by, firstly, conducting a systematic review to identify studies reporting treatment pathways for MT and IVT for AIS. It then presents the results of a study to identify the different treatment pathways being used in a range of treatment centres in the UK, as well as some centres in Germany, Italy and

Canada. This involved visiting each centre and collecting aggregate and patient level information on the actual pathway being used: beginning from the patients' route to the hospital; the initial assessment on arrival at the hospital; the diagnostic process; the different treatment options available and their use; and the discharge process and patients' destinations.

The aims and objectives of the chapter can therefore be summarised as follows:

1. To establish what is known from the existing literature about the range of treatment pathways for patients treated with IVT and MT, and how these have changed over time.
2. To identify the existing treatment pathways of MT for the treatment of AIS in routine clinical settings within the UK NHS, using a combination of summary and individual patient data.
3. To compare the identified UK treatment pathways with those from centres in other health care systems in Germany, Italy and Canada.

5.2 Literature Review: Published Treatment Pathways

The initial step in establishing what is known about the range of treatment pathways for patients treated with IVT and MT was to conduct a semi-structured systematic review (SR). This was undertaken to provide information on what is already known on the various treatment pathways of MT and IVT, and to identify key research gaps in the literature.

5.2.1 Literature Review Methods

The research question for the SR was formulated as: “What are the different treatment pathways for patients with AIS treated with MT and intravenous IVT”? The review was carried out in accordance with established review protocols of the Cochrane Collaboration (Higgins and Green, 2009). Systematic Reviews Centre for Reviews and Dissemination’s (CRD) guidance for undertaking reviews in health care (University of York, 2008) and followed the PRISMA standard (Moher et al., 2009) for reporting the findings. This is in addition to following the guidelines for grey literature search (Saleh et al., 2014, CADTH, 2019).

5.2.1.1 Inclusion Criteria

The final selection of full-text articles was based on the Population, Intervention, Control Outcomes and Study Design (PICO) criteria presented in Table 5:1.

Table 5.1. Selection Criteria

PICO Protocol	
Population	Stroke patients (>18 years) with documented blood vessel occlusion using either computed tomography angiography (CTA) or magnetic resonance angiography (MRA), eligible for treatment according to stroke clinical practice treatment protocol/guidelines.
Intervention	Mechanical thrombectomy therapy using thrombectomy devices with or without intravenous thrombolysis.
Comparator	Best medical treatment* with or without intravenous thrombolysis.
Outcomes	Treatment pathways
Study Designs	RCTs, observational studies, stroke guidelines, protocols, consensus statements, hospital workflow/ protocols, regional protocols, business cases, case series HTA.

* Best medical therapy (anti-thrombotic therapy)

5.2.1.2 Exclusion Criteria

Articles were excluded if they did not meet the PICO criteria, were published prior to 2015, were unpublished, published in abstract form only, or were letters or editorials.

5.2.1.3 Search Strategy

The literature search was conducted in the following databases: Ovid Medline, Ovid EMBASE, Cochrane Database of Systematic Reviews and the Cochrane Central Registry of Controlled Trials; Stroke Trials Registry; Clinicaltrials.gov and Current Controlled Trials; Health Technology Assessment Database (HTA); and Grey literature. Cross-referencing and hand-searching of reference lists of relevant articles and conference proceedings was also conducted. Papers published in any language and country between January 2015 and March 2019 were included.

The search terms used were ‘brain isch(a)emia’, ‘acute isch(a)emic stroke’, ‘cerebral infarction’, ‘cerebrovascular accident’, ‘CVA’, ‘stroke’, ‘large artery occlusion’ AND ‘mechanical thrombolysis’, ‘endovascular therapy’, ‘endovascular treatment’, ‘endovascular embolectomy’, ‘endovascular thrombectomy’, ‘intra(-)arterial intervention’, ‘intra(-)arterial treatment’, ‘intra(-)arterial therapy’, ‘intra(-)arterial thrombolysis’, ‘neuro(-) thrombectomy’, AND ‘Stroke Treatment pathways’, ‘treatment pathway’, ‘thrombectomy pathway’, ‘thrombectomy protocol’, ‘thrombolysis pathway’, ‘management pathway’, ‘pathway algorithms’, AND ‘randomized controlled trial‘, and ‘randomised controlled trial‘, ‘stroke guidelines’, ‘Health Technology Assessment’, ‘observational studies’,

‘thrombectomy workflow’(where parentheses indicate terms that were searched with and without the bracketed text). Search strategy in Appendix 5.A.

5.2.1.4 Study Selection

The titles and abstracts of studies were examined and then full texts were scrutinised for inclusion. Eligibility assessment and data extraction were performed and entered a standard format designed specifically for the review.

The PRISMA flow chart of study selection is shown in Figure 1. The background on the studies identified as eligible for inclusion in Appendix 5.B.

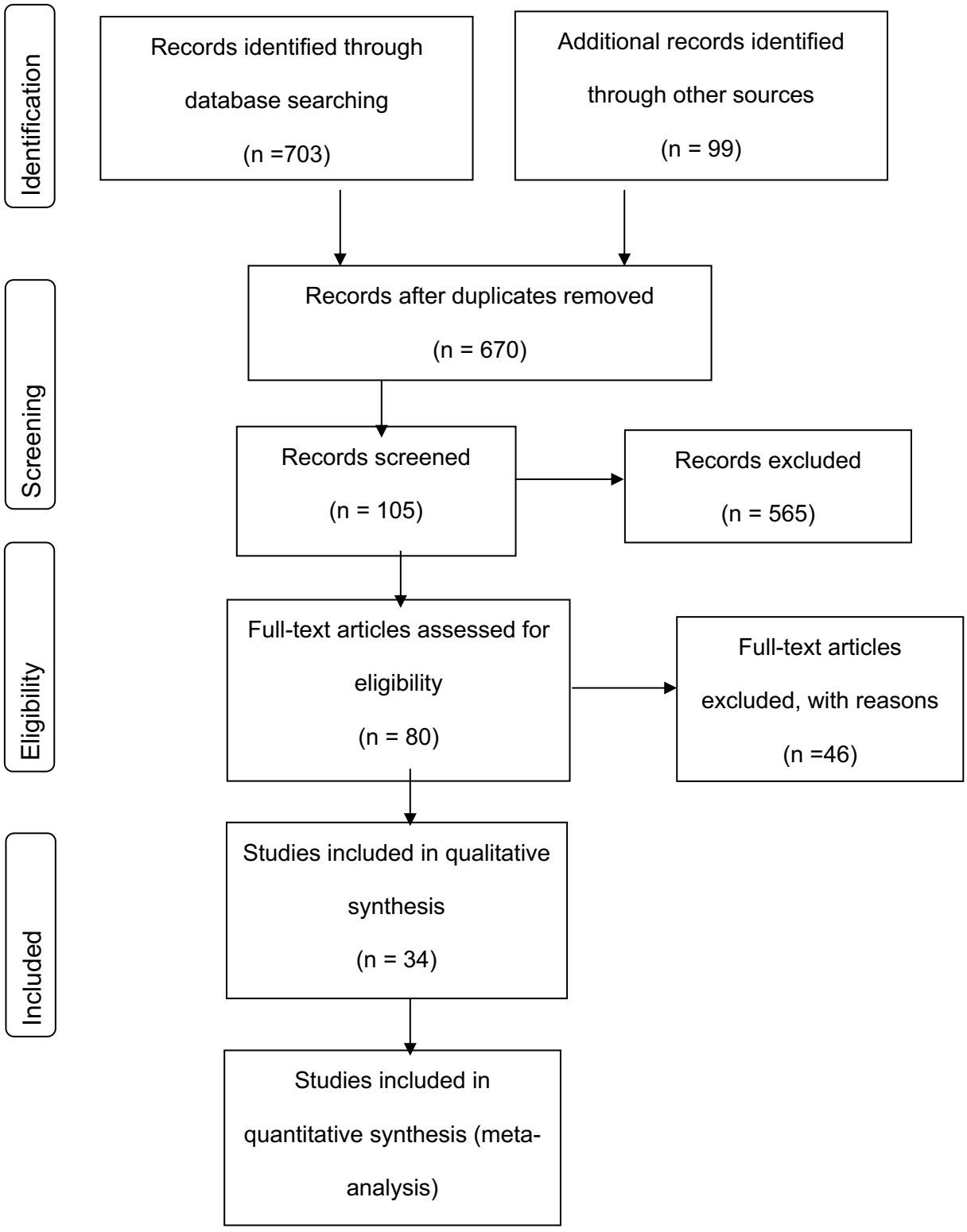


Figure 5 1. PRISMA flow chart of study selection

Adapted from Moher, 2009 (Moher et al., 2009).

5.2.1.5 Data Extraction

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

1. Background characteristics of the included studies (first author, location, publication year, study type, type of setting).
2. Components of pathways covered, inclusion criteria, type of imaging and components of pathway not covered (see Appendix 5.C).

5.2.1.6 Primary Outcome

The primary outcome of interest was the treatment pathway for patients treated with MT and IVT in clinical practice.

5.2.1.7 Critical Appraisal of Individual Studies

To assess the quality of the included studies, various assessment tools depending on the study designs, were used. For the RCTs, the Cochrane Collaboration's tool was used to assess the risk of selection, performance and reporting biases. (Higgins et al., 2011). The Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument (Brouwers et al., 2010) was used for published guidelines.

5.2.2 Literature Review Results

5.2.2.1 Study Characteristics

The search yielded 802 studies, 768 were excluded and 34 studies were included. Among the included papers, 12 were trials (ESCAPE, EXTEND-IA, MR CLEAN, REVASCAT, SWIFT PRIME, THRACE, THERAY, PISTE, EASI, EAST, DAWN, DEFUSE) (Berkhemer et al., 2015, Goyal et al., 2015, Campbell et al., 2015a, Saver et al., 2015, Jovin et al., 2015, Bracard et al., 2016, Mocco et al., 2016, Muir et al., 2017, Khoury et al., 2017, Jia et al., 2018); 10 were guidelines/ consensus statements by professional bodies and societies (Turc et al., 2019, Mokin et al., 2019, Sacks et al., 2018, Kim et al., 2018, Boulanger et al., 2018, Powers et al., 2019, Agostoni et al., 2018, McTaggart et al., 2017, Wahlgren et al., 2016, White et al., 2015); four were regional protocols (Safer Care Victoria, 2018, Christiana Care Health System, 2016, Victoria State Government, 2016, Alberta Health Services, 2016); six were hospital protocols /work flows (Goldstein et al., 2018, Smith, 2018, Wang et al., 2017, Ng et al., 2017, McTaggart et al., 2017, Zaidi et al., 2017), one case report (Zerna et al., 2016) and one was a business case (PASC, 2016).

Among the hospital clinical pathways: five included pre-hospital care (Wang et al., 2017, Ng et al., 2017, McTaggart et al., 2017, Zaidi et al., 2017, Zerna et al., 2016), while two (Goldstein et al., 2018, Smith, 2018) were mainly hospital work-flows/care. Most of the studies used NIHSS scoring (Lyden et al., 1994), whereas one study used the rapid arterial occlusion evaluation (RACE) (Ossa et al., 2014) scale and the other, Los Angeles Motor Scales (LAMS) (Llanes et al., 2004).

The non-trial pathways' origins were: two from the UK (White et al., 2015, Smith, 2018); five from USA (Powers et al., 2018, Goldstein et al., 2018, McTaggart et al., 2017, Christiana Care Health System, 2016, Zaidi et al., 2017); five from Australia (Safer Care Victoria, 2018, Victoria State Government, 2016, PASC, 2016, Ng et al., 2017, Wang et al., 2017); three from Canada (Boulanger et al., 2018, Alberta Health Services, 2016, Zerna et al., 2016); one from Italy (Agostoni et al., 2018) and one from the Republic of Korea (Kim et al., 2018). The others include joint European (Wahlgren et al., 2016) joint USA and Canada (Mokin et al., 2019, McTaggart et al., 2017), and joint USA, Canada, Europe and Australia (Sacks et al., 2018) guidelines.

5.2.2.2 Outcomes

The randomised controlled trials (RCTs) (see Appendix 5.C) focused mainly on patient selection and minimum requirements such as advanced imaging to establish LAO before recruitment into the RCTs, and they placed emphasis on acute in-hospital care provision of MT. MR CLEAN was the only trial that recruited patients with non-stringent criteria, similar to those in routine clinical settings. The ESCAPE study focused on quick image acquisition and interpretation, transfer to the angiography suite and thrombectomy procedures (Goyal et al., 2016).

While the trials emphasised patient selection and acute hospital care, the non-trial articles focused on pre-hospital triage care and acute in-hospital care through to discharge and eventual follow-up. The various components of the treatment pathways covered include: pre-hospital notifications, triage and care (n=17); arrival at the Emergency Department (n=16); imaging (all studies); in-hospital

care (n=19); inter-hospital transfers (n=10); discharge from hospital (nine studies) and follow-up care (four studies). The components of the in-hospital care vary, from: initiating IVT (n=11); obtaining informed consent (two studies); notification of interventional team and MT protocol (three studies); transfer to angiography suite (four studies); type of anaesthesia (seven studies); post MT care (nine studies) such as transfer to Intensive Care Unit / Hyper Dependency Unit (ICU/HDU) (three studies); transfer to acute stroke unit (two studies); post MT imaging (four studies); rehabilitation (one study); acute hospital discharge (nine studies) and follow-up (three studies). The other components covered by some of the protocols are quality improvement through regular monitoring and audits (two). Additionally, two guidelines looked at complications and reviews of mortality at 72 hours post-MT (Kim et al., 2018, White et al., 2017). One of the studies traced a patient's pathway from the onset at home to the emergency medical service at home, transportation to hospital, in-hospital workflow starting from clinical evaluation, imaging, intervention and post-op review to discharge from hospital and follow-up at three months (Zerna et al., 2016).

5.2.2.3 Literature Review Limitations and Strengths

There were some limitations to this literature search. Firstly, most of the relevant articles were obtained via the Grey Literature, rather than major and relevant scholarly databases. The Grey Literature checklist is not as exhaustive as that of the major databases. There is limited evidence as to whether or not studies from the Grey Literature are of poorer methodological quality than those of the published, mostly peer reviewed studies (Hopewell et al., 2007). Secondly, because the assessment of the included papers was performed by just one

researcher (JB), the inter-rater reliability of the inclusion decision could not be assessed using Cohen's Kappa statistic. It is possible, therefore, that the selection process was less stringent than if it had been performed by more than one reviewer.

Despite the above limitations of the review, the review also had some notable strengths. Firstly, articles were identified across a number of countries representing a range of delivery models for MT in routine clinical practice. Secondly, the articles included clinical trials, non-randomised studies and protocol/ guidelines. Thirdly, the review included material found in the Grey Literature and not just in major databases.

5.2.3 Literature Review Discussion and Conclusions

Effective treatment pathways are critical for improving delivery of stroke care, particularly for efficient delivery of MT. The pathway can have an important influence on time to diagnosis and treatment, and therefore on subsequent outcomes. It has been shown, for example, that for every 30 minutes of reperfusion delay, there is a 12-15% relative risk reduction for a favourable outcome (Khatri et al., 2014). Equally, a 6% absolute risk reduction in the likelihood of a good clinical outcome has been reported for every one-hour delay in time to reperfusion (Fransen et al., 2016).

This review identified wide variability in the workflow pathways for MT. This is in line with the findings from a survey which revealed variability in workflow practices in the USA (Kansagra et al., 2017).

The identified studies used a range of pre-hospital scoring systems for identification of large vessel occlusion, such as the rapid arterial occlusion evaluation (RACE) scale (Ossa et al., 2014), the Cincinnati Pre-hospital Stroke Severity Scale (CPSS) (Katz et al., 2015) and Los Angeles Motor Scales (LAMS) (Llanes et al., 2004) for stroke severity. The communication was generally between the Emergency Medical Service (EMS) and the Stroke Team, but in one of the articles, the interventional team, radiology department, neuro intensive care and emergency room (ER) were also pre- alerted (Zaidi et al., 2017). However, in general this review has found that there is very limited information on current treatment pathways for patients with AIS in routine clinical settings, particularly in the UK. None of the studies reported a comprehensive treatment pathway or populated the flow pathways with the numbers or proportions of patients flowing through them. Only one case report captured details at each step along the whole treatment pathway of one patient. Data on the workflow, particularly for pre-hospital settings, in-hospital care up to 24 hours after MT, post-MT imaging, hospital discharge, rehabilitation and follow-up were notably limited. A better understanding of current treatment pathways remains an essential first step towards improving the efficiency and effectiveness of MT delivery, and in achieving excellent functional outcomes.

5.3 TREATMENT PATHWAYS IN ROUTINE CLINICAL CARE

5.3.1 Introduction

Having established by means of the SR described above that there is very little published information on the treatment pathways currently being used in the delivery of MT, a decision was made to undertake a data collection exercise to describe the treatment pathways currently being used in a broadly representative range of different treatment centres. The objective was to establish the actual pathways, beginning with the patient's route to hospital, initial assessment on arrival at hospital, the diagnostic process, the available treatment options, the actual treatments used, and the discharge processes and destinations. The objective was to collect a combination of aggregate and individual patient information, in sufficient detail to be able to quantify the flows through the pathway in terms of proportions and probabilities and identify differences between centres. A decision was also made to collect information in sufficient detail to be able to set out the resources used and costs of the pathways: this is reported separately in Chapter 6.

5.3.2 Methods and Data

Based on data published by the Sentinel Stroke National Audit Programme (SNAPP), between April 2016 and March 2017 (SSNAP, 2017b), high-volume thrombectomy centres were identified in different parts of the UK. As of January 2019, there were 25 thrombectomy centres providing MT in England and one each in Northern Ireland and Scotland.

The Stroke Service Directors of eight hospitals were invited to participate in the study, initially via email and then followed-up by a phone call and /or visit to the individual MT centres to discuss the study. Three of the eight hospitals approached declined to participate in the study. One of the participating centres was not among the top high-volume centres but contributed data because it was already part of the on-going collaborative work with the Promoting Effective and Rapid Stroke Care Study (PEARS) (PEARS 2).

The NHS Research and Development Departments of the identified and willing centres were provided with the study protocol, other supporting documents and the ethics approval from the University of Oxford and Oxford University Hospital NHS Trust, which categorised the project as a service evaluation, not a research project. Nevertheless, each participating centre had to decide for itself which governance structure to apply to this study. Eventually, all participating hospitals approved the study as a service audit. The process for international hospitals differed in that applications were submitted to their Ethics Committees which approved the study.

Furthermore, in two of the MT centres in the UK and in Canada, an application for an observership/ clinical attachment for me was accepted for five to ten days to enable me to observe procedures and capture the resource use, along the individual patient pathways from pre-hospital notification and arrival at the Emergency Department, through to discharge from the thrombectomy centre.
After the audit approval, another visit was arranged to identify the treatment pathways and extract further information from individual hospital sources. Key NHS staff at each site with clinical and financial knowledge of delivering

thrombectomy for AIS, were interviewed. The participants included stroke consultants and stroke nurses; neuro-interventionists and radiographers; staff of the Interventional Radiology Suites (IRS) or Theatres; finance personnel; stroke and radiology managers; SNAPP data personnel and other staff involved with stroke care.

The treatment pathway based on the current or usual practice for stroke patient flow was identified by visiting the selected thrombectomy centres. The overall patient's progression through the treatment pathway was captured and included in the evaluation process of the study. Data were collected for all IVT and MT treated stroke patients going through the pathway. The primary data collection period covered patients treated from January 2015 to December 2018, but data were also collected where available from 2014 and earlier where available, as this offered an opportunity of making comparisons in a sub-analysis over a more extended period. Anonymised information was obtained from the local hospital stroke registry, Sentinel Stroke National Audit Programme (SSNAP) and the Safe Implementation of Thrombolysis in Stroke (SITS) registry databases. Only patients with confirmed diagnosis of stroke treated with IVT and MT were included in the pathway; and those with suspected stroke, non-vascular conditions that present with an acute neurological deficit (stroke mimics), transient ischaemic attack (TIA) and those outside the treatment window were not included. The time from stroke onset, arrival at hospital, to treatment/intervention times and outcomes with 90-day post stroke mRS were not measured or examined. The thesis was designed to determine the variations in treatment pathways and the cost of the pathways not the clinical outcomes.

Variations in each component of the treatment pathways across the participating centres were examined, and changes over time and between the local and transferred patients were compared. The study design would not determine which treatment pathways are associated with quicker treatment or better outcomes.

5.3.3 RESULTS

5.3.3.1 Treatment Pathway for Centre A

The results from Centre A are presented first and used as a reference for the other thrombectomy centres in the UK. Centre A was selected based on the high-volume numbers and because it was the first hospital in the UK to routinely perform MT for acute ischaemic stroke, commencing in 2010, before the publications of the positive MT RCTs in 2015.

The pathway for Centre A was mapped out during a period of clinical observership at the hospital. During the time of the observation, the whole stroke patient journey, both for the local patients admitted directly to Centre A and for the transferred patients from other non-thrombectomy centres, was captured. Similarly, the referral treatment pathway of patients who developed a stroke while already in hospital, was also observed. The path taken by all treated patients between January 2015 and December 2018 is illustrated in Figure 5.2.

Centre A

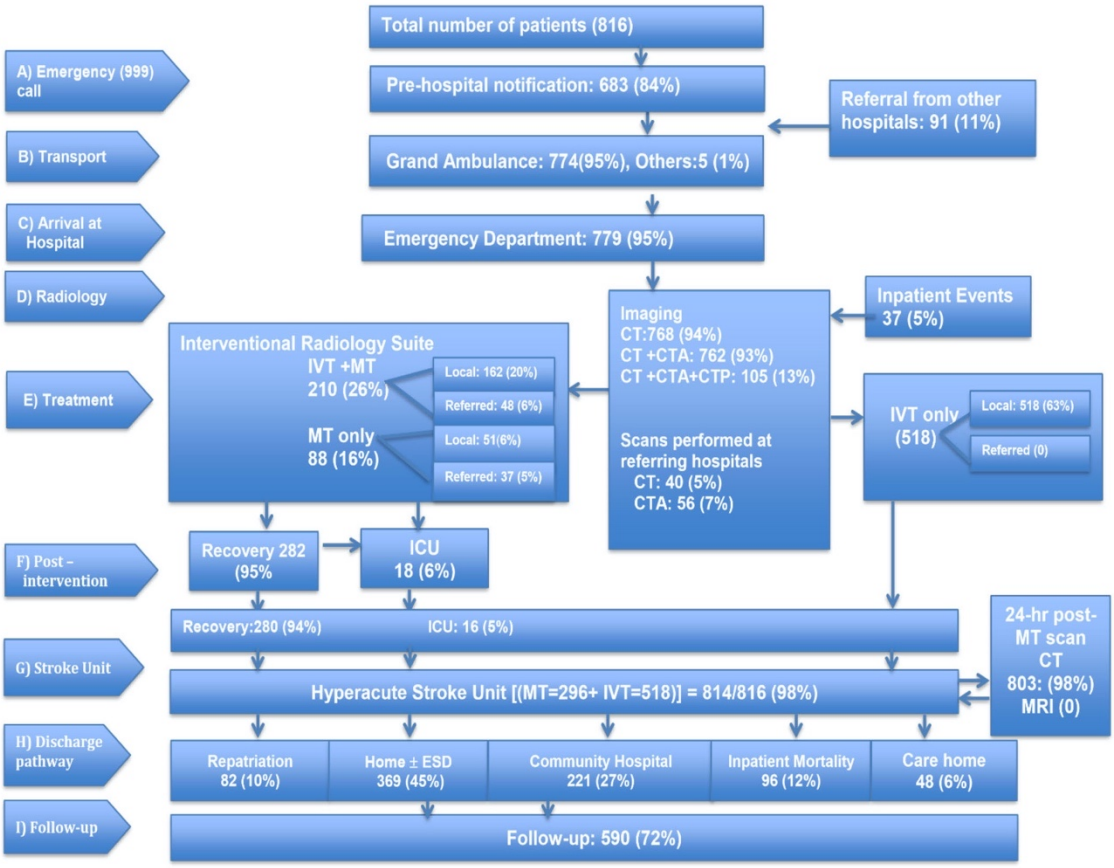


Figure 5.2. Treatment pathway and cohort of patients treated at Centre A

ESD= Early supported discharge

A total of 816 patients passed through the treatment pathway at Centre A between January 2015 and December 2018. Decisions are made at different points along the treatment pathway. An explanation of the pathway as the patients travel through different stages is as follows:

5.3.3.1.1 Pathway A: Prehospital Notification

The pathway begins with the recognition of stroke signs and symptoms. The paramedics are called for an initial assessment and transportation. The Stroke Nurse is pre-alerted first, followed by the Stroke Consultant and Emergency Department (ED). On rare occasions, following the recognition of symptoms, a patient may self-presented to ED. For patients referred from other hospitals, it is always a consultant-to-consultant referral, usually after prehospital notification and transfers to the non-MT centre. Among the 816 patients, 683/816 (84%) were pre-hospital notifications and 91/816 (11%) were consultant-to-consultant referrals from other non-MT hospitals in a Mothership and Drip-and-Ship pattern of care.

5.3.3.1.2 Pathway B: Mode of Transport to Hospital

Transportation to Centre A was all by overland, emergency ambulance; no patient was transported by helicopter. Stroke patients were either transported directly from a non-hospital setting, such as the site of the stroke occurrence or transferred to Centre A from a primary non-thrombectomy centre. Those transported from other hospitals are usually not escorted by a nurse or junior doctor, except if unconscious and intubated. These were all emergency cases with sudden onset of stroke. A total of 774/816 (95%) patients were transported

by ambulance; 5/816 (1%) via other means and no patient was transported by a helicopter.

5.3.3.1.3 Pathway C: Arrival at the Emergency Department

The Emergency Department (ED) is the initial entry route for the beginning of the pathway on arrival at the hospital for all stroke patients. The only exception is when a patient develops a stroke whilst an inpatient (an Inpatient-Event). Following a pre-hospital notification with an estimated time of arrival, the Stroke Team proceeds to the ED before the patient arrives. The Stroke Team receives the patient at the emergency entrance and while still on the ambulance trolley, a quick clinical assessment is performed to ensure medical stability. If the patient is clinically stable, they are transferred to the CT scanner; if not, they are moved into a resuscitation bay to be stabilised before being transported to the CT scan.

Transferred stroke patients from other hospitals transported by ambulance also have to go through the ED for registration and an initial quick assessment by the Stroke Team before having further investigations and treatment. The only exception is when a patient develops a stroke whilst being an inpatient (an Inpatient-Event). In total, 779/816 (95%) of patients were attended to in ED upon arrival. This is a combination of both local and transferred patients as well as patients transported by other means presenting to ED.

5. 3.3.1.4 Pathway D: Radiology Department

The Radiology Department is the first entry route into the treatment pathway for patients who developed stroke as inpatients, and second entry route for patients

who: 1) are moved from ED after assessment by the Stroke Team and 2) are transferred from other hospitals, who have not had head scans performed before arrival or needed a repeat scan. Other patients who need a repeat scan or who have had scans before arrival, join the pathway at the next point. Non-contrast CT and CT angiography (CTA) are the standard scans, but occasionally, CT perfusion (CTP) is performed in cases with unknown time of onset or of diagnostic uncertainty. The Stroke Consultant reviews the scans in the scanner before the formal report by the Radiology Registrar/Fellow or Consultant.

Along the radiology route, which is the first point of entry for the inpatients, 37/816 (5%) inpatients joined the pathway. A total of 768/816 (94%) patients had CT; 762/816 (93%) patients had combined CT/CTA brain scans and 105/816 (13%) had an additional CTP scan. Among the 91/816 (11%) external transferred patients, only 40/816 (5%) had a repeat CT brain scan and 56/816 (7%) repeated CT/CTA. None of the external patients received a CTP scan.

5.3.3.1.5 Pathway E: Determination of Treatment

Determination of the appropriate treatment in light of the radiological findings is determined by the Stroke Consultant and sometimes together with the Interventional Radiologist, subject to the eligibility criteria and complexity of the case. All patients then move to the next point in the pathway, the Treatment Phase.

5.3.3.1.6 Pathway F: Treatment Regimen

There are four possible pathway entry nodes:

(I) Local patients eligible for thrombolysis are returned to ED for IVT, and then either having completed their treatment or whilst still receiving IVT, can be transferred to the International Radiology Suite (IRS).

(ii) Local patients not eligible for IVT are transferred directly to the IRS.

(iii) Those who are external and have been treated with IVT in their primary hospital are transferred directly to the IRS from the CT scanner.

(iv) External patients who no longer need MT are transferred back to ED for repatriation, with presumably a care plan.

5.3.3.1.6 (i): Intravenous Thrombolysis

After brain imaging, patients are transferred back to the ED for thrombolysis before going for MT if indicated. External patients, who would have received their thrombolysis in the referring hospital, will usually proceed to the next stage in the treatment pathway and do not go back to ED. The majority of patients, 518/816 (63%) were treated with IVT-alone, and none of the referred patients had IVT at the MT Centre A, as those eligible for the treatment would have had the IVT before being transferred for MT.

5.3.3.1.6 (ii) Mechanical thrombectomy in the Interventional Radiology Suite

The decision-making for MT is based on the following: 1) the presence of proximal vessel occlusion, 2) ASPECTS score >6 and, 3), clinical parameters as per hospital protocol and National Guidelines. Once the decision is made, the Interventional Team are pre-alerted of the impending intervention.

Parallel preparations of the IRS are then initiated. For patients transferred from other hospitals, the intervention team is pre-alerted before their arrival. This is because the images would have been received via the picture archiving and communication system (PACS) and reviewed by the Radiologist, and the patient is then accepted for MT. Consent is obtained from the patient or obtained from the family, after an explanation of the procedure with the potential complications. Suitable patients for thrombectomy, based on the radiological findings of large vessel occlusion and other clinical parameters, are then moved into this section of the pathway. Patients are then transferred to the IRS by the Stroke Team. The pre-intervention assessment by an anaesthetist occurs in IRS, where all MT procedures are performed.

Out of the 298/816 (36%) transferred to the IRS for MT, one patient (0.3%) had spontaneous recanalisation and the procedure was abandoned. A total of 297/816 (36.7%) of patients were treated with thrombectomy, of which 210/816 (26%) were treated with combined MT and IVT and 87/816 (10.7%) with MT-alone. Among the 26% of patients treated with MT in conjunction with IVT, 162/816 (20%) were local patients and 48/298 (6%) were referred cases.

Similarly, of the 87 (10.7%) of MT-alone treated cases, 51/816 (6%) were local patients and 36/816 (4%) referred cases.

The majority (180/298 (60%)) of cases were performed under general anaesthesia (GA), 76/298 (26%) with local anaesthesia (LA) and 42/298 (14%) with conscious sedation (CS). Among the GA cases, 20/298 (8%) were started with LA and later converted to GA.

5.3.3.1.7 Pathway G: Post Intervention Care

Following thrombectomy, most of the patients are moved to the recovery area from the IRS. Only a few patients, particularly those with posterior circulation stroke and who are already on ICU/HDU at the time of their stroke, are transferred straight to the ICU/HDU from the IRS. The patients in recovery are monitored until they are awake and clinically stable. The next entry point into the treatment pathway is determined by the patients' clinical state. If they are clinically stable, they are transferred to the Hyperacute Stroke Unit (HASU), if not, they are then moved to the ICU/HDU.

Post-thrombectomy, 282/298 (95%) patients were transferred to the recovery area and 16/298 (5%) were directly transferred to ICU/HDU from the IRS. Among the patients transferred to Recovery, a further 2/298 (1%) were transferred to ICU/HDU, in total, 18/298 (6%) ICU/HDU admissions. The remaining 280/298 patients were transferred to HASU from the Recovery area.

5.3.3.1.8 Pathway H: Intensive Care Unit/Hyper Dependency Unit

Only a few clinically unstable patients are transferred directly from IRS to the Intensive Care Unit/Hyper Dependency Unit (ICU/HDU). The majority would have been in the Recovery Area before transfer to ICU if still indicated. Among the total 18/298 (6%) ICU/HDU patients, 16/298 (5%) were subsequently transferred to HASU, while 2/298 (1%) died in ICU/HDU.

5.3.3.1.9 Pathway I: Transfer to the Hyperacute Stroke Unit (HASU)

Patients eventually join this section of the pathway, either from the Recovery Area or ICU/HDU. Patients are generally monitored closely post-MT and get a repeat scan, usually CT head and in a few cases, an MRI next day after MT if clinically stable. A total of 814/816 (99.7%), comprising: 518/816(63%) IVT and 296/816 (36%) MT treated patients, were finally transferred to HASU. While in the Stroke Unit, all 518 of the thrombolysed patients had a repeat 24-hour CT. Among the MT treated patients, 285/816 (35%) had a repeat scan, while 11/816 (1%) patients were repatriated to their primary hospitals before the repeat 24-hour post MT scan. This is the exit section of the acute inpatient pathway and the next destination is determined by various factors ranging from degree of residual disability through to whether or not the referral was from another hospital.

5.3.3.1.10 Pathway J: Discharge Process

The discharge destination varies depending on the recovery made and whether the patient was transferred from another hospital to have thrombectomy. The sub-section of this treatment pathway includes:

i: Repatriation

The external patients are transferred back to their primary hospital or the referring centre within 24 hours, once the patient is medically stable.

They are repatriated often for ongoing rehabilitation. They are transferred with a discharge letter and appropriate medication where necessary.

Of the 91/816 (11%) referred patients, 82/91 (90%) patients were repatriated to the referring primary hospitals; 7/91 (8%) were discharged directly to their homes from Centre A and 2/91 (2%) died in hospital (inpatient mortality).

ii: Discharged Home

Patients who are assessed and declared medically stable by the Stroke Consultant and who have improved functional outcome (mRS 0-2) are discharged home with or without further home therapy as recommended by the Early Supported Discharge team (ESD).

In total, 369/816 (45%) patients were discharged home with or without ESD of which 118/816 (14%) were treated with MT+IVT and 251/816 (31%) with IVT-only.

iii: Discharged to a Community Hospital

Patients who are medically stable, but with moderate to severe disability are transferred for further rehabilitation to a community hospital. Only the local patients, 221/ 816 (27%), were transferred to a community hospital for further rehabilitation. These comprised 55/816 (7%) of the MT treated group with or without IVT and 166/816 (89%) IVT-only treated patients.

iv: Discharged to a Care Home

Those who are medically stable with severe disability and with no rehabilitation potential are normally discharged to a care home. Among the 48/816 (9%) discharged to a care home, 12/816 (2%) were treated with MT with or without IVT and 56/816 (7%) were IVT-only treated.

v: Inpatient Mortality

The inpatient mortality of 96/816(12%) comprised MT with or without IVT 31/816 (4%) and IVT only 65/816(8%).

5.3.3.1.11 Pathway K: Follow-up

All local patients discharged home and those in the Community Hospital, treated with MT/IVT and those treated with IVT-alone, are followed-up at three months post-discharge. Each patient was reviewed by a Consultant in the outpatient, follow-up clinic. The purpose for the outpatient face-to-face review is to assess the patient's functional state and ensure implementations of secondary stroke preventive measures. A total of 590/816 (72%) were followed-up at three months.

The treatment pathways and cohort of patients treated at four other UK thrombectomy centres (Centres B, C, D and E1/E2) in different regions in the country are illustrated in Figures 5.3 to 5.6 and the pooled results for all the five UK centres in Figure 5.7 below.

5.3.3.2 Populated Treatment Pathway for Centre B

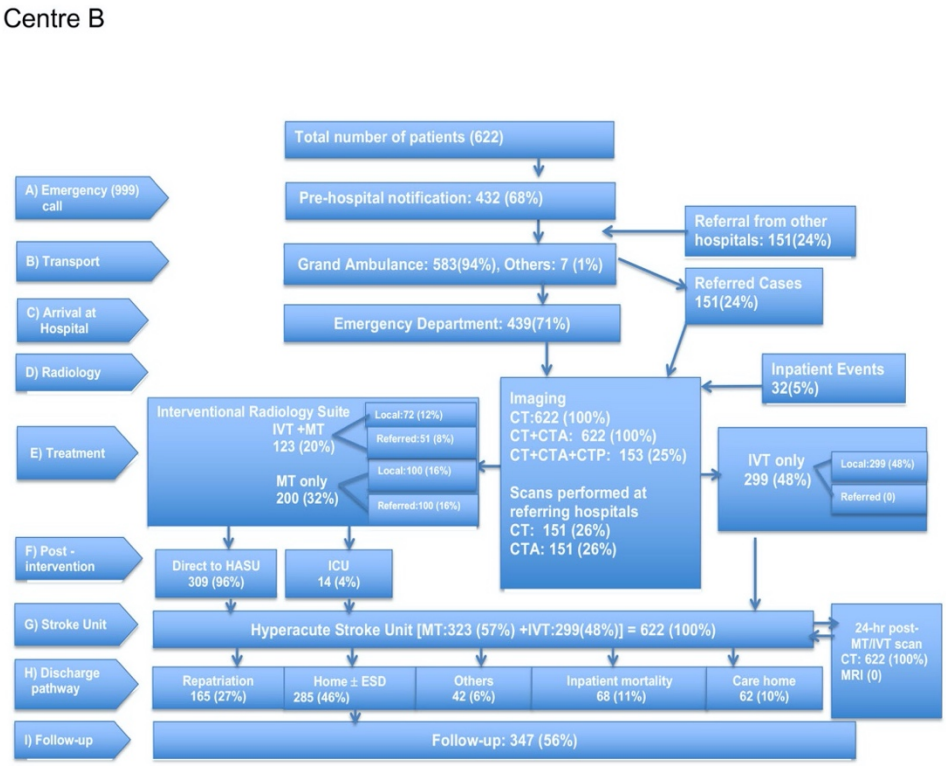


Figure 5.3. Treatment pathway with numbers and proportions of patients that have gone down different routes at Centre B

The point of entry for stroke patients on arrival at Centre B is via ED for the local patients and via the Radiology Department for the referred patients.

A total of 622 patients passed through this treatment pathway at MT Centre B between April 2015 and December 2018. Among the 622 patients, 232 (52%) were treated with combined MT and IVT and 299 (48%) with thrombolysis only. Of the thrombectomy treated patients, 174 (28%) were local patients and 151(24%) were transferred patients.

5.3.3.3 Populated Treatment Pathway Centre C

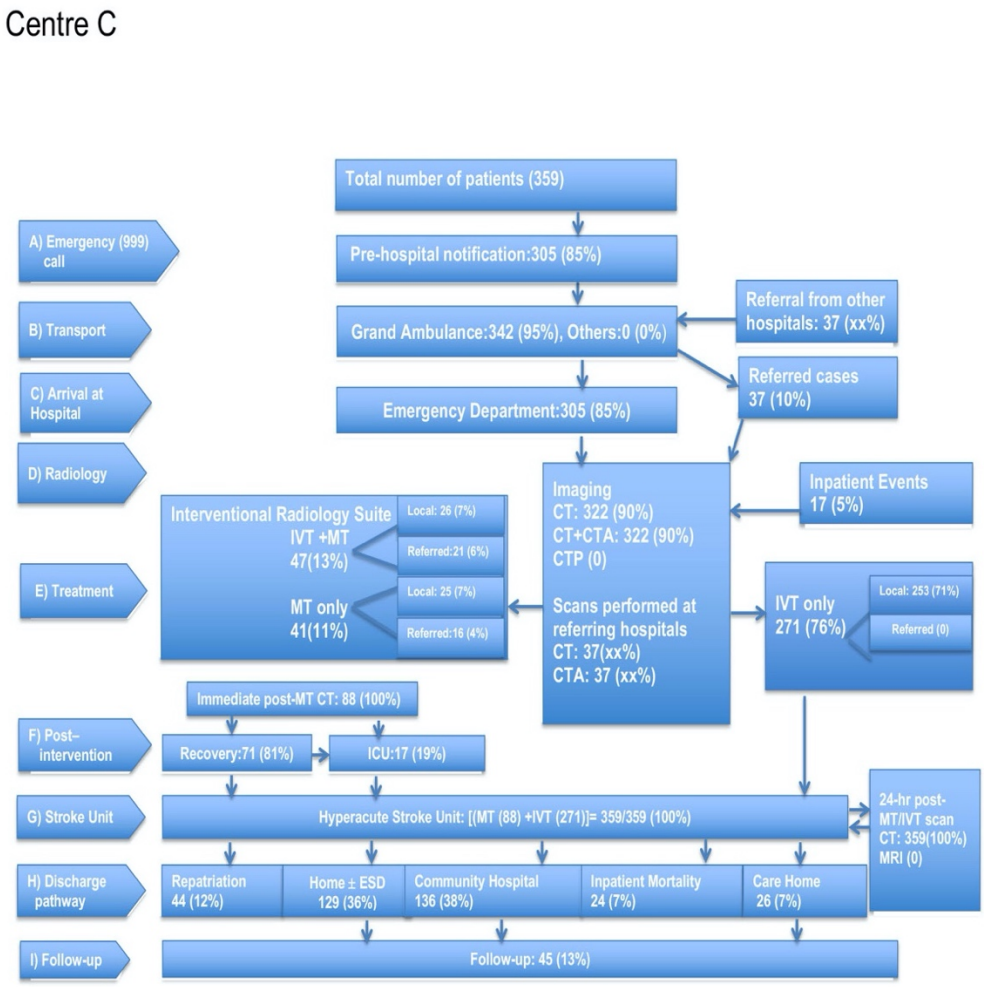


Figure 5.4. Illustrates the treatment pathway with numbers and proportions of patients that have gone down different routes at MT Centre C.

The point of entry for stroke patients on arrival at MT Centre C is via ED for local patients and via the Radiology Department for the referred patients similar to Centre B. A total of 359 patients passed through this treatment pathway at MT Centre C, between April 2015 and December 2018. Among the 359 patients 88 (24%) were treated with combined MT and IVT and 271 (76%) with IVT only.

5.3.3.4 Populated Treatment Pathway Centre D

Centre D

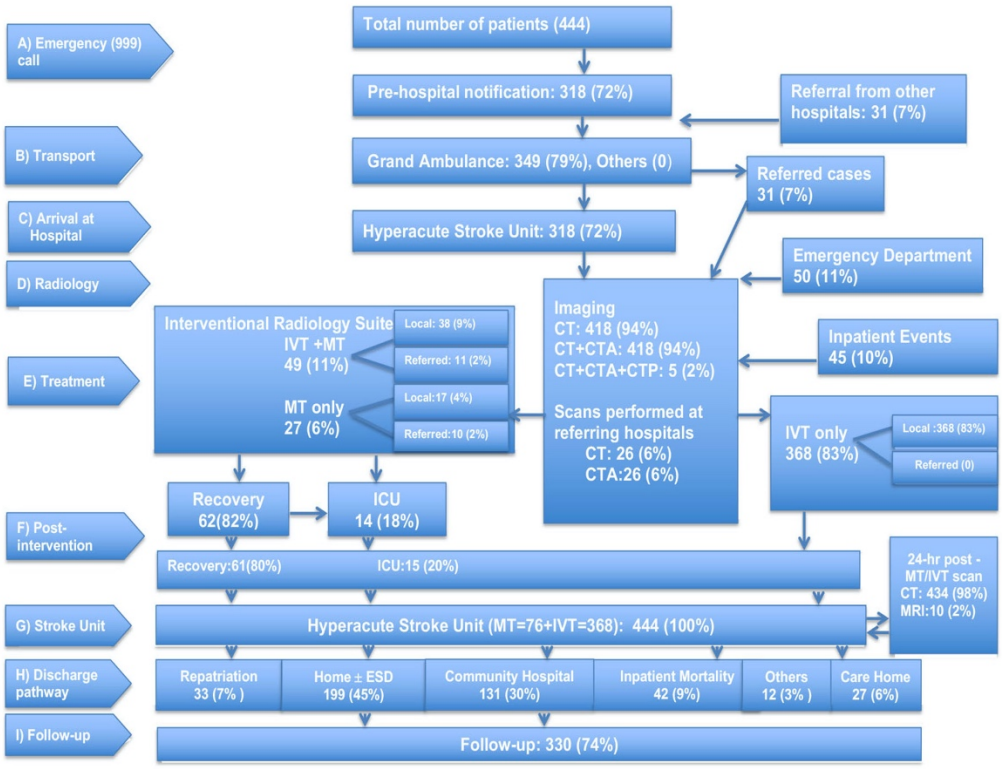


Figure 5.5. Illustrates the treatment pathway with numbers and proportions of patients that have gone down different routes at Centre D.

The point of entry for stroke patients on arrival at Centre D is directly via the Hyperacute Stroke Unit between 9 am to 9 pm, bypassing ED. Patients are then moved to the Radiology Department and thrombectomy is performed in the theatre. A total of 444 patients passed through this treatment pathway at Centre D between April 2015 and September 2018. Among the 444 patients, 76 (27%) were treated with combined MT and IVT and 368 (83%) with IVT only.

5.3.3.5 Populated Treatment Pathway for Centre E1/E2

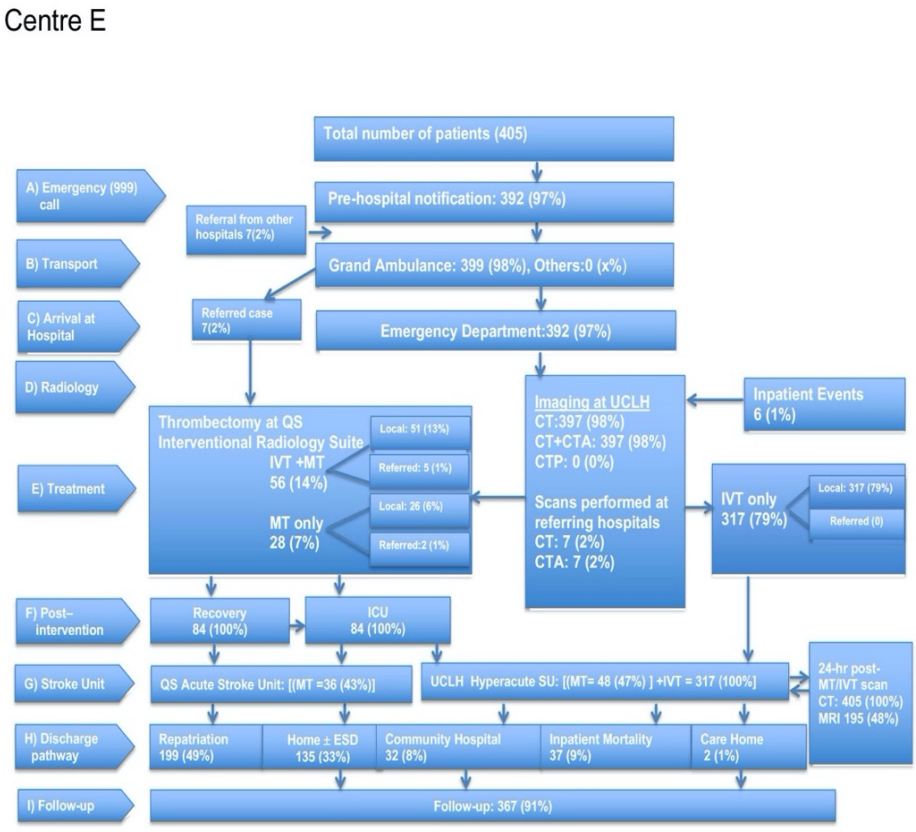


Figure 5.6. Illustrates the treatment pathway with numbers and proportions of patients that have gone down different routes at Centre E1/E2.

The point of entry for stroke patients at Centre E1/E2 is different from the others. Since the centralisation of stroke services in the region in 2010, patients are now transferred directly to the Hyperacute Stroke Unit, before being repatriated to their local Acute Stroke Unit. The first point of entry, therefore, is at Centre E1 for imaging and initiation of IVT, before transfer to Centre E2 for MT. The patients transferred from other HASUs, especially out of hours, are taken directly to Centre E2 for MT. A total of 404 patients passed through this treatment pathway at Centre E1/E2 between April 2017 and December 2018. Among the 404 patients, 7(2%) were transferred directly to Centre E2 from other Hyperacute and Acute Stroke Units for MT.

5.3.3.6 Pooled results of patients treated with MT from all five UK centres

All centres

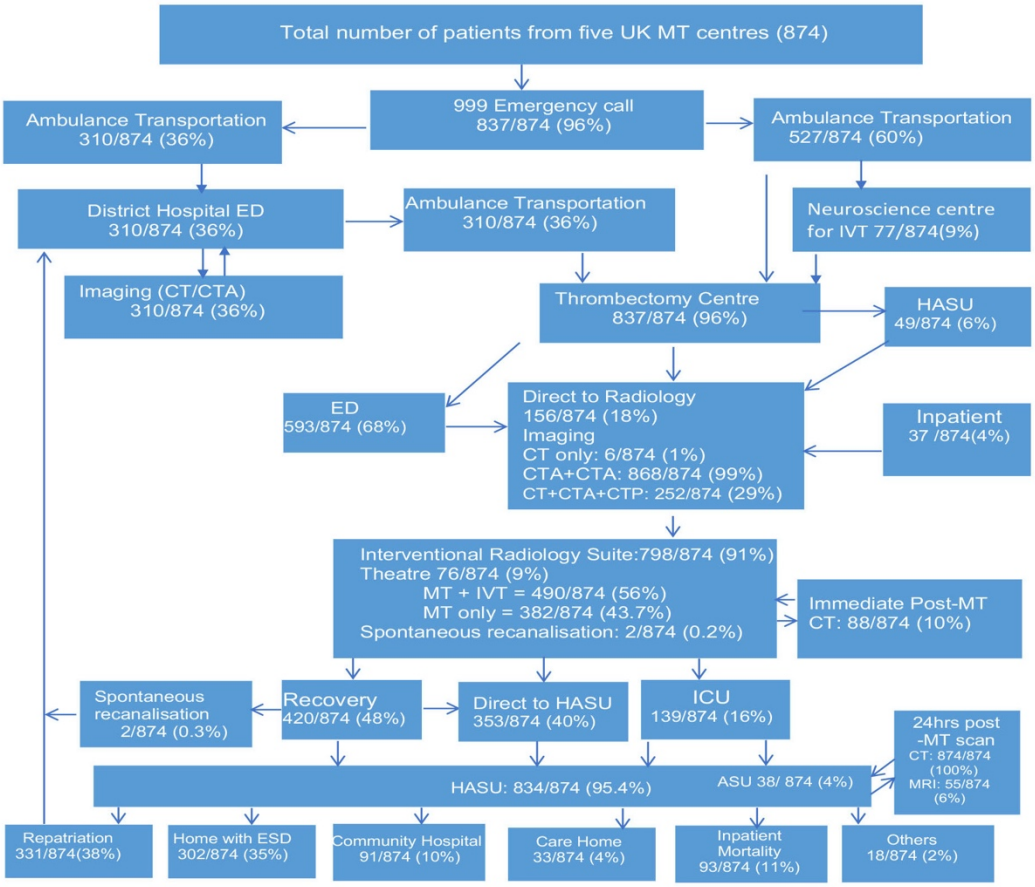


Figure 5.7. Illustrates the total cohort of patients treated with thrombectomy across the five UK centres included in this analysis.

A total of 2646 patients passed through the various treatment pathways across the four centres; 1772/2646 (67%) were treated with IVT only and 874/2646 (33%) with combined MT and IVT. The number of patients treated with thrombectomy across the various centres comprised: 298/874 (34%) from Centre A; 323/874 (37%) from Centre B; 88/874 (10%) from Centre C; 76/874 (9%) from Centre D and 84/874 (10%) from Centre E.

5.3.3.7 International Centres

The treatment pathway was also mapped out for two centres in Germany (Centre F and Centre G), 1 in Italy (Centre H) and 2 in Canada (Centre I and Centre J).

5.3.3.7.1 Populated Treatment Pathway for Centre F

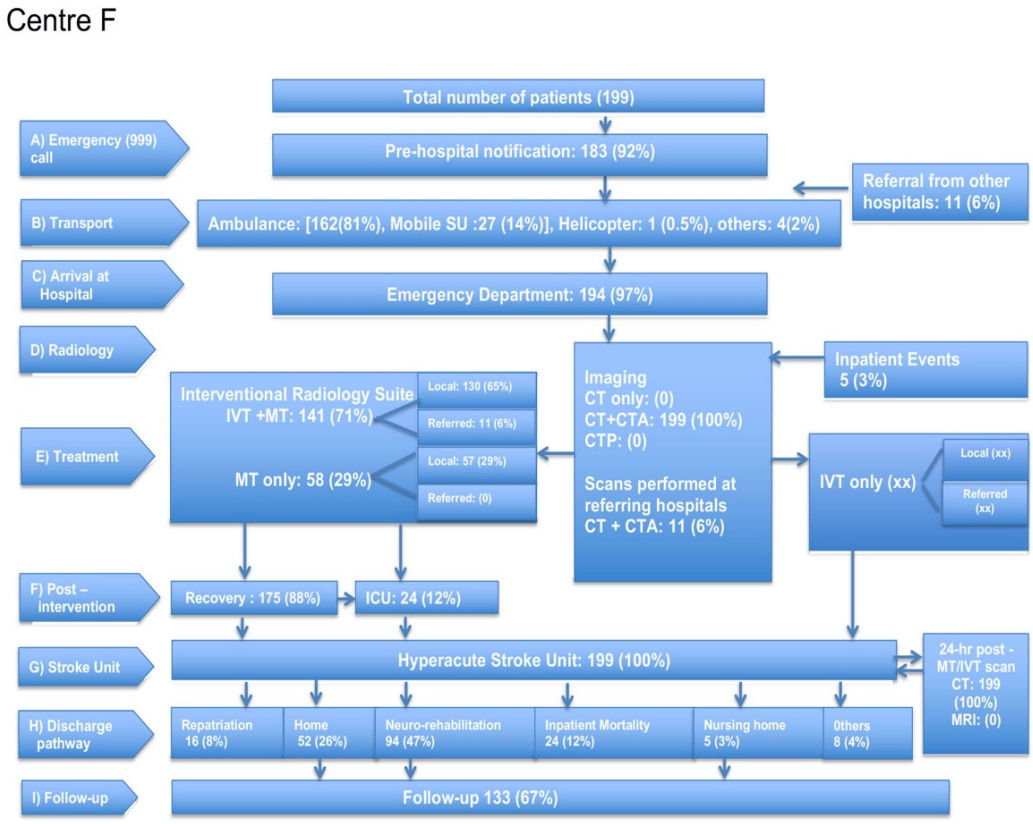


Figure 5.8. Illustrates the treatment pathway with numbers and proportions of patients that have gone down different routes at Centre F.

The point of entry for stroke patients on arrival at Centre F is via ED for both local and referred patients. Patients are transported by standard ambulance Mobile Stroke Unit (MSU) and occasionally by helicopter. A total of 199 patients passed through this treatment pathway between October 2015 and December 2017. All patients were treated with a combination of MT with IVT. There is no data available for IVT-only treated patients.

5.3.3.7.2 Populated Treatment Pathway for Centre G

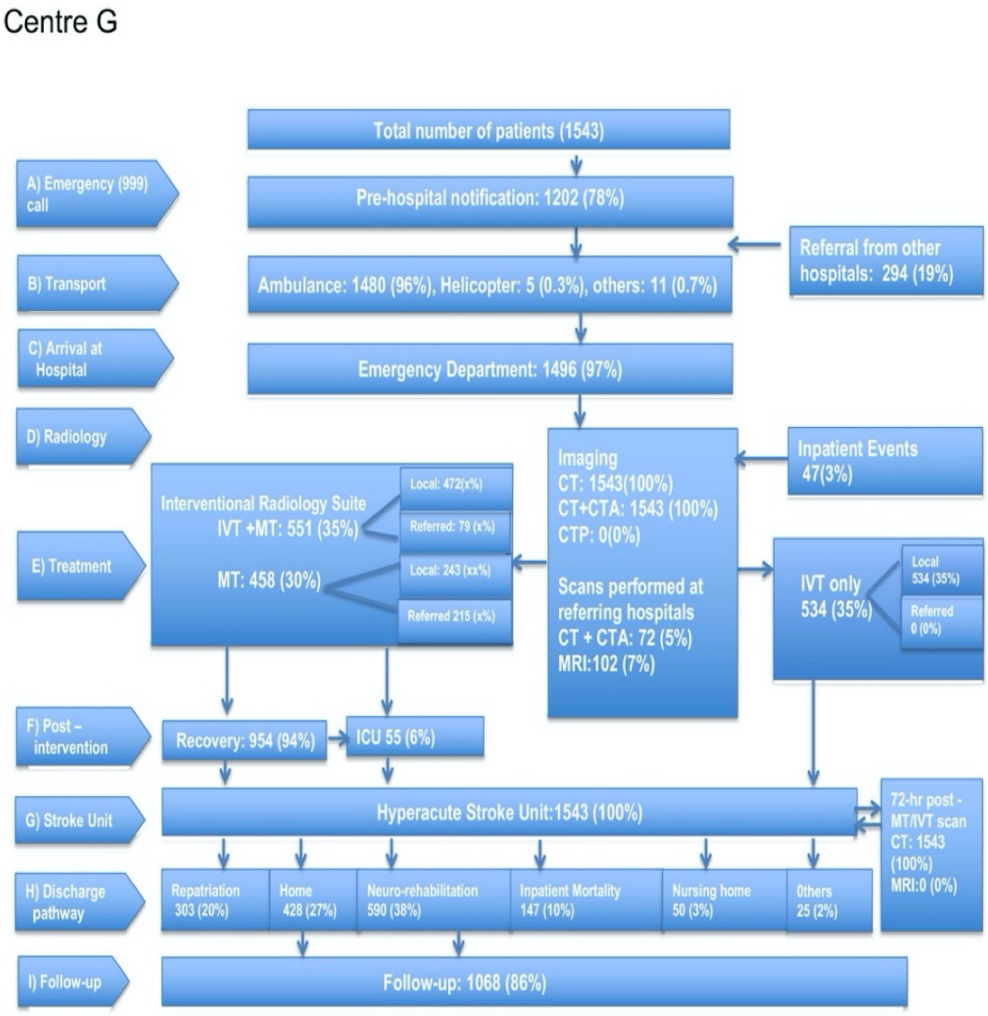


Figure 5.9. Illustrates the treatment pathway with numbers and proportions of patients that have gone down different routes at Centre G.

The point of entry for stroke patients on arrival is via ED for local and referred patients. Patients are transported by standard ambulance and occasionally by helicopter. A total of 1543 patients passed through this treatment pathway between January 2015 and June 2018. Among the 1543 patients, 1009 were treated with combined MT and IVT and the remaining 534 were treated with IVT only.

5.3.3.7.3 Populated Treatment Pathway for Centre H

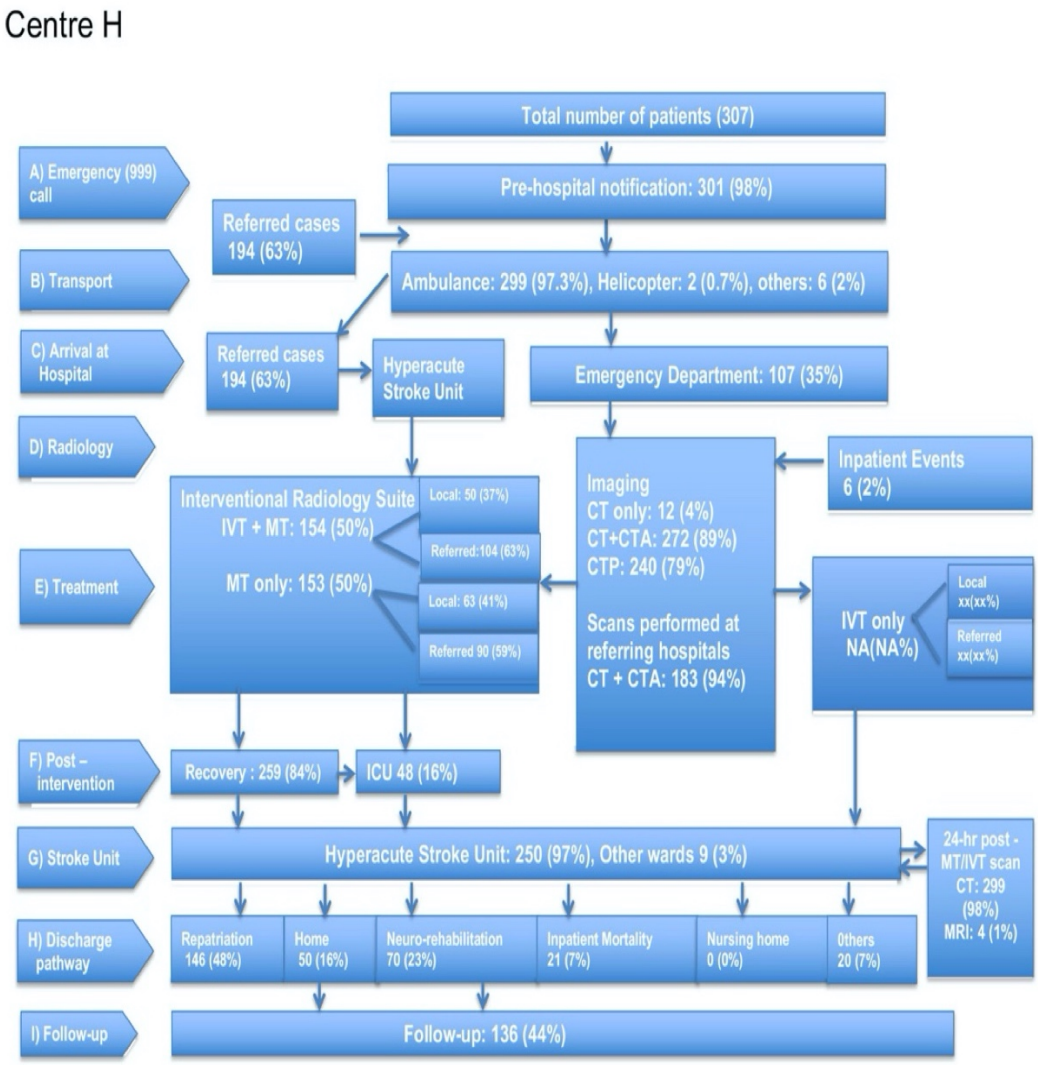


Figure 5.10. Illustrates the treatment pathway with numbers and proportions of patients that have gone down different routes at two Stroke Unit, Centre H.

The point of entry for stroke patients on arrival is via ED for local patients and directly to the Stroke Unit for referred patients. Patients are transported by standard ambulance and occasionally by helicopter. A total of 307 patients passed through this treatment pathway at Centre H between January 2015 and December 2018. All patients were treated with combined MT with IVT. There was no available data for IVT-only treated patients.

5.3.3.7.4 Populated Treatment Pathway for Centre I

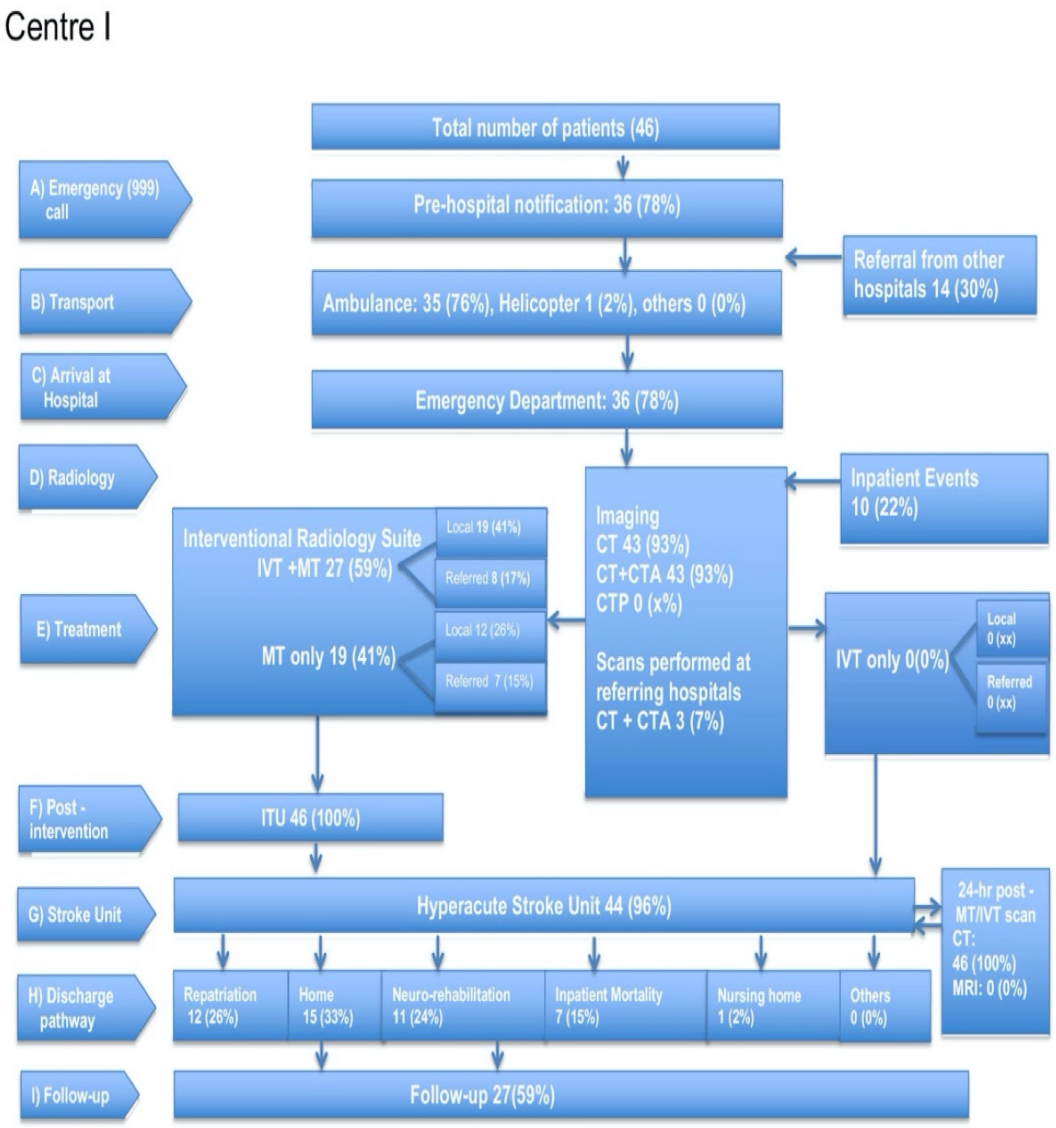


Figure 5.11. Illustrates the treatment pathway with numbers and proportions of patients that have gone down different routes at Centre I.

The point of entry for stroke patients on arrival is via ED for both local and referred patients and patients are transported by standard ambulance and occasionally by helicopter. Only 46 patients were treated with combined MT and IVT between July 2017 and April 2018 and there was no available data for IVT-only treated patients.

5.3.3.7.5 Treatment Pathway for Centre J**

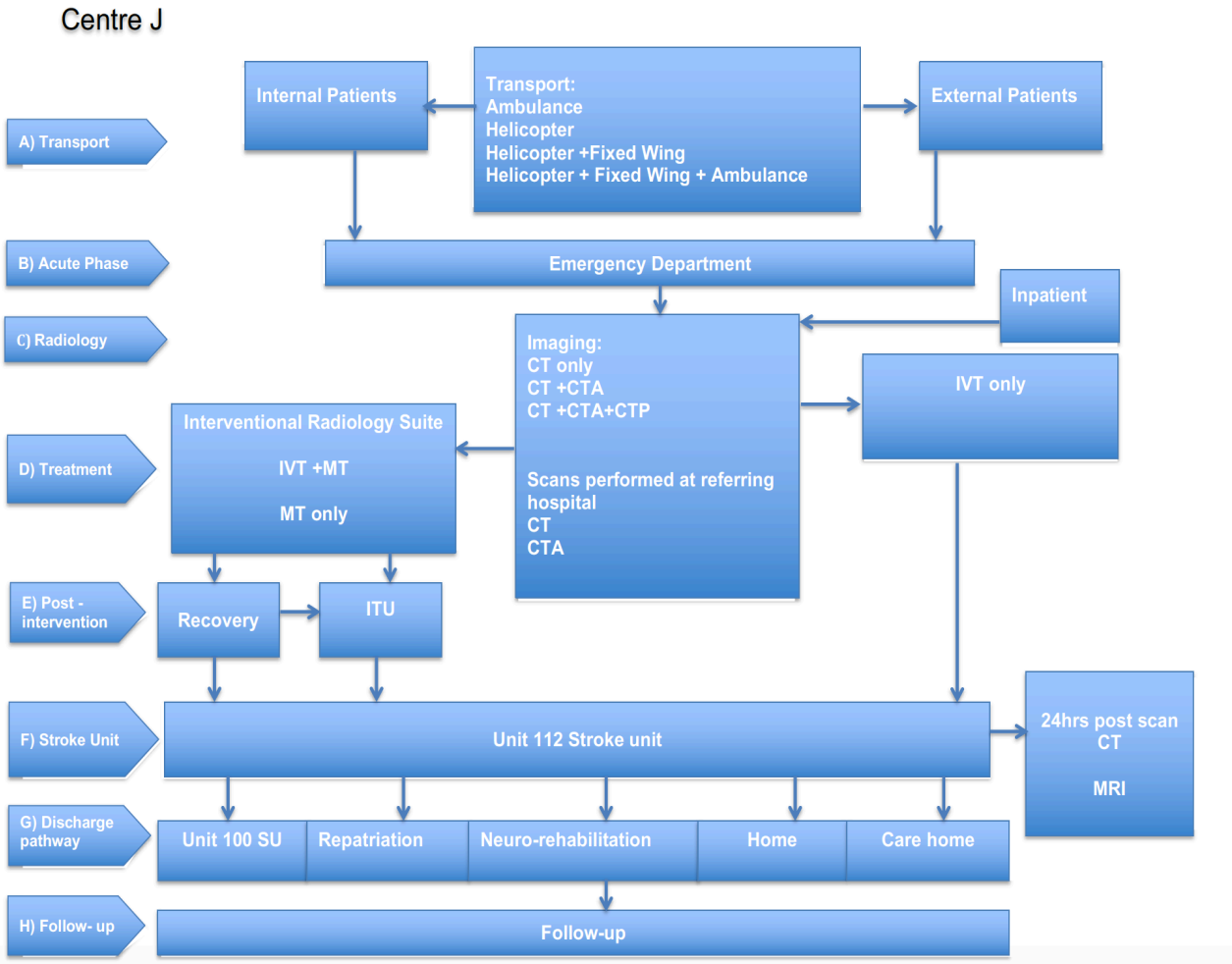


Figure 5.12. illustrates the mapped treatment pathway at Centre J.

**(I was unable to populate the identified treatment with numbers going through the pathway due to the pandemic)

The point of entry for stroke patients on arrival is via ED for both local and referred patients transported by ambulance and for patients transported by helicopter, is via radiology.

5.3.3.7.6 Pooled Results of Patients Treated with MT from All Centres (UK, Germany, Italy and Canada)

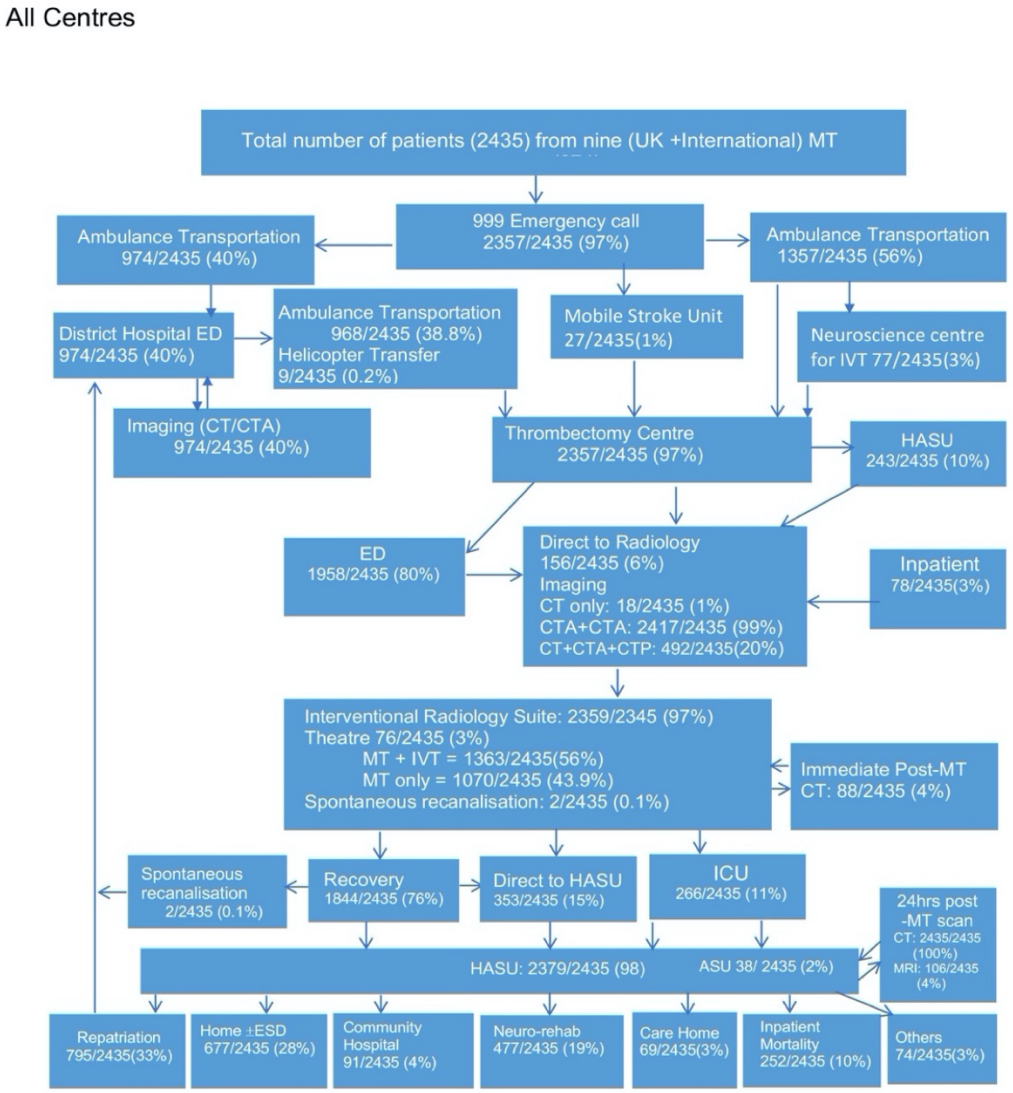


Figure 5.13. Illustrates the total cohort of patients treated with thrombectomy in the UK, Germany, Italy and Canada

The number of patients treated with thrombectomy from the different countries comprised of: 874/2435(36%) from UK (five centres); 1208/2435 (50%) from Germany (two centres); 307/2435 (12%) from Italy (one centre) and 46/2435 (2%) from Canada (one centre).

5.3.3.8 Variation in the Treatment Pathways Across MT Centres in the UK

Having identified the individual hospitals' pathways and pooled pathways for all five MT centres, variations were identified at each stage of the treatment pathways. The observed variations in pathway differences were either in terms of the structural design of the pathway or of the process differences in terms of service provision and staffing.

5.3.3.8.1 Structural design

Whilst the variations in the treatment pathways are detailed in Table 5.2, five main structural differences were identified.

Firstly, there were differences in pre-hospital transportation for patients transferred to an MT centre. At Centre B, for example, all patients transported from a non-MT centre were escorted by either a doctor or a nurse. The medical escort, especially the nurse, accompanies the patient into the IRS and remains until the end of the procedure. In cases where intervention is not required, the escort returns with the patient to the referring hospital. The policy of transporting patients with medical escorts is for patients' safety and for smooth clinical hand-overs. This was based on previous incidents regarding patients' safety and the escort safeguarded standards of care. Similarly, at Centre E1, all patients transferred to Centre E2 for MT were escorted by a doctor (Foundation Year 2 (FY2) or Core Medical Trainee (CMT)). This is because most of the patients would still be receiving IVT during the transfer. The junior doctor stays until the end of the procedure. The other centres generally transferred potential MT

patients from a non-MT centre without a nurse or medical escort, except for unconscious and intubated patients who are usually accompanied by a doctor. Even if a patient is accompanied by a medical escort, the escort might not necessarily be in the IRS with the patient nor wait till the end of the procedure. All the centres operate a combination of mothership (local patients admitted directly) and drip-and-ship (patients presenting first to their primary hospital before transfer to the mothership) model. Exceptionally, non-local patients are directly admitted at Centre D for MT and, after the treatment, are repatriated to their primary hospital. At Centre E1, the main model of care is the mothership and direct transfer, based on the centralisation of stroke services for the region in 2010.

Secondly, variations occur upon first entry to hospital. The sample's norm is that all local patients present first to the ED; inpatients will be transferred to radiology for imaging. Nevertheless, at Centre D, the first point of entry is the Stroke Unit. The referred patients are taken directly to the Radiology Department at both Centre B and Centre C. At Centre A, they go to the ED and at Centre D, to HASU, before being transferred to the Radiology Department or the IRS, in cases not needing repeat scans. Having the HASU as the first point of entry, bypassing the ED, potentially reduces the door-to-intervention time and can improve overall process duration. At Centre E1, the patients present first to the ED and are then transferred for CT. Thrombolysis is commenced in the CT scanner room and from CT, the patients are transferred to Centre E2 for MT.

The third main difference relates to imaging. At Centre B, both CT and CTA are repeated on all transferred patients from other hospitals and, in some cases, an

additional CTP is performed. Elsewhere, if the referred patients from other hospitals arrive within an hour, imaging is generally not repeated unless they have deteriorated neurologically or significantly improved, as the occluded artery may have recanalised, as indicated by the NIHSS score or consciousness level by the Glasgow Coma Scale (GCS). Regarding post-MT imaging, Centre C is the only centre that performs two scans post-MT: an immediate post-intervention CT and a 24-hour post-MT CT. The rationale for the immediate post-op scan is that complications, in particular malignant MCA, can be detected early and potentially proactively managed. The other centres perform only a 24-hour CT or MRI, except where the patient deteriorates neurologically, whereupon a scan can be repeated before the standard 24-hour post-intervention scan. Notably, Centre A is the only centre that repatriates stable patients before a 24-hour post-MT scan. About 4% of the transferred patients had their 24-hour CT post-MT performed after repatriation to their primary hospital. This has the potential to increase available beds. Additionally, Centre D is the only centre that performs an MRI 24-hour post-MT; the other centres perform a CT scan.

The fourth variation is around the area of immediate post-MT care. At Centre B, after the procedure, patients are transferred directly to HASU, except when MT is performed under GA or if they are unstable, in which case, they are transferred to ICU/HDU. At Centre E2 all patients are transferred to the Neuro-Intensive Care Unit (NICU) and once stable, are stepped down to Centre E2 ASU unit, transferred back to Centre E1 HASU or repatriated back to primary hospital. At the other centres, post-MT patients are usually moved to the Recovery Area for observation and, once stable, transferred to the HASU or otherwise to ICU/HDU.

Lastly, Centre B, is the only hospital without community stroke rehabilitation beds. Consequently, all the local patients remain on the Stroke Unit for ongoing therapy if needed, before they are finally discharged to a care home or to home with or without ESD. The other MT centres discharge local patients to community hospitals for further rehabilitation.

5.3.3.8.1 Process and Organisational Differences

Process and organisational differences were observed, but the main variations involved staffing and provision of MT. Concerning staffing resources, Centre A is the only centre staffed only by a stroke nurse and stroke consultant as part of the stroke team, present both in the ED and the IRS. The other centres have additional stroke/neurology registrars or CMT doctors as part of the Stroke Team. At Centre C, the procedures are performed by both Interventional Neuro-radiologists (INRs) (96%) and Interventional Radiologists (IRs) (4%). Similarly, at Centre E2, the procedures are performed by both INRs (90%) and IRs (10%). In the other centres, MT is performed by the INRs. The use of general interventionists to perform MT has the potential to ease the shortage of INRs. Centre A alone had just two interventionists until April 2019, while other centres had between three and four. Generally, there is one INR during the procedure, but at Centre B more than one could be present, particularly in the daytime on weekdays. This has been a form of training for the less experienced interventionist, but it is unlikely always to be available. Regarding the Anaesthetic Team, the Anaesthetists are generally not present during the procedure at the Centre B, unlike at the other centres. At Centre B, there is always a scrub nurse/ anaesthetic nurse present during the intervention and the Anaesthetist is

available if the procedure is under GA or converted to GA. At Centre B, an Assistant Nurse Practitioner (ANP)/Scrub Nurse (SN) is used instead of the Practitioner or Assistant (ODP/ODA) and is always present during MT, with or without an anaesthetist present. Furthermore, the type of anaesthesia used varies across centres. The use of GA totalled 13% at Centre B; 31% at Centre D; 39% at Centre C; 65% at Centre A and 69% at Centre E1/E2.

The second variation is the location for performing the thrombectomy. At Centre C, MT is performed in the operating theatre, while at other centres it is performed in the IRS.

The third key variation concerns the accessibility of MT provision both on weekdays and at weekends. Centre A is the only centre performing MT 24/7. Centre D provides MT from 9 am to 5 pm; Centre B and Centre E2 provide MT mainly from 9 am to 8 pm on weekdays and ad hoc at weekends. The period of MT provisions has a correlation with the number of cases performed.

Lastly, the types of thrombectomy devices used differ across the centres. Stent-retrievers are the predominant devices used at Centre B, whilst other centres use a mixture of devices, but predominately thrombo-aspirators. Additionally, there are variations in the number of devices used per patient. Whereas some use fewer devices per patient, others use multiple devices per patient. The number of devices used depends on the experience of the interventionist, the location of the clot, the technical complexity of the procedure and vascular anatomy.

During thrombectomy procedures, Centre A performs more carotid stenting/angioplasty for carotid stenosis using a CASPER device than other centres (in 60% of cases).

5.3.3.9 Variation in the Treatment Pathways Between UK Centres and Other Countries

This section makes comparisons between the different UK pathways and the international ones from three countries: Germany, Italy and Canada. There are several differences in the structure and provision of MT as well as differences across health care systems. There are five main differences, four of which have particular relevance to potential improvements in UK provision.

Firstly, regarding pre-hospital transportation overseas, helicopters are regularly used, especially in Calgary (Canada), but less frequently in Heidelberg (Germany) and Florence (Italy). In Calgary, for example, helicopters are used both solely and in conjunction with an aeroplane (Fixed Wing) and even combinations of helicopter +Fixed Wing +ambulance before patients arrive at an MT centre. Various means of transportation are used to transfer patients from rural areas and mountain regions. This is because Calgary covers a land area the size of the UK and land transport is not viable for many remote communities. In the UK, helicopter transfers are infrequently used. When they are employed, it is mostly for secondary rather than for primary patient transfers. Mobile Stroke Units (MSU) are widely used in Berlin, Germany, with thrombolysis initiated in the MSU. Mobile Stroke Units are not commonly used in the UK; they were introduced as pilot studies in Essex and Suffolk/Norfolk (Grunwald et al., 2020).

Secondly, concerning imaging, in Canada and Italy, multi-phase CTs are performed, whilst in the UK and Germany, non-contrast CTs and CTAs are used. In Kingston, Canada, they have started using the RAPID software based on the DAWN/DEFUSE 3 trial. Post MT scans in Germany can be performed either at 24 or 36 hours, except if the patient deteriorates clinically, whilst in the UK, Italy and Canada repeat scans are scheduled at 24-hours post MT.

Thirdly, with regards to MT provision and the deployment of the interventionist for the procedure, the norm is for the procedure to be performed by an INR. In Kingston, however, the service has started with the procedure being performed by general interventionists through remote support from an INR via video link. Notably, the Interventional Team has just one INR. At Centre J in Canada, the procedure is performed by INRs and Neurosurgeons and very recently by a locally trained Interventional Neurologist.

Fourthly, the post-op care is different at Centre I in Canada, where all patients are moved to ICU, even if the procedure is performed under LA or CS. This has become customary since the MT service was set-up to be performed and was a safety measure to ensure that patients had one-to-one monitoring in ICU in the event of any deterioration in the early post-op period. It also reflects the much higher ICU capacity that the Canadian health care system has. Once stable, they are then transferred to the Stroke Unit after 24 hours post-MT. At Centre E2, all patients are taken to NICU, due to the unavailability of HASU at the centre site. Once stable, they are transferred back to HASU at Centre E1 or stepped down to ASU at Centre E1.

Finally, regarding the Stroke Team, the UK is the only country where most stroke teams are comprised predominately of stroke physicians who initially trained in geriatrics and/or internal medicine, whilst in other countries they are predominately Neurologists.

Tables 5.2 and 5.3 summarises the variations in treatment pathways across MT centres.

Table 5.2. Summary of variations in treatment pathways in multiple centres offering MT services

Items	Centre A	Centre B	Centre C	Centre D	Centre E	Centre F	Centre G	Centre H	Centre I	Centre J
Transport	Land ambulance	Land ambulance	Land ambulance and occasional helicopter	Land ambulance	Land ambulance	Land ambulance Mobile Stroke Unit (MSU) helicopter	Land ambulance and helicopter	Land ambulance and helicopter	Land ambulance	Land ambulance, helicopter and Fixed-Wing air ambulance
Medical Escort	Unconscious or intubated patients	All referred patients are escorted by a doctor or nurse	Unconscious or intubated patients	Unconscious or intubated patients	All patients accompanied by a junior doctor from UCLH to QS for MT	Unconscious or intubated patients	Unconscious or intubated and those with running rtPA during transfer	Unconscious or intubated patients	Unconscious or intubated patients	Unconscious or intubated patients and during Air transfers
Hospital Arrival	Both local and referred patients presented first to the ED.	Local patients presented first to the ED and transferred patients bypassed the ED to radiology.	Local patients presented first to the ED and transferred patients bypassed the ED to radiology.	The Stroke Unit was the first point of entry for both local and referred patients (9 am to 9 pm)	Local patients presented first to UCLH- ED and transferred patients with imaging direct to QS-IRS	Both local and referred patients presented first to the ED.	Local patients presented first to the ED and transferred patients bypassed the ED to radiology/IRS.	Local patients presented first to the ED and referred patients are admitted directly to the Stroke Unit.	Both local and referred patients presented first to the ED.	Local and referred patients transported by land presented first to the ED. Patients transported by air bypassed the ED to Radiology/IRS
Imaging	Image transfers from non-MT centres via PACS All patients had both CT and CTA with additional CTP when time of onset was unknown. Some referred patients had additional CTP. All patients had a 24-hour post-MT scan.	Image transfers from non-MT centres via PACS All patients had CT and CTA and CTP when time of onset was unknown. Most of referred patients had additional CTP. All patients had a 24-hour post-MT scan.	Image transfers from non-MT centres via CRIS All patients had CT and CTA with no CTP Referred patients only had repeat scan if they arrived one hour after initial scan at the primary hospital. Or if deteriorates All patients had an immediate post-intervention CT in addition to a 24-hr CT scan.	Image transfers from non-MT centres via PACS All patients had CT, CTA and CTP if time of onset unknown Referred patients only had repeat scan if arrived >1hr after initial scan at the primary hospital or if deteriorates All patients had a 24-hour post-MT CT or MRI.	Image transfers from non-MT centres via PACS All patients had both CT and CTA with no CTP. Referred patients only had repeat scan if they deteriorate All patients had a 24-hour post-MT CT and MRI at 72 hours or only MRI at 24 hours if available	Image transfers from non-MT centres via PACS If ≥NIHSS 6 CT/CTA is performed and for NIHSS <6 MRI Repeat Imaging for referred patients if: previous imaging is >2hrs or patient deteriorates Repeat images 24 - 36 hour post- MT	Image transfers from non-MT centres via PACS Repeat Imaging for referred patients if: previous imaging is >2hrs or patient deteriorates (haemorrhage?) or improves (ongoing occlusion?) Repeat images 24 - 36-hour post- MT	Image transfers from non-MT centres via central PACS All patients had both CT and CTA even at referring hospital. Repeat imaging CT multiphase CTA+CTP, when time of imaging at referring hospital >1h, neurological worsening or time of onset unknown All patients had a 24-hour post-MT scan. Usually CT with few MRI	Image transfers from non-MT centres via PACS All patients had both CT and CTA with additional CTP when time of onset was unknown. Majority of local patients had multiphase CTA. All patients had 24-hour post-MT scan. Usually CT with few MRI	Image transfers from non-MT centres via central PACS All patients had both CT and CTA with additional CTP when time of onset was unknown. Majority of local patients had multiphase CTA. All patients had a 24-hour post-MT scan. Usually CT with few MRI

Items	Centre A	Centre B	Centre C	Centre D	Centre E	Centre F	Centre G	Centre H	Centre I	Centre J
Interven-tion	All Procedures performed in the IRS.	All procedures were performed in the IRS.	All procedures performed in the Interventional Neuroradiology Suite (INRS).	All procedures were performed in the Theatre.	All Procedures performed in the IRS.	All Procedures performed in the IRS.	All Procedures performed in the IRS.	All Procedures performed in the IRS.	All Procedures performed in the IRS.	All Procedures performed in the IRS.
Anaes-thesia	Predominately GA	Predominately LA	Predominately LA	Predominately LA	Predominately GA	Predominately GA	Predominately CS	Predominately LA	Predominately CS	Predominately LA
Devices	Mixture of devices. Casper device for carotid stenosis	Predominantly stent retrievers.	Predominately Thrombo-Aspirators.	Mixture of devices, but fewer stent retrievers.	Mixture of devices	Stent retrievers and Thrombo-Aspirators.	Aspirators and Stent retrievers	Mixture of devices	Mixture of devices	Mixture of devices, but predominant SR Casper device for Tandem occlusion
Interventional Team	Team of 5 Anaesthetic team Consultant Practitioner or Assistant (ODP/ODA). Anaesthetic SpR Nurse/Radiographer: 2 Scrub nurses 1 Radiographer Interventionist: INR All procedures performed by an INR Usually one INR present during procedure	Team of 4-5 Anaesthetic team The Practitioner (ANP)/Scrub Nurse (SN) was used instead of ODP/ODA. Nurse/Radiographer: 2 Scrub nurses 1 Radiographer Interventionist: INR All procedures performed by an INR Usually more than one INR present day-time on weekdays (for training and more experience)	Team of 5-6 Anaesthetic team Consultant Practitioner or Assistant (ODP/ODA). Nurse/Radiographer 2 Scrub nurses 1Radiographer Interventionist: INR/IN INR SpR Procedures performed by an INR and an IR Usually one INR present during procedure	Team of 4-5 Anaesthetic team Practitioner or Assistant (ODP/ODA). Nurse/Radiographer 2 Scrub nurses 1 Radiographer Interventionist: INR All procedures performed by an INR. Usually, one INR present during procedure	Team of 6-7 Anaesthetic team Consultant Practitioner or Assistant (ODP/ODA) Anaesthetic SpR Nurse/Radiographer 2 Scrub nurses 1 Radiographer Interventionist: INR 1 INR ± Rad SpR Procedures performed by an INR and an IR Usually more than one INR present day-time on weekdays	Team of 4-5 Anaesthetic team Anaesthesiology nurse instead of Anaesthetist Nurse/Radiographer 1Scrub nurses 1 Radiographer Interventionist: INR All procedures performed by an INR. Usually, one INR present during procedure	Team of 4-5 Anaesthetic team Anesthesiology Neurologist instead of Anaesthetist Nurse/Radiographer 1 Scrub nurses 1Radiographer Interventionist: INR All procedures performed by an INR Usually, one INR present during procedure	Team of 5 Anaesthetic team Anaesthetic Consultant Nurse/Radiographer 1 Scrub nurses 1 Radiographer Interventionist: INR Interventionist resident All procedures performed by an INR. Usually one INR present during procedure	Team of 6-7 Anaesthetic team Practitioner or Assistant (ODP/ODA). Nurse/Radiographer x Scrub nurses x Radiographer Interventionist: IN/INR Procedures performed by general IR. Occasionally more than one interventionist present day-time on weekdays (For training	Team of 6-7 Anaesthetic team Consultant (rarely present) Nurse/Radiographer 1 Scrub nurses 1Radiographer 1 Stroke nurse Interventionist: IN/INR Resident Procedures performed by INR, interventional neurologist and Neurosurgeons Occasionally more than one INR present day-time on weekdays (For training)

Items	Centre A	Centre B	Centre C	Centre D	Centre E1/E2	Centre F	Centre G	Centre H	Centre I	Centre J
Post-MT Care	All patients are observed in Recovery for about an hour, and once stable they are moved to the HASU but, if not stable to ICU/HDU (few cases).	After MT, patients are transferred straight to the Stroke Unit but, if unstable, then to ICU/HDU (few cases).	All patients are observed in Recovery for about an hour, and once stable they are moved to HASU if not stable in few cases to ICU/HDU.	All patients are observed in Recovery for about an hour, and once stable they are moved to HASU, if not stable into ICU/HDU (few cases).	All patients go to NICU. Local patients are transferred from ICU to Centre E1 HASU and transferred patients to Centre E2 ASU	After MT, patients are transferred straight to the Stroke Unit, except it intubated or unstable, then to ICU/HDU (few cases).	After MT, patients are transferred straight to the Stroke Unit, except it intubated or unstable, then to ICU/HDU	All patients are transferred to stroke Unit unless: intubated or instable (ICU) bed not available in Acute Stroke Unit	All patients are observed in Recovery and then moved ICU/HDU. When stable, or bed available then moved to the stroke unit.	Patients moved to an HDU equivalent unit with 1-1 nursing care equivalent to neuro HDU Unstable or BAO go to ICU
Repatria-tion	Usually within 24-48 hours when stable to the referring hospital.	When stable and a bed available at referring hospital	When stable and a bed available at the referring centre.	Usually up to 72 hours when stable to the referring hospital.	When stable and a bed available at the referring centre mainly from Centre E2	Usually after 72 hours post- MT	Usually after 72 hours post -MT	Usually within 48 hours if stable	When stable and a bed available at referring centre.	When stable and a bed available at referring centre (5-7 days)
Communi-ty stroke rehabilitat-ion	Local patients with rehab potential are transferred to a dedicated stroke rehabilitation unit.	No community rehabilitation beds, so all rehabilitation overseen in the Stroke Unit.	Local patients with rehab potential are transferred to a dedicated stroke rehabilitation unit.	Local patients with rehab potential are transferred to a dedicated stroke rehabilitation unit.	Local patients with rehab potential are transferred to community rehab bed from both Centre E2-and Centre E1	16 neurorehab beds on site and community rehab	Several community rehabilitation units	Community neurorehabilitation units	Local patients with rehab potential are transferred to a dedicated stroke rehabilitation unit.	Local patients with rehab potential are transferred to a dedicated stroke neuro rehabilitation and community rehabilitation units
Home with ESD	Available	Available	Available	Available	Available	Not available	Not available	Not available	Available	Available
Follow-up	All local patients are followed-up	Not all local patients are followed-up, depending upon resources available.	Not all patients are followed-up, depending upon resources available.	All local patients are followed-up	All patients are followed in the clinic. If follow-up not possible then a telephone call, usually for care home discharges and hose repatriated abroad.	Follow-up by telephone including repatriated patients (death registry contacted)	All patients including repatriated patients followed up in person or vis telephone	All local patients are followed-up at three months at outpatient clinic. Patients from referring hospitals are followed-up at the referring hospital. For patients enrolled in clinical studies there is a dedicated follow-up.	All local patients are followed-up	All local patients are followed-up

PACS (Picture archiving and communication system), CRIS (Central Radiological Image Sharing)

Table 5.3. Variations in treatment pathways across MT centres

Items	Centre A	Centre B	Centre C	Centre D	Centre E1/E2	Centre F	Centre G	Centre H	Centre I	Centre J**
Total Number (MT +IVT vs IVT only)	816 (298 vs 518)	622 (323 vs299)	444(76 vs 368)	359 (88 vs271)	404 (83 vs 321	*MT- 199	1543 (1009 vs 534)	*MT-307	*MT 46	0(0 vs 0)**
2015	114(59 vs 55)	125 (54 vs 71)	79 (5 vs 74)	66 (4 vs 62)	0(0 vs 0)	MT- 21	311 (198 vs 113)	MT-79	MT -O	X (X vs X)**
2016	246 (76 vs 170)	136 (64 vs 72)	98 (19 vs 79)	88 (22 vs 66)	0(0 vs 0)	MT-82	412 (256 vs 156)	MT-139	MT-7	X (XX vs XX)**
2017	214(68 vs 146)	133 (67 vs 66)	162 (26 vs 136)	97 (28 vs 69)	17070(21 vs 149)	MT-96	531 (357 vs 174)	MT-161	MT-27	X (XX vs X)**
2018	242 (95 vs 147)	205 (114. +91)	105 (26 vs 79)	108 (34 vs 74)	234(62 vs 172)	MT-XX	289 (198 vs 91)	MT-110	MT-12	X (XX vs X)**
Referring hospitals	12	8	5	7	5	5	12	8	3	**4-6**
% of Referred patients	11%	47%	41%	37%	2%	6%	29%	63%	30%	**(XX%)****
Team during MT	Team of 4-6*	Team of 4	Team of 4-5	Team of 5-6	Team of 5-6	Team of 4-5	Team of 4-5	Team of 5	Team of 4-5	Team of 6.7
Interventionist	INR -100%	INR -100%	INR -100%	INR -90% IR-10%	INR -90% IR-10%	INR -100%	INR -100%	INR -100%	INR -10% IR-90%	INR Neurosurgeons Neurologist
Anaesthesia	LA-26% CS-9% GA-65%	LA-80% CS-4% GA- 16%	LA-32 CS-37 GA-31%	LA-41% CS-20-% GA-39%	LA-29% CS-2% GA-69%	LA-3% CS- 17% GA-80%	LA-2% CS-57% GA-40%	LA- 48% CS-14% GA- 4% Others-36	LA-1% CS-94% GA:5%%	LA -85 CS-5% GA-10%
ICU/HDU admission	6%	4%	3%%	20%	100%	12%	6%	16%	100%	10%
Repatriation	10%	27%%	7%%	12%	49%	4%	6%	48%	26%	(XX)**
Follow-up	100%	56%	74%	10%	91%	95%	100% (person or Telephone)	44%	59%	

- Less at night, ** Data not available (unable complete data collection due to Covid-19)

5.3.3.10 Changes in Pattern of Use of MT between 2015 and 2018*

There have been structural and organisational changes in the provision of thrombectomy services between 2015 and 2018, all aimed at improving MT. The pattern of use of thrombectomy has changed during this period, as described below and in Table 5.4.

5.3.3.10.1 Structural/process changes to the pathway

Firstly, both the pre-hospital and inter-hospital notification processes have improved. Communication has improved between hospitals (MT and non-MT centres) and ambulance services, for timely transfer of stroke patients to MT centres, particularly from non-MT centres. Faster responses have been achieved through education and training of the ambulance crews on early recognition of LAO and the importance of reduction in transfer delays. Similarly, the referral process of patients from non-MT to thrombectomy centres has also improved, enabling swifter decision-making regarding initiating transfer of patients to MT centres.

Secondly, the use of imaging facilities to diagnose large vessel occlusion has increased over the years. All hospitals, especially the non-thrombectomy centres, now perform both CT and CTA before referring patients to MT centres. Likewise, the imaging software has been upgraded and improvements made to the process for transferring images from non-MT centres to MT centres. This has facilitated faster and more efficient transfers of images. In the Midlands, for example, there has been a centralisation of the system, replacing PACS software with Central Radiological Image Sharing (CRIS). Moreover, there has been an increase in the

use of additional CTP, particularly for patients with wake-up stroke or with unknown time of onset. Centre C is the only hospital amongst the five UK centres not performing CTP. Similarly, most centres, apart from Centre B, rarely repeat imaging for transferred patients, except for arrivals more than one hour after referral or if there is neurological deterioration.

Thirdly, most centres now have a pre-packed thrombectomy kit in the IRS. The MT kit contains regularly used items such as drapes, syringes, trays, sterile gauze, guide sheath, catheter and devices (experience shows that these are the most important items to have immediately to hand). The time saved assembling the items in advance, can significantly improve door-to recanalisation times. Furthermore, there have been developments and improvements in the types of devices used over the years with more CME approved devices for MT. The types of devices being used depends both upon the centres' policies and the interventionists' professional choices. Likewise, NICE approved two types of devices (Stent retrievers and Aspiration catheters) in July 2018.

Lastly, the use of GA over LA or LACS has decreased in the last two years, particularly at Centre A, where about 65% of cases were performed under GA. All the centres are now performing more MT under LA. Similarly, there has been a decline in the number of admissions to ICU post-MT, which could be partly due to the decrease in the use of GA and more centres becoming more experienced and competent in managing post-MT patients on HASU.

The Covid pandemic has had an impact on the use of GA, with a much lower proportion of thrombectomy procedures performed under general anaesthesia.

A recent study, for example, reported that the use of general anaesthesia fell significantly from 85% to 32% (Kwan et al., 2020).

5.3.3.10.2 Organisational Changes

Firstly, there have been changes to MT services- availability. The opening hours for performing thrombectomy have been extended from 9 am to 5 pm through to 7 pm to 8 pm for most centres and for Centre A, the service is now provided 24/7. Additionally, the weekend service, which was non-existent or only an ad hoc service, has now been transformed into a full weekend service at Centre A. Centre C only provided MT from 9 am-5pm but has become more robust and aimed to provide services 24/7 by September 2021. The 9 am-5 pm service at centre B has been expanded to 9 am-8 pm and at time of writing, is also planning to provide a 24/7 service. Similarly, at Centre E1/E2, the 9 am to 5 pm service has been extended from 8 am to 10 pm since March 2018.

Secondly, relating to the development of Standard Operating Procedures (SOPs)/ local Guidelines and due to the increasing demand, MT centres have developed or updated their various SOPs/ local Guidelines for safer and more efficient workflows. Similarly, there have been internal structural changes, such as increasing numbers of HASU beds and consequent re-arrangements of wards to accommodate the increasing number of admissions. Centre A Stroke Unit, for example, recently relocated to a bigger unit with 29 beds, which includes 12 HASU beds. Centre D is aiming to create more bed capacity to be able better to admit cases from across the region.

Thirdly, reflecting the increasing numbers of MT procedures performed since 2015 and owing to expansion in the hours provided for MT, as well as restructuring and expansion of services, there have been yearly increases of between 5% and 10% in the number of cases treated with MT. The increase has been both among local patients and those referred from non-MT centres. The number of centres referring patients for MT since 2015 has also grown.

Fourthly, concerning the development of repatriation policies, in order to deal with the increasing number of cases and the consequent shortages of beds, centres are now developing regional policies to facilitate early repatriation to primary hospitals to maintain adequate bed provision for new admissions. The repatriation policy, already fully implemented at Centre A, has facilitated early repatriation of clinically stable patients, who are now transferred back within 24 hours, even before a repeat 24-hour scan. A regional repatriation policy has been agreed for Centre C, but not yet fully implemented, as is the case at Centre A.

Lastly, there was an increase in the number of staff appointments. Based on demand and on progressive rises in the numbers of cases, there has been an increase in the appointments of radiologists and stroke consultants. At Centre C, for example, four INRs were appointed, facilitating the formation of a new team of four INRs and seven diagnostic neuroradiologists. Separate rotas for diagnostic and intervention duties were established.

Similarly, there was an increase in newly appointed stroke consultants for an on-call stroke rota as well as of anaesthetists and radiographers at the various MT centres.

Similar changes took place between 2015 and 2018 in Germany and Canada. These countries have had improved pre-hospital and inter-hospital communications, expansion of MT services and more appointed staff. At Centre I in Canada, for example, an INR has been appointed to join the general interventionists who had been performing the procedure. Similarly, at Centre J in Canada, a Neurologist and a Neurosurgeon have been trained locally and are now part of the Intervention Team. The numbers of patients treated with MT has also continued to increase in Germany and Canada. At Centre G in Germany, referred patients bypass the ED and are taken directly to imaging since June 2018. Table 5.4 summarises the changes between 2015 and 2018.

Table 5.4. Summary of Changes between 2015 and 2018 in UK

Items	Changes in pattern of use of MT from January 2015 to December 2018
Pre-hospital Communication	Improved communication with ambulance services for timely transfer of stroke patients to MT centres, particularly from non-MT centres.
Referral from Non-MT to MT Centres	Improved patient selection; telephone referral; linkage and viewing of images and faster decision-making regarding patient transfers to MT centres.
Imaging	Upgrades and improvements to image transfers from non-MT centres to MT centres, resulting in faster and more efficient transfers. An increase in the use of additional CTP, particularly for patients with wake-up stroke or with unknown time of onset.
MT Service Availability	Expansion for MT provision from 9 am to 5 pm through to 7-8 pm and now MT provision 24/7 at Centre A. Similarly, the previously non-existent or only ad hoc weekend service has now transformed into a full weekend service at those centres. The 9am-5pm MT service at Centre C is more robust with plans for expansion to 24/7. The 9am-5pm service at Centre B has expanded to 9am-8 pm with plans to provide a 24/7 service. Centre E1/E2 moved from 9am- 5pm to 8 am -10 pm from March 2018. There are plans for 24/7 with a pan London rota.
Anaesthetic Provision	Decreasing use of GA over LA or LACS in the period, particularly at Centre A, where about 60% of cases were performed under GA. All the centres now most often use LA.
Post-MT Admission	Decreasing number of admissions to ICU/HDU post-MT, with more patients managed in HASU.
Devices	Advances in the types of devices used during the period with more CME approved devices for MT.
Pre-packed MT Kit	Increasing utilisation of pre-packed Thrombectomy Kit in the IRS facilitating an efficient workflow.
Increase Number of MT	Increasing number of procedures performed since 2015.
Staff Appointments	Increasing appointments of radiologists, stroke consultants, anaesthetists and radiographers. Centre C has expanded to 4 INRs enabling the formation of a new team of 4 INRs and 7 diagnostic neuroradiologists (DNRs), for establishment of separate rotas for diagnostic and interventional duties.
SOPs/local guidelines	Development of SOP/local guidelines for safer and more efficient workflows.
Repatriation Policy	Development of regional repatriation policies for facilitation of early repatriation to primary hospitals to make beds available for new cases.
Follow-up	More patients are now being followed-up enabling better recording of 90-day outcome data.
Data Collection/Databases	During the period, various centres have developed robust, local data bases and continually improve the capture of complete data onto the SNAPP National Database. Centre A has a comprehensive MT database.
Training	Ongoing training of ambulance crews and staff involved with providing MT, particularly interventionist. Simulation courses and interpretation of CTA by stroke consultants.
Conclusion	Improvement of flow pathways and continuous improvement of standards of care.

5.3.4 DISCUSSION

This study has identified considerable differences in the treatment pathways for delivering MT and IVT across a range of thrombectomy centres in the UK and internationally. The literature review also identified wide variability in the flow pathways for MT provision across several countries. These were either structural design or process design variations which affect decision- making and potentially impact on accessibility of MT, the process times and the number of cases treated.

The variations in the structural design along the pathway mainly involved pre-hospital transport either for direct transfer to an MT centre before repatriation or for the typical mothership vs drip-ship; inter-hospital transfers with or without any medical escort; first point of entry at hospital either first to the ED or straight to the Stroke Unit, and imaging either both immediately post-MT and 24-hour post MT or only 24-hour post MT scan.

In contrast to the general mothership vs drip-and-ship model of care, the transfer of some patients directly to Centre E1 is based on the centralisation of stroke services in London. The direct transfer to Centre D for MT, and repatriation after treatment to their primary hospital, has potential for future development and for being rolled out to other regions in the UK. This can facilitate immediate transfer to an MT centre for treatment and subsequent repatriation.

However, the immediate repatriation of patients could be faced with numerous very difficult challenges to overcome. Such challenges include lack of availability of beds at the primary hospitals to accept patients after MT, once clinically stable.

If patients are not repatriated, the MT centres will be faced with limited bed capacity to accept new patients for thrombectomy.

Both pre-hospital and inter-hospital transfers are important routes along the thrombectomy pathway which, if strategically planned, have the potential for optimising immediate access for thrombectomy and improved clinical outcomes. The practice of transporting all referred patients, with medical escorts to Centre B from non-MT centres and to Centre E2 from Centre E1 by a doctor, is aimed at safeguarding standards of care.

Differences in organisational set-up determines the rapidity of flow of patients. The Helsinki Model (Meretoja et al., 2012) for example, which consisted of 12 interventions including direct transfer to CT on an ambulance trolley instead of transfer first onto an ED trolley, was aimed at reducing treatment delays prior to thrombolysis and has been shown to reduce process times.

The adaptation of this model with real life resources in Melbourne reduced, within 4 months, the time delay before thrombolysis by 18 minutes, thus achieving a process time of door- to- needle of 25 minutes (Meretoja *et al.,* 2013) (Meretoja et al., 2013), although the processes worked speedily mainly Monday–Friday within usual working hours (8 am to 5 pm).This model has been successfully validated in other centres and was also found to reduce process times (Wu et al., 2018).

Similarly, a 10-step intervention (Fonarow et al., 2011) recommended by the American Heart Association/American Stroke Association Target, resulted in an

80% increase in the number of t-PA administered within 60 minutes of hospital arrival (Fonarow et al., 2014).

At Centre D, for example, the set-up is such that patients admitted between 9 am and 9 pm go straight to the Stroke Unit, thus reducing the time spent in the ED, compared with other hospitals, where patients present firstly to ED, unless referred or are already inpatients. Transferring the referred patients directly to radiology at Centres B, C and D reduces the time from onset-to-recanalisation, potentially increasing chances for a better clinical outcome. Early repatriation of stable patients from Centre A for the scan to be performed at the primary hospital, even before the 24-hour post MT scans, has the potential to increase available beds, especially with the increasing number of MT procedures being performed and the growing demand for beds.

There were also variations in MT service provision coverage. The service is 24/7 at Centre A only. The coverage for MT provision is dependent on the staffing capacity, especially for a compliant rota to provide and maintain around-the-clock service for MT. It has been estimated that at least five operators would be required to provide a 24/7 service with at least 150 MTs performed per year, for the interventionists to maintain clinical competence (Allen et al., 2019).

The challenge is that there are limited numbers of trained INRs in the UK. There were about 80 INRS in the UK as of 2017 (Clifton, 2017). The official plans to roll out stroke thrombectomy services 24/7 would require around 150 fully-trained INR expert across the UK (The Royal College of Radiologists, 2020). Similarly, it

is estimated that a HASU with 600 new admissions per year would require a minimum of 10.5 medical staff/day (White et al., 2015).

In comparison with other countries, one of the key differences in the UK relates to pre-hospital notification and transportation. In Canada, for example, pre-hospital and inter-hospital transfers are well established, based on the sparse distribution of the population in this geographical region. The organisational structure and communication set-up facilitates efficient process times for early transfers to MT centres. Helicopters are potentially a form of transportation that could be more widely used in rural regions in the UK. Leira and Colleagues (Leira et al., 2016) have suggested the use of inter-hospital helicopter transfer for early arrival at MT centres for patients living in rural areas or even congested urban areas. Recently, the PEARS 2 Study has shown how helicopter transfers from rural areas could be cost-effective, particularly for some regions in the UK where rapid transport to the nearest MT centre can be challenging (Coughlan et al., 2021).

The other main difference between the UK and Canada relates to the use of General Interventionists instead of INRs in Centre I, Canada. This has the potential to be replicated in the UK, particularly, in view of the shortages of INRs in the UK.

On a similar, albeit smaller scale, at Centre C in the UK, 4% of MT procedures were performed by Interventional Radiologists (IRs). In Germany all referred patients are repatriated after 72 hours, if clinically stable, while in the UK,

particularly at Centre A, patients can be repatriated even within 24 hours post-MT, once medically stable and beds are available at the referring hospital.

Similarly, the study identified structural and organisational changes in the provision of thrombectomy between 2015 and 2018. The changes have influenced the pattern of use of thrombectomy during this period. The main drivers of the changes in the UK, particularly since 2016, have been the recommendations for MT by NICE in February 2016 (NICE, 2016), published guidelines by the RCP in 2016 (RCP, 2016) and the introduction of a thrombectomy tariff by NHS England in 2018 (NHS England, 2018). The changes were all aimed at improving the efficiency and efficacy of the delivery of MT.

Notably, the study revealed that the number of patients treated with MT was consistently below the estimated 10-15% of patients likely to benefit from the treatment. The number of patients treated with MT will continue to improve with expansion of services. There should be further ongoing changes as the services continues to evolve, particularly with the training of more interventionists. Unfortunately, the training of interventionists is still an on-going issue and will continue to be for some time to come. The NHS has plans to train non-interventionists to help with the shortage of INR.

The wide variations in the treatment pathways across MT centres could be explained by differing geographical locations; varied organisational and service configurations; disparate availability of resources and professional staffing levels, particularly with regards to the availability of INRs. Decisions are made at each point in the treatment pathway and these decisions could have implications in

terms of patient flow, suitability for people to receive treatment, process times, expected clinical outcomes and readiness of discharge from hospital. Resolving such issues that lead to variations in pathways, would help deliver a more efficient system and improve overall patient outcomes.

5.3.4.1 Strengths and Limitations

The main strengths of this study are the identification of clinical pathways in multiple centres and comparisons of the variations across the centres involved. Furthermore, valuable detailed data has been captured regarding: the numbers of patients passing through every phase of the pathways; the type of imaging used; forms of treatment through to final discharge destinations both for the individual centres and collectively. There were limitations due to lack of wider regional coverage. Ideally, all the regions in the UK should have been included to give a comprehensive picture of the various treatment pathways currently in use. It was not possible, however, to collect information from most regions. In Scotland, for example, comparatively few patients with LAO stroke were treated at the single MT centre (Western General Hospital in Edinburgh) up to mid-2018 (NHS National Services Scotland, 2018). Additionally, high volume London hospitals were not captured as they declined to participate in the study. Only one low volume centre in London contributed data.

The study was reliant on local practice and available NHS data, not a research study with consent for 90 days follow up.

5.3.4.2 Conclusion

This study has identified considerable differences in the treatment pathways for delivering MT and IVT across a range of thrombectomy centres in the UK, as well as in two MT centres in Germany and Canada, and one in Italy. The literature review also identified wide variability in the flow pathways for MT provision across several countries.

The main differences across the UK centres were shown to arise from the following factors: using direct admission to an MT centre before repatriation to primary hospital, as opposed to the mothership or drip-and-ship model; whether or not patients go straight to the SU instead of first presenting to the ED; instigating immediate-post MT imaging and 24-hr scans as opposed to only 24-hr post MT scans and promoting early repatriation of stable patients within 24 hours with 24 post-MT scan performed after repatriation. Furthermore, there were process differences of the MT accessibility in terms of 24/7 availability, weekend services, staffing capacity and provision of community rehabilitation beds. These process differences impact on the process times and the subsequent number of cases treated.

Similarly, the main differences between the UK and other countries were prehospital and inter-hospital helicopter transportation and the use of general interventionists to perform MT in Centres I and J in Canada, respectively. In Germany compared with the UK, patients are repatriated 72-hours post-MT.

Overall, there is no evidence from this study or from the literature review to suggest that one treatment pathway is superior to the other. This is because of the different factors responsible for the variations described above.

Between 2015 and 2018, the study has identified changes along the treatment pathways across all the centres. The main changes, particularly in the UK, have reflected improved pre-hospital and inter-hospital communication, the expansion and accessibility of services, and the yearly increase in the number of MTs performed. The changes were all aimed at improving the efficiency and efficacy of the delivery of MT.

5.3.4.3 Implications for future research

The study revealed variations in the treatment pathways in four regions of the 12 regions in the UK (Greater London, North East and West Midlands of England, and in Northern Ireland). There is a clear need for a larger study involving significantly more regions in the UK, to evaluate the effects of variations in treatment pathways and clinical outcomes across MT centres. This should optimise the standard of care for stroke patients throughout the country. It would be important to see the effect on process times of direct transfer to SU, particularly, for times-to-imaging, door-to-needle and door-to-recanalisation and, most importantly, on mortality rates and subsequent clinical outcomes. Similarly, futures studies would be helpful in clarifying if immediate post-MT scans can pro-actively identify early bleeds and cerebral oedema (malignant MCA syndrome) for early intervention.

Furthermore, there is a need to establish the resources used and unit costs along the identified treatment pathways: this is done in the next chapter, which describes the resource use and unit costs across the identified treatment pathways both individually and collectively, and the resulting costs per patient following different pathways.

CHAPTER 6

6 Resource Use, Unit Costs and Cost of Mechanical Thrombectomy and Intravenous Thrombolysis for Treatment of Acute Ischaemic Stroke

6.1 INTRODUCTION

Mechanical thrombectomy may be performed using a variety of devices including stent-retrievers and thrombo-aspirators, along with other accessories or auxiliary devices such as micro-catheters, guide wires, balloon catheter and other consumables. There have been many advances and continuous improvements over time in thrombectomy devices, with at least 15 CE-marked MT devices for use in AIS (EUnetHTA, 2016). In July 2018, NICE published the Medtech innovation briefings (MIBs), providing evidence-based advice on MT devices of two types: stent retrievers (SR) and aspiration catheters (AC) (NICE MIBs, 2018). The devices differ in cost, ranging from £550 to £1,349 for AC and £1,500 to £5,000 per unit (excluding VAT) (NICE MIBs, 2018).

Mechanical thrombectomy is performed by an interventionist - usually an interventional Neuroradiologist (INR) - but delivering the treatment requires a multidisciplinary team (MDT) in addition to the INR. The MDT consists of: the Stroke Team (stroke nurse, consultant stroke physicians) who are involved in the initial assessment of the patient on arrival to hospital and initiation of IVT if indicated; radiographers and sometimes a diagnostic radiologist for performing imaging and interpretation of the brain scans respectively; the Anaesthetic Team

(anaesthetic consultant and operational dependent practitioner or assistant (ODP/ODA) involved with the administration of general anaesthesia or sedation during the procedures; and scrub nurses and other INR or theatre staff.

Other resources are required for providing MT services such as rapid advanced imaging, neurocritical care facilities (ICU/HDU), neurosurgical support in the event of intra or post-operative complications, hyperacute stroke unit (HASU) and outpatient follow-up facilities (White et al., 2015, Allen et al., 2018). There has been guidance from various professional bodies regarding the requirement or standards for MT provision (White et al., 2017, Turc et al., 2019).

Being a relatively new intervention, the cost of the procedure has been based on data mainly derived from clinical trials (Ganesalingam et al., 2015, Lobotesis et al., 2016, de Andres-Nogales et al., 2017, Steen Carlsson et al., 2017, Leppert et al., 2015, Kunz et al., 2016). Furthermore, limited data is available on the real costs of providing the treatment in a clinical setting (Vega-Valdes et al., 2018) and none of the CEAs or cost-analysis studies to date have covered the whole treatment pathway. Previously published cost-analysis studies have varied in the different components of resources and costs included. While some studies provide the procedural costs of MT, including the costs of devices and staffing (Lobotesis et al., 2016, Leppert et al., 2015, Kunz et al., 2016), others have reported only the costs of devices and procedures (Kass-Hout et al., 2015, Turk et al., 2014, Comai et al., 2015, Turk et al., 2015). Some studies, such as Vega-Valdes and colleagues (Vega-Valdes et al., 2018), include the costs of emergency admission, imaging, physician consultation, hospital admission up to

24-hours after intervention, rehabilitation sessions and 90-day outpatient follow-up, while others report only the costs for the acute hospitalisation episodes (Leppert et al., 2015, Kunz et al., 2016, Simpson et al., 2014, Rai and Evans, 2015), and do not cover the costs of transportation or other periprocedural staff costs associated with MT.

Being predominantly based on clinical trial data derived from research settings, published studies of costs and cost-effectiveness may also fail to capture the real costs in routine clinical practice. No studies to date have provided a detailed account of the resources involved along the whole treatment pathway for MT in routine clinical practice, particularly in the UK. Additionally, previous studies have typically not included the staffing costs for providing MT. This limits the validity of extrapolating their results to the real-life clinical setting. For example, the additional costs of inter-hospital transfer to a thrombectomy centre and repatriation to the referring hospital, are not included in these studies. There is, consequently, a paucity of data on the true costs of MT in a routine clinical setting. Knowledge of detailed resources required, and their costs are essential for efficient resource distribution and service planning, particularly given the limited availability of thrombectomy centres in the UK and the on-going restructuring of the service. This study begins to address these questions, by first identifying in detail the resources used along the treatment pathways characterised in the previous chapter for all treated patients in the study centres, then quantifying the resources used and attaching unit costs to the resources used. From this, it is possible to calculate the total and average cost for all patients who have gone through the pathway. Based on a sample of individual patients treated in participating hospitals, as

described in Chapter 5, this chapter then calculates the cost per individual patient across their treatment pathway, giving a more nuanced and detailed picture of individual patient costs, and of the variability and heterogeneity around the average. The chapter will examine such variations in the cost of delivering MT across different hospitals in the UK, between the Mothership and Drip-and-Ship models of care, and the drivers of cost. Finally, results from the individual patient data (IPD) will be compared with the total cost estimated across all treated patients.

Research hypotheses:

1) The total cost of providing MT within the hyperacute phase of care (24 to 72 hours) would be more than the current NHS England tariff (reimbursement) of £11,750.

2) The cost is expected to be highly variable across individuals and sub-groups when estimated from the individual patient data analysis.

The aims and objectives of the chapter can therefore be summarised as follows:

1 To identify in detail, the resources used by each patient along the treatment pathway.
2 To identify the most appropriate and representative unit costs for each of the resource items and categories identified.
3 To use the identified resource use and unit cost information to improve on existing cost estimates of MT for the treatment of AIS in routine clinical settings within the NHS.
4 To determine the cost per patient and variations in the cost based on a sample of individual patient data.
5 To explore the main factors associated with variations in costs.

6.2 METHODOLOGY

This current study is a cost analysis from the perspective of the UK National Health Service (NHS). Two costing methods - top-down (gross-costing) and bottom-up (micro-costing) - were adopted as a comprehensive approach to measure the actual cost of MT for the treatment of AIS in a non-research setting. The top-down method (Jones et al., 2019) is a total patient data-based costing (TPD) approach, covering all patients being treated in each of the hospitals and the proportions going through different routes along the whole treatment pathway. This method has the advantage of allowing the total cost and overall average cost per patient to be calculated based on information collected on all patients, and permits differences between hospitals to be estimated, but not differences between patients or patient groups within or across hospitals.

The bottom-up method, on the other hand, is an individual patient data-based costing (IPD) approach, which allows the exploration of heterogeneity between patients. If based on a sufficient sample, the bottom-up approach can be a reliable and accurate method for estimating resource usage and costs (Gold et al., 1996, Drummond et al., 2015, Jones et al., 2019).

6.2.1 Measuring resource use

Resources involved in each stage of the pathway for a stroke patient were identified and quantified. Resource use was measured for patients treated with both MT and IVT and was recorded through the various stages of the pathway. The stages included: the patients' journey from the onset of stroke, patients' transfer to the thrombectomy hospital, diagnostic and treatment procedures

through to discharge from a thrombectomy centre. Further information and qualifying observations concerning resource usage were obtained by interviewing stroke physicians, stroke nurses, interventional radiologists, anaesthetists, theatre staff, radiographers, stroke managers and finance personnel.

6.2.2 Identifying realistic unit costs

Once the type and volume of resources used by each patient had been identified, a set of unit costs were assembled. During the interviews described in Chapter 5, costs unique to MT and those common to both IVT and MT were collected. The costs specific to MT included: advanced radiological imaging for large vessel occlusion, particularly CTA; thrombectomy devices; other devices such as guide wires, catheters, and femoral sheaths; intervention- related materials; interventional radiology suite/theatre time; procedure time; post-procedural care; time in recovery area; time on intensive care unit/ high dependency unit (ICU/ HDU) and staff time. The costs common to both IVT and MT included: CT head scan; the standard hospital costs; time on stroke unit; medications and post-treatment care on the stroke unit. While most unit costs such as those for transportation, imaging, devices and consumables, are specific to each hospital, others such as staffing costs, GA cost, IRS/theatre time and thrombolysis cost were applied across all centres. Individual hospital finance departments were initially contacted for their local costings of the identified resources, and in the absence of any hospital specific cost, the NHS Healthcare Resource Group (HRG) reference cost was used (NHS Improvement, 2018).

The unit costs of thrombectomy devices used were derived from individual hospital specific, manufacturers costs or published literature. There were no NHS national tariffs for thrombectomy devices until July 2018, when NICE published the cost for two types of devices, Stent-retrievers and Thrombo-Aspirators (NICE, 2018b).

Unit costs for different staff categories along the treatment pathway were obtained from the Personal Social Services Unit (PSSRU)/ Medical Consultant (Curtis and Burns, 2017). The estimated time spent during the procedure was based on published literature (Lobotesis et al., 2016) and from expert opinion of stroke managers, INR, theatre staff and stroke consultant/nurses. A gross domestic product (GDP) deflator (Treasury, 2019) was used to adjust prices where necessary to 2017/18 prices. All costs are reported in Great British Pounds (GBP).

Information on the costs of pre-hospital transportation and inter-hospital transfers was obtained from ambulance services from the various regional Ambulance NHS Trusts. The costs of transportation for repatriation of MT patients were provided by the individual MT centres. Similarly, the charities providing Helicopter Emergency Medical Service (HEMS) were contacted for the costs of transferring stroke patients to thrombectomy centres. The cost of Alteplase for IVT was obtained from the British National Formulary website (BNF: British National Formulary).

6.2.3 Deriving cost

The same unit cost information was used in the TPD and the IPD.

Typically, a cost was calculated for pre-hospital notification calls and pre-hospital ambulance transport, either directly to thrombectomy facilities or initial transfer to a non-MT centre before secondary transfer. Repatriation to the local hospital after treatment was also costed and included.

Further cost calculations were made for: the initial hospital attendance at the MT centre, either at the Emergency Department (ED) or the Hyper-acute Stroke Unit (HASU); the initial attendance at the primary hospital; the telephone call referral to discuss acceptance of the patient for transfer; the imaging performed at MT centre and, for referred cases, both the imaging performed at the local hospital and if repeated, at the MT centre. Imaging transfer via picture archiving and communication system/Central Radiological Image Sharing (PACS/CRIS) from the local hospital to the MT centre was included.

All costs associated with the intervention phase were calculated and totalled. These included: use of an interventional radiology suite (IRS) or theatre per hour; type of anaesthesia, either general anaesthesia (GA), local anaesthesia (LA) or conscious sedation (CS); thrombectomy devices with ancillary devices and other consumables; and staff time. A cost was also calculated for the immediate post-intervention care, whether in the recovery area, before transfer to HASU, or for the length of stay on ICU/HDU.

The interventional staff time was costed at three hours. The Stroke Consultant time was costed to a maximum of up to four hours within 24 hours, starting either from patient arrival or from the telephone call from the referring hospital discussing acceptance before arrival at the MT centre, and up to 24-hours of post interventional care. The Stroke Nurse time was costed at three hours from patient arrival through treatment and either up to transfer to HASU or on admission to ICU/HDU. The sources/references of staff timings applicable to all participating centres are reported in Appendix 6.A.

6.2.3.1 Total Patient Data (TPD)

The costs for TPD were derived once resource use and quantity had been recorded and the observed probabilities of patients using different types and quantities of resources on different routes along the treatment pathway, had been established. This allowed a cost to be calculated for each route of the pathway and then totalled. The calculated total cost was then divided by the number of patients, to obtain an average cost per patient. The same approach was used to estimate costs by type of treatment received, either IVT+MT or IVT only, and the costs for individual hospitals as well as the total for all hospitals.

6.2.3.2 Individual patient data (IPD)

While the TPD costing was valuable in giving a clear estimate of the totality of costs and the average across all patients, it does not give any insight into cost variability between patients. To address this question, IPD were collected for a sample of patients in each hospital studied and were used to calculate estimates of the costs for each patient in the sample, taking into account the type and

number of devices used for each individual patient, their length of stay in ICU/HDU, and their specific route through the treatment pathway. Once resources used and their quantity had been recorded for each patient and appropriate unit costs identified, a total cost per patient was determined. This was done for the initial 24-hour post-intervention period, and then from the end of that period until the patient's discharge from the MT centre, to establish an overall total.

For the IPD based costing, where reporting costs per patient, means and standard deviations are reported, when comparing costs, for example between patient groups or hospitals, 95% confidence intervals around mean differences were also calculated.

6.3 DATA: pathways, resource use and unit costs

This section describes how patients were identified, the proportions of patients going through different stages of the pathway, the resources used along the treatment pathway and the unit costs. Data are presented first for the TPD analysis, and then for the IPD analysis.

6.3.1 Total patient data (TPD)

Information is presented first for Centre A, then other centres, and then combined across all centres. Centre A was selected first because it was the first centre to provide MT with a well-established pathway. This was also the reason why Centre A was used as the template for mapping other MT centres in Chapter 5.

6.3.1.1 Mechanical Thrombectomy Centre A

From the identified treatment pathway in Chapter 5, a total of 816 patients passed along the treatment pathway at Centre A between January 2015 and December 2018. These were patients treated with MT with or without IVT, MT alone and IVT-only. The different stages of the overall pathway for all categories of treatment were described in Chapter 5 (section 5.3.3.1).

6.3.1.1.2 Centre A: Resource use at different stages of the overall pathway

Different resources were used along each point of the treatment pathway. The details of all the resources used are described in Appendix 6.B.

6.3.1.1.2.1 Prehospital Notification

The paramedics were called out via an initial 999 emergency telephone call to the location of symptom onset, usually at the patient's home for initial assessment and transportation. The paramedics then pre-alerted the Stroke Nurse (Band 6), who in turn, informed the Stroke Consultant and ED. For patients referred from other hospitals, a consultant-to-consultant referral was made.

6.3.1.1.2.2 Transport to Hospital

Land ambulances which fall under the category of 'Red type 2', meaning response within eight minutes, transported all patients - both local and referred - from other hospitals to Centre A. There were usually two paramedics present during the transport and no medical escort was generally required for inter-hospital transfers, except for unstable or intubated patients. The referred patients

from non-MT centre (drip-and-ship) were transported twice: ambulance transfer to primary hospital and transfer from primary hospital to Centre A.

6.3.1.1.2.3 Arrival at Emergency Department

The Emergency Department (ED) was the first point of entry for all patients joining the treatment pathway, except for inpatient stroke cases. The Stroke Team was pre-alerted about any potential thrombolysis patient by the Ambulance Team before arrival at ED. The referred patient came via ED to be registered then reviewed by the Stroke Team, usually the Stroke Nurse and Stroke Consultant. After 8 pm, the initial assessment was performed only by the Stroke Nurse with support from the ED Team. Referred patients also had to present to ED for registration and initial quick assessment. The resources used were the same for all patients admitted to ED, which included: registration, initial assessment; routine blood investigations and an electrocardiogram.

6. 3.1.1.2.4 Radiology Department

All patients had a Non-contrast CT, the majority had additional CT angiography (CTA) and those with unknown time of onset got an additional CT perfusion scan. The scans were performed by one radiographer (Band 7). Images were reported initially by the Radiology SpR and later by the Stroke Consultant Radiologist for patients having IVT only. The Consultant Radiologist reviewed all scans for patients undergoing MT before the procedure.

6.3.1.1.2.5 Treatment Regimen

The therapy was determined by the treatment protocol/guidelines based on the criteria for treatment.

6.3.1.1.2.5 (I): Intravenous Thrombolysis

Intravenous thrombolysis using alteplase was provided to all eligible patients before MT and patients referred from other hospitals were thrombolysed if eligible, before being transferred to Centre A for MT. The Stroke Consultant assessed and authorised all thrombolysis between 8 am to 8 pm and the Stroke Nurse administered the alteplase in ED. Out of hours, the Stroke Nurse assessed the patient with the help of the ED consultant and thrombolysis was authorised by the Stroke Consultant by telephone.

6.3.1.1.2.5 (II): Mechanical thrombectomy in the Interventional Radiology Suite

All thrombectomy procedures were performed in the IRS using existing infrastructure. Within working hours (9 am to 8 pm) the Interventional Team consisted of more staff (two band 7 radiographers and two scrub nurses, band 5 and 6), while out of hours (between 8 pm and 9 am), the Interventional Team consisted of only one band 6 Scrub Nurse and one band 7 Radiographer. The anaesthetic team consisted of a consultant anaesthetist and one band 6 Operational Dependent Practitioner or Assistant (ODP/ODA).

The procedure was usually performed by one INR and the Stroke Consultant was usually in attendance at the IRS workstation. The intervention was performed under GA, LA or CS. Different devices were used depending on the location of the occlusion and presence or absence of carotid occlusion.

6.3.1.1.2.6 Post Intervention Care

Post-thrombectomy, patients were transferred to the Recovery Area outside the IRS where they were monitored. While in recovery, they were monitored by the Recovery Nurse (band 5) and OPD/ODA for about one hour. They were also reviewed by the Consultant Anaesthetist and Stroke Consultant before being transferred to the Stroke Unit or ICU/HDU if unstable.

6.3.1.1.2.7 Intensive Care Unit/Hyper Dependency Unit (ICU/HDU)

Post-thrombectomy, all unstable patients were transferred directly to ICU/HDU. The rest were moved first to the Recovery Area and if unstable after one hour, were then transferred to ICU/HDU.

6.3.1.1.2.8 Transfer to the Hyperacute Stroke Unit (HASU)

All patients went to HASU either from the Recovery Area or ICU/HDU. All patients had a 24-hour CT head scan, while a small proportion had an MRI head scan. Additional routine blood tests were performed when needed. This is in addition to a review by the Stroke Consultant and other multidisciplinary team.

6.3.1.1.2.9 Discharge

Patients referred from other hospitals were repatriated to their primary hospital using land ambulance. The repatriated patients were without paramedic escort because they were stable. Transport to a community hospital or a care home was by a different transport service and discharge home was by hospital taxis or by private family cars.

6.3.1.1.3 Centre A: unit costs of resources used at different stages of the overall pathway

Whereas the staff costs per hour were obtained from the Personnel Social Services Research Unit (PSSRU)/ (Curtis and Burns, 2017), the estimated staff time spent during the procedure was based on published literature (Lobotesis et al., 2016) and from expert opinion from the radiographers, INRs and stroke consultants /nurses (Appendix 6.A). Other unit costs were centre-specific. The references for all unit costs used are summarised in Appendix 6.C.

6.3.1.1.3.1 Prehospital Notification

The unit cost for the emergency 999 telephone call was £7 per call. The cost covers the emergency and urgent calls presented to the switchboard, answered calls and all administration relating to the call. Patients rarely recognise the import of their symptoms at onset and self-refer to ED. For secondary hospital transfers, it was always a consultant-to-consultant referral, usually after prehospital notification and transfers to the non-MT centre. Consultant to consultant telephone referral of potential cases was estimated at £6 per call at a rate of 2p/min for a duration of 15-30 minutes.

6.3.1.1.3.2 Transport to Hospital

The ambulance unit cost per incident was £205 (to see, treat and transfer), which also covers staff costs. This was based on the regional Ambulance Service NHS Foundation Trust and applied to both transfer from home and for secondary transfer from referring hospitals.

Referred patients incurred two costs of transportation: the cost for ambulance transfer to the primary hospital and transfer from the primary hospital to Centre A. The transport cost is similar for both IVT and MT treated patients, but patients referred for MT were transported first to their primary stroke centre before the transfer to MT Centre A.

6.3.1.1.3.3 Arrival at Emergency Department

The Emergency Department attendance unit cost of £322, covers the cost of registration, routine blood investigations and all supportive care provided in ED, excluding the cost of imaging and Stroke Team attendance. The ED attendance unit cost for referred patients was £299. The Stroke Nurse and Consultant attendances were costed for one hour for the initial assessment, investigations and treatment plan. The unit costs were £58 and £140 per hour respectively. The Stroke Consultant may not necessary be in ED for the initial assessment before imaging or thrombolysis, particularly out of hours (8 pm-8 am).

6.3.1.1.3.4 Radiology Department

The unit costs of imaging were £71.60 for CT, £85 for CTA and £133 for CTP. All patients had a combined CT and CTA; a minority with unknown time of onset had CT perfusion. The tariff includes the cost of reporting by a diagnostic consultant radiologist. Referred patients could incur two costs for an initial scan at the primary hospital and repeat scans at Centre A. The transfer of CT/CTA images via a picture archiving and communication system (PACS) from referring centres to MT centre was costed at £0.6 per image transfer.

6.3.1.1.3.5 Treatment Regimen

The unit cost was based on treatment received:

6.3.1.1.3.5(I): Intravenous Thrombolysis

The unit cost for alteplase was £578 and the tariff of £1,671 for IVT only.

6.3.1.1.3.5 (II): Mechanical thrombectomy in the Interventional Radiology Suite

A unit cost of £6.75/min was applied to the use of IRS, based on the unit cost for the use of theatre. It was estimated that the IRS would be out of use for other procedures for approximately two hours, hence it was costed for two hours per case. For the Anaesthetic Team, the unit cost for the Anaesthetist Consultant was £157/hour and £58/hour for the OPD/ ODA and both were costed for three hours. The Scrub Nurses were costed for three hours at unit cost of £58/hour for band 7 and £49/hour for band 5. The Radiographers were costed for two hours at £58/hour. The unit cost for both the INR and the Stroke Consultant are £140/hour, but the INR was costed for three hours and the Stroke Consultant for four hours. The unit cost for GA was £3.79/min and £2.79/min for CS, both were costed for one hour. The unit cost for local anaesthesia was £27.06 per case. Different devices were used depending on the location of the occlusion and presence or absence of carotid occlusion.

6.3.1.1.3.6 Post Intervention Care

A unit cost of £1.51/min was applied for stays in the Recovery Area for a maximum of one hour based on expert opinion. This is in addition to the unit cost for Recovery Nurse and OPD at £58 per hour, also costed for one hour.

6.3.1.1.3.7 Intensive Care Unit/Hyper Dependency Unit (ICU/HDU)

The unit cost for ICU/HDU was £1,420 per day, based on the number of organ systems being supported. The costs included: the medical and nursing staff on the unit, other investigations and overheads. The total cost per patient depends on the length of stay on the unit.

6.3.1.1.3.8 Transfer to Hyper acute Stroke Unit

The cost of a stay on HASU was calculated as £480 per day for the first 48 hours and after that £300 per day. The cost for HASU includes ward-based nursing, allied staff and administrative staff. It also covers the cost of routine ward-based investigations and consumables. Included in the costs are medical staffing and visits from other allied health professionals. Additionally, the costs for other members of the Stroke Team on the Stroke Unit such as Speech and Language Therapy, Physiotherapy, Occupational Therapy and Dieticians, were each based on an hourly rate. The 24-hour post treatment scan, usually a CT, was costed at £71 per scan.

6.3.1.1.3.9 Discharge

The unit cost of transportation for patients repatriated without paramedic escort was £115, and £140 for repatriation with paramedic escort. Transport to a community hospital, a care home or discharge to home was by hospital taxis or by relatives.

6.3.1.2 Mechanical Thrombectomy Centres A to E

Details of the resources used along each point of the treatment pathway, as set out above for Centre A, are described for other MT centres in Appendix 6.D (1-4), and the unit costs of resources used at different stages of the overall pathway for each centre are given in Appendix 6.E (1-4). Differences in the resources used along the treatment pathways by different MT centres are shown in Tables 6.1, while Table 6.2 illustrates variations in unit costs across the different MT centres. Unit costs which are nationally derived, and therefore applied across all MT centres in these analyses, are given in Table 6.3. A comparison of the cost of devices as quoted by the MT centres included in this analysis and the costs used by NICE are given in Appendix 6F.

Table 6.1. Resources used along the treatment pathways: centres A to E

Item(s)	Centre A	Centre B	Centre C	Centre D	Centre E1/E2
Transport	Land ambulance No escort	Land ambulance Nurse or doctor escort for referred patients	Land ambulance and limited Helicopter No escort	Land ambulance No escort	Land ambulance with escort during secondary transfer from Centre E1 to Centre E2
Emergency Hospital Attendance (EHA)	ED (Local and transferred patients) Staff • Stroke Nurse • Stroke Consultant/Neurology	ED (local patients) Staff • Stroke Nurse • Stroke SHO (FY2/CT1-2) • Stroke SpR • Stroke Consultant/Neurology Radiology department (transferred patients) Staff • Stroke Nurse • Stroke SHO (FY2/CT1-2) • Stroke SpR • Stroke Consultant/Neurology •	ED (local patients) Staff • Stroke Nurse • Stroke SpR • Stroke Consultant/Neurology Radiology department (transferred patients) Staff • Stroke Nurse (Band 6) • Stroke SpR • Stroke Consultant	Stroke Unit (Local and transferred patients Staff • Stroke Nurse • Stroke SHO (FY2/CT1-2) • Stroke SpR • Stroke Consultant	ED (local patients and direct transfers before repatriation) Staff • Stroke Nurse • Stroke SpR • Stroke Consultant/ • Neurology Radiology department Staff • Stroke Nurse (Band 6) • Stroke SpR • Stroke Consultant Radiology department at Centre E2 (All patients from Centre E1 and secondary transfers from other hospitals)
Imaging	Pre-intervention • CT • CTA • CTP All patients had both CT and CTA with additional CTP when time of onset unknown. Majority of referred patients had additional CTP. Post-intervention 24-hour post intervention CT Scan	Pre-intervention • CT • CTA • CTP All patients had CT and CTA and CTP when time of onset unknown. Majority of referred patients had repeat CT/CTA and additional CTP. Post-intervention • 24-hour post intervention CT scan	Pre-intervention • CT • CTA All patients had CT and CTA. Referred patients only had repeat scan if they arrived one hour after initial scan at the primary Hospital. Post-intervention • Immediate post intervention CT • 24-hour post intervention CT All patients had an immediate post intervention CT in addition to a 24-hr CT scan.	Pre-intervention • CT • CTA • CTP All patients had CT and CTA, and CTP for unknown time of onset. Referred patients only had repeat scan if they arrived one hour after initial scan at the primary Hospital. Post-intervention • 24-hour post intervention CT • 24-hour post intervention MRI All Patients had a 24-hr CT or MRI scan.	Pre-intervention • CT • CTA All patients had CT and CTA. Post-intervention • 24-hour post intervention CT • 72-hour MRI scan

Item(s)	Centre A	Centre B	Centre C	Centre D	Centre E1/E2
Intervention	Venue • Interventional Radiology suite (IRS). Staff Anaesthetic team: • Anaesthetic Practitioner or Assistant (ODP/ODA). Interventionist All procedures performed by INR.	Venue • Interventional Radiology suite (IRS). Staff Anaesthetic team: • Anaesthetic Nurse Practitioner (ANP)/Scrub Nurse (SN) was used instead of Practitioner or Assistant (ODP/ODA). Interventionist • All procedures performed by INR.	Venue Interventional Neuroradiology Radiology suite (IRS). Interventionist • Procedures performed mainly by INR. Occasionally by interventional Radiology (IR)	Venue • Theatre. Anaesthetic team: • Anaesthetic Practitioner or Assistant (ODP/ODA). Interventionist • All procedures performed by INR.	Venue • Interventional Radiology suite (IRS). Staff Anaesthetic team: • Anaesthetic Practitioner or Assistant (ODP/ODA). Interventionist All procedures performed by INR.
Anaesthesia	Predominately GA	Predominately LA	Predominately LA	Predominately LA	Predominately GA
Devices	Mixture of devices.	Predominantly stent retrievers.	Predominately ThromboAspirators.	Mixture of devices, but fewer stent retrievers.	Mixture of devices.
Recovery Area/ ICU/HDU.	All patients are observed in Recovery for about an hour, and once stable they are moved to the stroke, if not stable in few cases to ICU/HDU.	After MT, patients are transfer straight to the Stroke Unit, if unstable, then to ICU/HDU.	All patients are observed in Recovery for about an hour, and once stable they are moved to the stroke, if not stable in few cases to ICU/HDU.	All patients are observed in Recovery for about an hour and once stable they are moved to the stroke, if not stable in few cases to ICU/HDU.	All patients are moved to ICU/HDU.
Repatriation	Usually within 24-48 hours when stable.	When stable and a bed available at referring centre.	When stable and a bed available at referring centre.	Usually up to 72 hours when stable.	When stable and a bed available at referring centre.
Community Hospital	Local patients with rehab potential are transferred to a dedicated stroke rehabilitation unit.	No community rehabilitation beds. All rehabilitation on the Stroke Unit.	Local patients with rehab potential are transferred to s dedicated stroke rehabilitation unit.	Local patients with rehab potential are transferred to a dedicated stroke rehabilitation unit.	Local patients with rehab potential are transferred to s dedicated stroke rehabilitation unit. Direct transfers for repatriation are repatriated to their primary hospital.

Table 6.2. Unit costs specific to five different MT centres

Items	Centre A	Centre B	Centre C	Centre D	Centre E1/E2
Transport	Land ambulance: £204.77	Land ambulance: £210 Medical Escort: £58	Land ambulance: £204.77 Helicopter: £2500	Land ambulance: £196	Land ambulance: £291.84 Medical Escort: £58
EHA	ED: £328	ED: £152	ED: £165	Stroke Unit: 273.36 ED £299	ED: £328
Imaging	NCCT: £71.60 CTA: £85 CTP: £133	NCCT: £100 CTA: £150 CTP: £250	NCCT: £81.28 CTA: £ 93.78 CTP: £120.39 MRI: £342:14	NCCT: £87.24 CTA: £100 CTP: £133 MRI: £140.86	NCCT: 91 CTA: £105 CTP: £136 MRI: £136
Devices$ Casper stent	Mixture of devices. SR: £3,200 TA: £1,340 DAC: £595 800	Predominantly stent retrievers. SR: £3,144.75 DAC:£640 800	Predominately Thrombo-Aspirators. SR: £3,720* TA: £1,608 DAC: £780 954	Mixture of devices, but fewer stent retrievers. SR: £3,100 TA: £1,340 DAC: £495 800	Predominately Thrombo-Aspirators. SR: £ 3,720* TA: £1,608* DAC: £834* 804
Stroke Unit	£480 (first 48hrs) 300/day post 48 hrs	£255/Day	£300/day	£269.57/day	£583/day
ICU/HDU	ICU/ HDU: 1,420	ICU: £2,282 HDU: £1,245	£1,420	ICU/ HDU: £1,331	£1,083 -1,420***
Repatriation	£115	£210	£115	£100	£90 - 237^^
Follow-up	£129	£265	£129	£149.14	£235

*Including VAT, ^^ Based on distance. *** cost dependent on number of organs supported, ^^ Cost per distance and type of transport based on degree of disability, $ Cost in Appendix 6

Table 6.3. Unit costs applied across all MT centres (A to E)

Item	Unit Cost (£)	unit	Total Cost	References
ED attendance^				
Stroke Nurse Band 6	58	1		Personal Social Services Research Unit (PSSRU).
Stroke Consultant	140	1		Personal Social Services Research Unit (PSSRU) [Medical Consultant).
Stroke SpR	60	1		Personal Social Services Research Unit (PSSRU).
Imaging				
Staff: Radiographer	58	1-2		Personal Social Services Research Unit (PSSRU)
Transfer of images PACS/CRIS	0.6	1		Expert clinical opinion*
Treatment				
Intravenous thrombolysis	576	1	576	British National Formulary
Mechanical thrombectomy				
Interventional Radiology Suite	450 (6.75/min x60 min)	2		Expert clinical opinion (Based on cost of theatre).
Consultant Anaesthetist	157	2		Expert clinical opinion.
Operational Dependent Practitioner or Assistant (ODP/ODA) Band 6	58	3		Personal Social Services Research Unit (PSSRU).
Consultant Interventional Neuroradiology	140	3		Personal Social Services Research Unit (PSSRU) [Medical Consultant).
Scrub Nurses				
Band 6/7	58	3		Personal Social Services Research Unit (PSSRU).
Band 5	49	3		Personal Social Services Research Unit (PSSRU).
Radiographer (Band 6/7)	58			Personal Social Services Research Unit (PSSRU).
Post- procedure care Recovery Area	90.6	1		Expert clinical opinion
Nurse Band 6	58	1		Personal Social Services Research Unit
Nurse Band 5	49	1		Personal Social Services Research Unit
Stroke Team (up to 24 hours post -MT)				
Stroke Consultant	140	3		Personal Social Services Research Unit (PSSRU) [Medical Consultant).
Stroke Nurse	58	2		Personal Social Services Research Unit (PSSRU).
Stroke SpR	60	2		Personal Social Services Research Unit (PSSRU).

6.3.2 Individual Patient data (IPD)

Data on pathway, resource use and unit costs presented above was based on all patients treated at the five MT centres over a period of four years, and the observed probabilities of them using different types and quantities of resources at different points of the treatment pathway. The key difference between this section and the TPD is that the IPD allowed for detailed data extraction on parameters such as the individual length of stay and the exact type/number of devices used per intervention. Selection and characteristics of the patients for whom individual patient data were collected are given in Chapter 5. These were patients treated in both Mothership and Drip-and-Ship models between 2015 and 2018 and treated with thrombectomy with or without intravenous thrombolysis.

I now present data on the pathways and resource use of these patients, beginning, as in the previous section with MT Centre A followed by data from other centres and all centres.

6.3.2.1 Mechanical Thrombectomy Centre A

The different stages of the overall pathway are similar to those described for the TPD analysis as identified in Chapter 5. Data was collected on 68 individual patients treated with thrombectomy (MT +/- IVT and MT only).

6.3.2.1.1 The probability of patients going along the pathway via different routes.

6.3.2.1.1.1 Prehospital Notification

Before arrival at Centre A, 59% (38/68) patients were pre-hospital notifications by the Paramedics and 38% (26/68) referred from their primary hospital after initial transfer to the non-MT centre.

6.3. 2.1.1.2 Transport to Hospital

Among the 68 patients, 94% (64/68) patients were transported by Ambulance and 6% (4/68) were already inpatients. No patient was transported via other means or by helicopter.

6.3. 2.1.1.3 Arrival at Accident and Emergency Department (ED)

In total, 94% (64/68) of patients were attended to in ED upon arrival of whom, 59% (38/68) were local patients and 38% (26/68) were transferred from other hospitals in a Mothership and Drip-and-Ship pattern of care.

6.3. 2.1.1.4 Radiology Department

Along the Radiology route, 87% (59/68) of patients had combined CT/CTA brain scans and 25% (17/68) had an additional CTP scan. Among the 38% (26/68) external transferred patients, 24% (16/68) had repeated CT and CTA scans.

6.3. 2.1.1.5 Treatment Regimen

Along the treatment regimen route, all 100% (58/68) patients were treated with thrombectomy, of whom 71% (48/68) had both IVT with MT and 29% (20/68) had MT only. A large proportion of MT cases, 69% (47/68) of the total, were performed with GA, 13% (9/68) with LA and 18% (12/68) with CS.

6.3.2.1.1.6 Post Intervention Care

Immediately post-thrombectomy, 82% (56/68) patients were transferred to the Recovery Area. All the patients transferred to the Recovery Area were subsequently transferred to HASU.

6.3.2.1.1.7 Intensive Care Unit/Hyper Dependency Unit (ICU/HDU)

Post-MT, 18% of patient (12/68) were directly transferred to ICU/HDU from the IRS and subsequently, 16% (11/68) were discharged to HASU.

6.3.2.1.1.8 Transfer to the Stroke Unit

Along the HASU route, a total of 99% (67/68) were finally transferred to HASU.-All 100% (68/68) of patients had a repeat scan, and none of the transferred patients were repatriated to their primary hospitals before the repeat 24-hour post MT scan.

6.3.2.1.1.9 Discharge

Finally, along the discharge route, 35% (24/68) of patients were repatriated to the referring primary hospitals; 27% (18/68) were discharged directly to their homes from Centre A with or without input from Early Supported Discharge (ESD);

24% (16/68) transferred to a community hospital; 1% (1/68) were discharged to a care home and 13% (9/68) died in hospital (inpatient mortality).

6.3.2.1.2 The amount of resources used along the pathway

The identified resources were similar to those identified in section 6.3.1.1.2, but in addition more detailed information was collected for a total of 68 individual patients treated with thrombectomy (MT +/- IVT or MT only) at centre A. For example, the type and number of devices and consumables used per patient and length of stay were as shown in Table 6.4. Stent-retrievers (SR) were used predominantly in 77% of cases, with Thrombo-Aspirators (TA) and Direct Access Catheter (DAC) used equally in 65% of cases and Proximal Balloon Flow Arrest Guide Catheter (PBFC) in 16% of cases. Casper carotid stents were used during thrombectomy to obtain access in 18% of cases with carotid stenosis. The median age of patients was 72 years (range: 33 to 91 years); 39 (57%) patients were males and 29 (43%) were female. The median baseline NIHSS score on admission was 18 (range 7 to 35) and median 24-hour NIHSS was 12 (range 0 to 35). The median length of inpatient stay at the MT centre was 3 days (range 1 to 55 days).

6.3.2.1.3 The unit cost and cost of the used resources along the pathway.

The unit costs for the resources were similar to those collected for the TPD in section 6.3.1.3 and in Table 6.2. Additionally, collection of the number of devices and other consumables for individual patient allowed the actual total cost of the devices and consumables used per patient to be calculated.

6.3.2.2 Mechanical Thrombectomy Centres A to E and all Centres

Individual patient data were collected on a total of 310 patients from all centres treated with thrombectomy with or without IVT. The median age of patients was 72 years (range: 23 to 101 years) and 161 (52%) were male. The median baseline NIHSS score on admission was 17 (range 3 to 35) and median 24-hour NIHSS was 9 (range 0 to 35). The median length of inpatient stay at the MT centre was 6 days (range 1 to 103 days) and for repatriated patients for inpatient stay at MT centres, 4 days (range 1 to 72 days). Overall, TA was the predominately used device in 71.8% of the interventions followed by SR in 56.7% of cases; DAC in 43.2%; PBFC in 7% and Casper carotid stents in 8.7% of cases. The details for individual centres and for all patients are given in Table 6.4.

Table 6.4. Patient characteristics and quantity of resources used along the pathways for Centres A to E and all centres

Characteristics	Centre A	Centre B	Centre C	Centre D	Centre E	All (Centres) Patients
Number of patients	68	65	60	52	65	310
Age (median, IQR)	72 (33-91)	69 (25-101	71 (26-87)	72 (23-92)	76 (30-90	72 years (23 to 101)
Male [n(x%)]	39 (57%)	28 (43%)	33 (55%)	31 (60%)	30 (46%)	161 (52%)
Female [n(x%)]	29 (43%)	37 (57%)	27 (45%)	21 (40%)	35 (54%)	149 (48%)
Baseline NIHSS (median, IQR)	18 (7-35)	15 (3-32)	16 (4-34)	19 (7-30)	16 (5-32)	17(3 to 35)
24-hour NIHSS (median, IQR)	12 (0-35)	8 (0-27)	6 (0-34)	8 (0-28)	8 (0-35)	9 (0 to 35)
Pre-admission mRS (median, IQR)	0 (0-3)	0 (0-3)	0 (0-2)	1 (0-3)	0 (0-4)	0 (0 to 4)
Discharge mRS (median, IQR)	3 (0-6)	3 (0-6)	5 (0-6)	4 (0-6)	4 (2-6)	4 (0 to 6)
Length of inpatient stay at the MT (median, IQR)	3 (1-55)	4 (1-67)	5 (1-103)	6 (1-84)	8 (1-72)	5 (1 to 103)
Length of stay on ICU (median, IQR)	0 (0-29)	0 (0-7)	0 (0-14)	0 (0-4)	2 (0-23)	2 (0 to 29)
Devices (type/ number)						
Stent-retrievers ([n(x%)]	53 (77%)	59 (91%)	16 (27%)	16 (31%)	30 (46%)	174 (56.7%)
Thrombo-Aspirators [n(x%)]	44 (65%)	21(32%)	50 (83%)	44 (85%)	60 (92%)	219 (71.8%)
Proximal Balloon Flow Arrest Guide Catheter [n(x%)]	11 (16%)	3 (5%)	0 (0%)	3 (6%)	6 (9%)	23 (7.%)
Direct Access Catheter [n(x%)]	44 (65%)	14 (22%)	4 (6.7%)	25 (48%)	43 (66%)	130 (43.2%)
Carotid Stent [n(x%)]	12 (18%)	4 (6%)	5 (8%)	3 (6%)	3 (5%)	27 (8.7%)
Type of Anaesthesia						
Local anaesthesia [n(x%)]	9 (13%)	63 (97%)	22 (37%)	20 (38%)	24 (37%)	138 (45%)
General Anaesthesia [n(x%)]	47 (69%)	2 (3%)	29 (48%)	16 (31%)	40 (62%)	134 (43%)
Conscious Sedation [n(x%)]	12 (18%	0 (0%)	9 (9%)	16 (31%)	1 (1%)	38 (12%)

6.4 RESULTS

The results are presented for two analyses: firstly, for the TPD analysis (top-down approach) and secondly, for the IPD analysis (bottom-up approach). The TPD analysis will be presented first, in summary form for all centres, with the full results recorded in Appendix 6.G. Then the IPD costs will be presented in similar order. Finally, the results of the TPD analysis and the IPD analysis will be compared.

6.4.1 Total Patient Data Costing

The average cost per patient in the top-down analysis was calculated using information on the probability of patients going down the different routes of the overall clinical pathway, the number of resources used and the unit cost for each component. The resulting total cost was then divided by the number of patients to derive an average. This was done for all patients and also for three sub-groups: patients treated with MT with or without IVT (MT +/- IVT), patients treated with thrombectomy only (MT only), and patients treated with IVT only. Costs for this top-down analysis were captured for all patients treated, but only over the first 24 hours of the episode in all centres.

6.4.1.1 Total cost for all patients

A total of 2,646 patients across five MT centres were included in the top-down total cost analysis. Table 6.5 summarises data for each of the five centres and for all five combined. The total 24-hour cost for all 2,646 patients who passed through the various treatment pathways across the five centres, including all those treated with MT +/- IVT, MT only and IVT only, was £14,959,207, giving an average cost

per patient of £5,654. This varied from £3,944 in Centre D to £7,181 in Centre B. The total cost of devices (£4,688,932) accounted for 66% of the total procedure cost of £7,104,676.

Table 6.5. Total cost analysis: costs along the treatment pathway at Centres A to E and all centres, for all patients

Category of cost for Items (£)	Centre A	Centre B	Centre C	Centre D	Centre E1/E2	All (Centres) Patients
Number of patients	816	622	359	4444	405	2646
Pre-hospital Notification (Total cost)	£4,781	£3,024	£2,138	£2,226	£2,744	£14,910
Transportation (Total cost)	£158,492	£131,188	£70,031	£68,404	£143,382	£571,497
Emergency Hospital Attendance (Total cost)	£450,489	£275,890	£147,478	£225,231	£254,009	£1,353,097
Diagnostic Imaging (Total cost)	£248,876	£322,805	£103,011	£134,647	£126,860	£936,199
IVT-only (Total cost)	£865,578	£499, 629	£452,841	£614,928	£536,391	£2,969,367
MT Procedure (Total cost)	£2,374,961	£2,848,848	£688,527	£475,003	£717,337	£7,104,676
• Venue*	£241,380 (10%)	£261630 (9%)	£71,280 (10%)	£61,560 (13%)	£68,040 (10%)	£703,890
• Staffing*	£516,434 (22%)	£635987 (22%)	£173,624 (25%)	£131,708 (28%)	£145,572 (20%)	1,603,325
• MT Device*	£1,566,288 (66%)	£1,930,248 (68%)	£431,904 (63%)	£270,940 (57%)	£489,552 (68%)	£4,688,932
• Anaesthesia*	£50,859 (2%)	£20,983 (1%)	£11,719 (2%)	£10,795 (2%)	£14,173 (2%)	£108,529
MT+ IVT (Total cost)	£121,380	£71,094	£27,166	£28,322	£32,368	£280,330
Immediate Post-op Care (Total cost)	£114,727	£79,722	£48,991	£27,299	£33,986	£304,725
HDU/ICU stay (24hrs) (Total cost	£25,560	£17,430	£24,140	£19,965	£119,280	£206,375
Stroke unit Stay (24hrs) (Total cost)	£390,720	£155,040	£102,600	£115,646	£187,143	£951,149
Post -treatment scan (Total cost)	£57,013	£62,200	£71,542	£39,271	£36,855	£266,881
Overall Total 24hrs cost	£4,812,577	£4,466,870	£1,738,463	£1,750,942	£2,190,355	£14,959,206
Average 24hrs cost per patient	£5,898	£7,181	£4,843	£3,944	£5,408	£5,654

* (% of total costs of MT procedure),

6.4.1.2 Total cost for patients treated with MT +/- IVT

Across all 5 centres, 869 patients (33%) were treated with MT +/- IVT, at a total cost of £9,326,873 and an average cost of £10,733 per patient. Costs of the thrombectomy procedure, which include the costs of the venue, staffing, anaesthesia, devices and consumables, accounted for £7,104,675 (76%) of the total costs, with devices contributing 66% (£4,688,932) of these procedure costs. The different components of these costs for each centre and all centres combined are summarised in Table 6.6.

6.4.1.3 Total cost for patients treated with MT only

Across all 5 centres, 384 patients (15%) were treated with MT only, at a total combined cost for all the five centres combined of £4,300,290 and an average cost of £11,199. The different components of these costs for each centre and all centres combined are summarised in Table 6.7.

Table 6.6. Total cost analysis: costs along the treatment pathway at Centres A to E and all centres, for patients receiving MT +/- IVT

Category of cost for Items (£)	Centre A	Centre B	Centre C	Centre D	Centre E1/E2	All (Centres) Patients
Number of Patients	298	323	88	76	84	869
Pre-hospital Notification (Total cost)	£1,386	£2,149	£329	£231	£553	£4,648
Transportation (Total cost)	£59,179	£74,068	£17,201	£12,544	£52,036	£215,028
Emergency Hospital Attendance (Total cost)	£195,689	£134,716	£38,344	£51,575	£54.315	£474,639
Diagnostic Imaging (Total cost)	£106,944	£212,773	£23,592	£22,319	£27,322	£392,950
MT Procedure (Total cost)	£2,374,961	£2,848,848	£688,527	£475,002	£717,337	£7,104,675
• Venue*	£241,380 (10%)	£26,1630 (9%)	£71,280 (10%)	£61,560 (13%)	£68,040 (10%)	£703,890 (10%)
• Staffing*	£516,434 (22%)	£635,987 (22%)	£173,624 (25%)	£131,708 (28%)	£145,572 (20%)	£1,603,325 (23%)
• MT Device* (^^)	£1,566,288 (66%)	£1,930,248 (68%)	£431,904 (63%)	£270,940 (57%)	£489,552 (68%)	£4,688,932 (66%)
• Anaesthesia*	£50,859 (2%)	£20,982 (1%)	£11,719 (2%)	£10,795 (2%)	£14,173 (2%)	£108,529 (2%)
MT+ IVT with alteplase (Total cost)	£121,380	£71,094	£27,166	£28,322	£32,368	£280,330
Immediate Post-op Care (Total cost)	£114,727	£79,722	£48,991	£27,299	£33,986	£304,725
HDU/ICU stay(24hrs) (Total cost)	£25,560	£17,430	£24,140	£19,965	£119,280	£206,375
Stroke unit stay (24hrs) (Total cost)	£142,080	£78,795	£21300	£16,444	£27,984	£258,619
Post-treatment scan** (Total cost)	£20,235	£32,300	£17,537	£7,167	£7,644	£84,883
Overall Total 24hrs cost	£3,162,141	£3,551,895	£907,127	£660,869	£1,044,841	£9,326,873
Overall Average 24hrs cost per patient	£10,611	£10,997	£10,308	£8,696	£12,439	£10,733

* (% of total costs of MT procedure), ** 1%(11/816) repatriated before repeat scan, ^^ Rate variable, used value based on the mean cost from Individual patient data IPD)

Table 6.7. Total cost analysis: costs along the treatment pathway at Centres A to E and all centres, for patients receiving MT only

Category of cost for Items (£)	Centre A	Centre B	Centre C	Centre D	Centre E1/E2	All (Centres) Patients
Number of Patients	88	200	41	27	28	384
Pre-hospital notification (Total cost)	£357	£700	£175	£119	£182	£1533
Transportation (Total cost)	£18,020	£47,800	£8,396	£5,292	£16,684	£96,192
Emergency Hospital Attendance (Total cost)	£64,223	£86,200	£18,559	£20,635	£17,706	£207,323
Diagnostic Imaging (Total cost)	£41,055	£135,460	£11,065	£7,780	£8,793	£204,153
MT Procedure (Total cost)	£698,863	£1,765,148	£320,514	£168,853	£245,589	£3,202,999
• Venue*	£71,280 (10%)	£162,000 (9%)	£33,210 (10%)	£21,870 (13%)	£22,680 (9%)	£311,040 (10%)
• Staffing*	£152,504 (22%)	£393,800 (22%)	£80,893 (25%)	£46,791 (28%)	£55,020 (22%)	£729008 (23%)
• MT Device*	£462,528 (66%)	£1,195,200 (68%)	£201,228 (63%)	£96,255 (57%)	£163,184 (67%)	£2,118,395 (66%)
• Anaesthesia*	£12,551 (2%)	£14,148 (1%)	£5,183 (2%)	£3,937 (2%)	£4,705 (2%)	£40,524 (1%)
Immediate Post-op Care [Total cost (Average)]	£34,813	£41,796	£29,785	£7,681	£19,169	£133,244
HDU/ICU stay (24hrs) [Total cost (Average)]	£8,520	£11,205	£8,520	£5,324	£39,760	£73,329
Stroke unit Stay (24hrs) [Total cost (Average)]	£42,240	£48,705	£10,500	£6,200		£107,645
Post -treatment scan [Total cost (Average)]	£6,248	£20,000	£8,171	£2,516	£2,548	£39,483
Overall Total 24hrs cost	£914,339	£2,157,014	£415,685	£224,400	£350,431	£4,061,869
Average 24hrs cost (£) per patient	£10,390	£10,785	£10,144	£8,311	£12,515	£10,578

* (% of total costs of MT procedure), ^^ Rate variable, used value based on the mean cost from Individual patient data IPD)

6.4.1.4 Total cost for patients treated with IVT only

A total of 1,777 patients (67%) were treated with IVT only, at a total cost across all five centres combined of £5,632,334 and an average cost of £3,170. None of the IVT treated patients was admitted to HDU/ICU. The different components of these costs for each centre and all centres combined are summarised in Table 6.8.

Table 6 8. Total cost analysis: costs along the treatment pathway at Centres A to E and all centres, for patients receiving IVT only

Category of cost for Items (£)	Centre A	Centre B	Centre C	Centre D	Centre E1/E2	All (Centres) Patients
Number of Patients	518	299	271	368	321	1777
Pre-hospital Notification [Total cost (Average)]	£3,395	£875	£1,806	£1,995	£2,191	£10,262
Transportation [Total cost (Average)]	£99,313	£57,120	£52,831	£55,860	£91,346	£356,470
Emergency Hospital Attendance [Total cost (Average)]	£254,800	£141,174	£109,134	£173,656	£199,694	£878,458
Diagnostic Imaging [Total cost (Average)]	£141,932	£110,032	£79,419	£112,328	£99,538	£543,249
IVT-only	£865,578	£499,629	£452,841	£614,928	£536,391	£2,969,367
MT Procedure [Total cost (Average)]	-	-	-	-	-	-
• Venue						
• Staffing*						
• MT Device						
• Anaesthesia						
MT+ IVT	-	-	-	-	-	-
Immediate Post-op Care	-	-	-	-	-	-
HDU/ICU stay (24hrs) [Total cost (Average)]	-	-	-	-	-	-
Stroke unit Stay (24hrs)	£248,640	£76,245	£81,300	£99,202	£187,143	£692,530
Post -treatment scan [Total cost (Average)]	£36,778	£29,900	£54,005	£32,104	£29,211	£181,998
Total 24hrs cost	£1,650,436	£914,975	£831,336	£1,090,073	£1,145,514	£5,632,334
Average 24hrs cost per patient	£3,186	£3,060	£3,068	£2,962	£3,569	£3,170

6.4.1.5 Differences in costs across all five centres

Substantial variation was found in the distribution of costs across different cost categories and in the average cost per patient for different categories. For example, HDU/ICU stay costs over the first 24 hours for the MT +/- IVT patients varied from 0.5% of the total costs to over 5%, and average costs per patient varied from £3,944 in Centre D to £7,182 in Centre B. Similarly, the cost of devices varied from 57% for Centre D to 68% for Centre B (Table 6.6). The higher cost of devices for Centre B was due to the predominate use of SR in 91% of cases compared to other centres where the use of SR was between 31% and 77% (Table 6.4). The percentage of the total costs for the MT +/- IVT also varied from 38% for Centre D to 66% for Centre A, and for MT only, from 13% for centre D to 48% for Centre B (Table 6.9).

Many of these differences reflect differences between centres in the proportion of patients treated with either MT +/- IVT, MT alone or IVT only. Centre B, for example, had a greater proportion of patients (52%) treated with MT than IVT when compared with other centres (Table 6.6). Additionally, more patients (32%) were treated with MT alone than MT + IVT when compared with other centres (Table 6.7). Related to these variations, the proportion of total costs attributable to patients treated with either MT +/- IVT, MT alone or IVT only, also varied as shown in Table 6.9 and Figure 6.1. Finally, the average cost per centre by MT+IVT, MT alone and IVT only, are shown in Table 6.9, Figures 6.2 and 6.3. Most centres were close to the average for each sub-category of patients, with Centres D and E showing more variation from the average than other centres.

Table 6.9. Total cost and average cost per centre by MT+IVT, IVT only, and all patients

	Centre A (N =816)	Centre B (N=622)	Centre C (N=359)	Centre D (N =444)	Centre E (N=405)	All (Centres) Patients (N=2646)
MT +/- IVT						
Total cost (24 hours) % of total	£3,162,141 66	£3,551,895 80%	£907,127 52%	£660,869 38%	£1,044,841 48%	£9,327,921 62%
Average cost (24 hours) Ratio of average for all centres	£10,611 0.99	£10,997 1.02	£10,308 0.96	£8,696 *0.81	£12,439 1.16	£10,733 1.00
MT only						
Total cost (24 hours) % of total	£914,339 19%	£2,157,014 48%	£415,685 24%	£224,400 13%	£588,854 27%	£4,061,869 27%
Average cost (24 hours) Ratio of average for all centres	£10,390 0.98	£10,785 1.02	£10,139 0.96	£8,311 0.79	£12,515 1.18	£10,578 1.00
IVT only						
Total cost (24 hours) % of total	£1,650,436 34%	£914,975 20%	£831,336 48%	£1,090,073 62%	£1,145,514 52%	£5,632,334 38%
Average cost (24 hours) Ratio of average for all centres	£3,186 1.01	£3,060 0.97	£3,068 0.97	£2,962 0.93	£3,569 1.13	£3,170 1.00
All patients (MT +/- IVT, MT only and IVT only)						
Total cost (24 hours)	£4,812,577	£4,466,870	£1,738,463	£1,750,942	£2,190,355	£14,959,206
Average cost (24 hours) Ratio of average for all centres	£5,898 1.04	£7,181 1.27	£4,843 0.86	£3,944 0.70	£5,408 0.96	£5,654 1.00

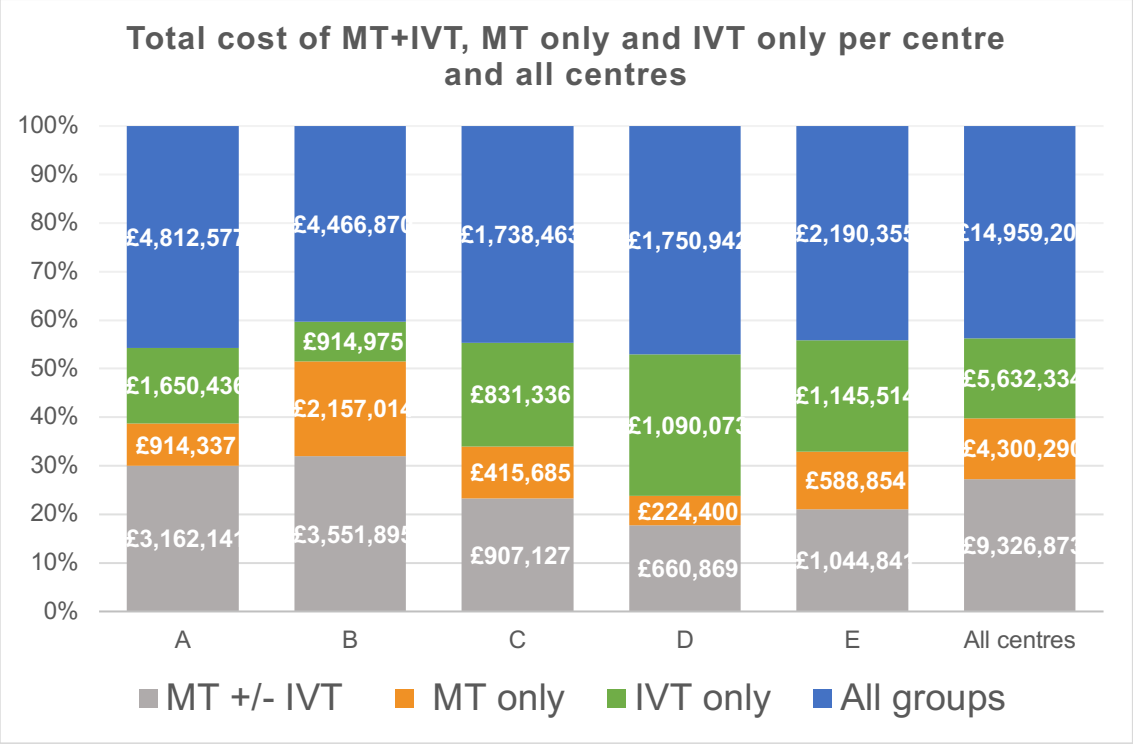


Figure 6.1. **Total cost of MT+IVT, MT only and IVT only**

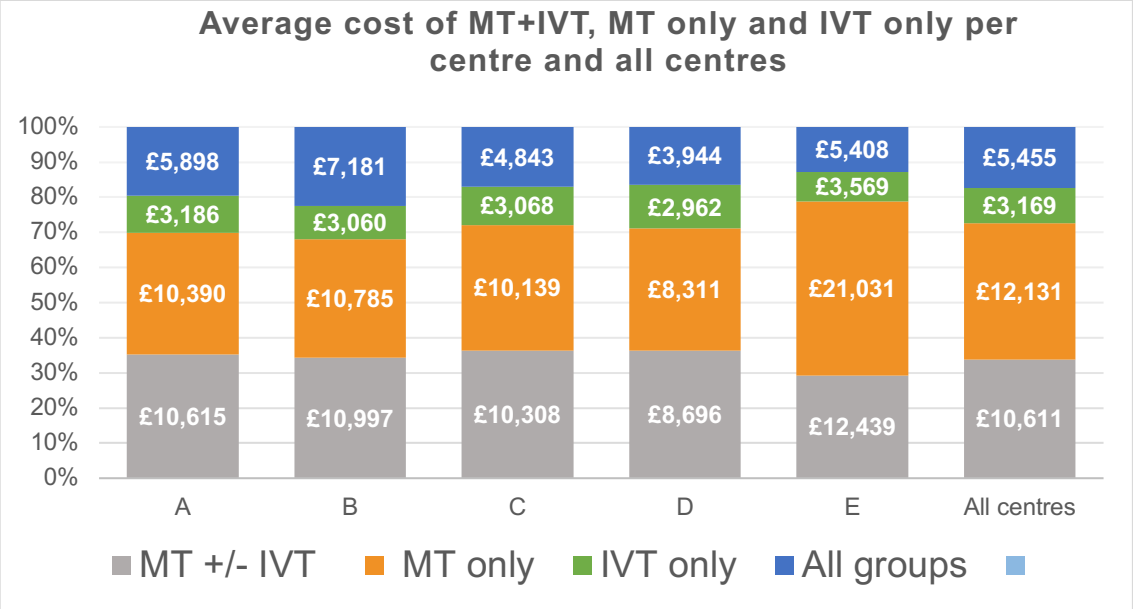


Figure 6.2 **Average cost of MT+IVT, IVT only**

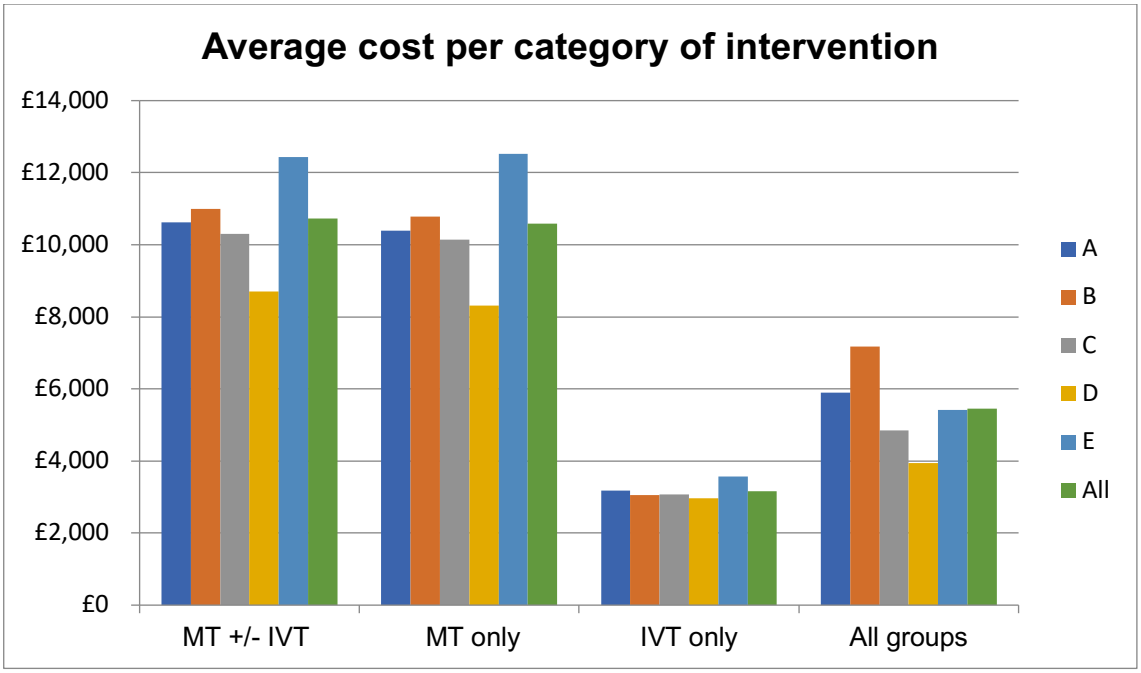


Figure 6.3. Average cost per category of intervention

6.4.2 Individual patient data (IPD) costing

The cost analysis presented above was based on all patients treated at the five MT centres. The TPD costing approach allowed a total cost to be calculated across all patients, and the average cost per patient was simply the total cost divided by the number of patients treated. While valuable in giving a clear estimate of the totality of costs in each hospital, this approach does not give detailed insight into the cost variability between patients treated with thrombectomy. To address that issue, individual patient data (IPD) were collected for a sample of 310 patients from the five hospitals studied. Using the IPD, variations related to factors such as the model of care can be analysed. In addition, the IPD analysis includes not only the costs of hospital care and stay up to 24 hours, but also costs incurred up to 72 hours, up to repatriation and up to discharge to different destinations from the MT centre.

Again, in this section I will start with the results for all patients, then, as the IPD did not collect data on patients treated only with IVT, costs will be presented for just two sub-categories: patients treated with MT with or without IVT (MT +/- IVT) and those treated with thrombectomy only (MT only).

6.4.2.1 All patients

Data were collected for a total of 310 individual patients treated with MT +/- IVT across 5 centres, of whom 114 were treated with MT only. Details of the costs for these two treatment groups in each centre and for all centres are summarised in Tables 6:10 and 6:11.

6.4.2.2 IPD costs for patients treated with MT +/- IVT

The mean cost within 24 hours of care per patient from the IPDA of the 310 patients treated with MT+IVT, was £10,866 (SD £2,801). Including all costs incurred after 24 hours until discharge, the mean cost per patient increased to £14,369 (SD £6,664). Across all centres, 73% of the 24-hour cost (£7,943/£10,866) and 55% of the costs to discharge (£7,943/£14,369) could be attributed to MT procedure costs, with 65% of these procedure costs involving device costs. Table 6.10 provides details for each centre and all centres combined.

6.4.2.3 IPD costs for patients treated with MT only

The mean cost within 24 hours of care per patient from the IPDA of the 114 patients treated with MT only was £10,706 (SD £2,801). Including all costs incurred after 24 hours until discharge, the mean cost per patient increased to £14,696 (SD £7,319). In this subgroup, across all centres, 76% of the 24-hour cost (£8,127/£10,706) and 55% of the costs to discharge (£8,127/£14,696) could be attributed to MT procedure costs, with 67% of these procedure costs involving device costs. Table 6.11 provides details for each centre and all centres combined.

Table 6.10. IPD cost analysis: costs along the treatment pathway at Centres A to E and all centres, for patients receiving MT +/- IVT

Category of cost	Centre A	Centre B	Centre C	Centre D	Centre E	All (Centres) Patients
Number of patients	68	65	60	52	65	310
Pre-hospital notification [Mean cost (SD)]	£6.70 (£1.45)	£6.14 (£2.3)	£ 6.53 (£1.76)	£6.33 (£2.08)	£6.89 (£0.87)	£6.43) (£1.76)
Transportation [Mean cost (SD)]	£310 (£160)	£417 (£244)	£400 (£394)	£280 (£144)	£677 (£75)	£422 (£268)
Emergency Hospital Attendance [Mean cost (SD)]	£609 (£137)	£463 (£37)	£503 (£98)	£644 (£131)	£611 (£84)	£564 (£124)
Diagnostic Imaging [Mean cost (SD)]	£283 (£70)	£650 (£189)	£369 (£77)	£293 (£34)	£350 (£68)	£393 (£173)
MT Procedure [Mean cost (SD)]	£8,244 (£2,256)	£7,958 (£2,275)	£7,966 (£2,644)	£6,262 (£1,749)	£8,937 (£3,261)	£7,943 (£2,630)
• MT Devices [Mean cost (SD)]	£5256 (£2,334)	£5,976 (£2,252)	£4908 (£2,614)	£3,564 (£1,760)	£5,828 (£3,263)	£5,176 (£2,614)
• Venue [Mean cost (SD)]	£810 (£0)	£810 (£0)	£810 (£0)	£810 (£0)	£810 (£0)	£810 (£0)
• Staffing [Mean cost (SD)]	£1,900 (£266)	£1,137 (£132)	£2,028 (£276)	£1,664 (£166)	£2,146 (£000)	£1,777 (£413)
• Anaesthesia [Mean cost (SD)]	£191 (£68)	£35 (£39)	£136 (£95)	£134 (£91)	£153 (£97)	£130 (£96)
• Post-MT Recovery [Mean cost (SD)]	£87 (£17)	£0 (00)	£84 (£23)	£90 (£0)	£0 (£0)	£50 (£45)
Post-op care [Mean cost (SD)]	£705 (£39)	£507 (£00)	£645 (£37)	£655 (£00)	£565 (£00)	£614 (£76)
HDU/ICU [Mean cost (SD)]	£439 (£1,576)	£140 (£553)	£1,980 (£5,082)	£410 (£1,104)	£4,761 (£3,654)	£1,576 (£3,408)
Hospital stay (24hrs) [Mean cost (SD)]	£1,111 (£256)	£990 (£464)	£1,100 (£561)	£980 (£422)	£1,994 (£857)	£1,247 (£672)
Total 24-hour costs [[Mean cost (SD)]	£10,961 (£2,225)	£10,749 (£2,347)	£10,670 (£2,854)	£8,864 (£1,727)	£12,949 (£3,246)	£10,866 (£2,801)
Until discharge from MT Centre [[Mean cost (SD)]	£13,919 (£7,330)	£13,247 (£5,814)	£14,691 (£7,642)	£11,087 (£4,245)	£18,896 (£5,047)	£14,369 (£6,664)

Table 6.11. IPD cost analysis: costs along the treatment pathway at Centres A to E and all centres, for patients receiving MT-only

Category of cost	Centre A	Centre B	Centre C	Centre D	Centre E	All (Centres) Patients
Number of patients	20	34	25	14	21	114
Pre-hospital notification	£6.30 (£2.16)	£6.18 (£2.3)	£ 6.44 (£1.9)	£5.50 (£2.98)	£6.67 (£1.53)	£6.26 (£2.19)
Transportation [Mean cost (SD)]	£238 (£142)	£417 (£244)	£354 (£185)	£232 (£142)	£642 (£78)	£390 (£229)
Emergency Hospital Attendance [Mean cost (SD)]	£529 (£116)	£458 (£37)	£502 (£122)	£605 (£157)	£643 (£10)	£531 (£124)
Diagnostic Imaging [Mean cost (SD)]	£289 (£71)	£637 (£186)	£398 (£98)	£286 (£23)	£344 (£69)	£428 (£187)
MT Procedure [Mean cost (SD)]	£8,408 (£2,019)	£8,135 (£2,391)	£8,375 (£2,781)	£5,833 (£1,033)	£9,073 (£2,977)	£8,127 (£2,557)
• MT Devices [Mean cost (SD)]	£5,450 (£2,168)	£6,166 (£2,383)	£5,337 (£2,688)	£3,105 (£1,029)	£5,947 (£2,970)	£5,442 (£2560)
• Staffing [Mean cost (SD)]	£1,896 (£341)	£1,122 (£115)	£1,996 (£310)	£1,693 (£89)	£2,146 (£0)	£1,711 (£457)
• Cost of anaesthesia [Mean cost (SD)]	£171 (£87)	£37 (£41)	£145 (£89)	£135 (£95)	£170 (£93)	£120 (£96)
• Venue [Mean cost (SD)]	£810 (£0)	£810 (£0)	£810 (£0)	£810 (£0)	£810 (£0)	£810 (£0)
• Post-MT Recovery [Mean cost (SD)]	£81 (£28)	£0 (£0)	£87 (£18)	£90 (£0)	£0 (£0)	£44 (£45)
Post-op care [Mean cost (SD)]	£696 (£55)	£507 (£00)	£649 (£30)	£655 (£00)	£565 (£00)	£600 (£77)
Hospital stay (24hrs) [Mean cost (SD)]	£1,077 (£200)	£1,043 (£551)	£1,185 (£619)	£1,004 (£452)	£1,797 (£203)	£1,214 (£537)
ICU/HDU Stay [Mean cost (SD)]	£355 (£1,575)	£140 (£657))	£2,442 (£5,264)	£285 (£567)	£4,041 (£4,151)	£1,484 (£3,462)
Total 24- hour cost [[Mean cost (SD)] MT- only	£10,605 (£1,950)	£10,761 (£2,491)	£10,843 (£3,042)	£7,965 (£1,089)	£12,656 (£3,208)	£10,706 (£2,801)
Until discharge from MT Centre [[Mean cost (SD)]	£12,798 (£1,384)	£14,127 (£5,815)	£16,810 (£1,238)	£9,297 (£2,295)	£19,108 (£4,090)	£14,696 (£7,319)

6.4.2.4 Differences in IPD costs across MT Centres

The mean 24-hour cost for MT +/- IVT treated patients varied widely between centres, ranging from £8,864 (SD £1,727) for Centre D to £12,949 (SD £3,246) for Centre E, with a significant mean difference of £4,085 (95% CI: to £3,080 to £5,087, p<0.001). Similarly, the mean total cost to discharge for the MT +/- IVT treated patients from each MT centre also varied from £11,087 (£4,245) in centre D to £18,896 (£5,047) for centre E with a mean difference of £7,809 (95% CI: to £6,033 to £9,595, p<0.001). Differences between centres in the costs of the MT procedure, 24-hour costs and total cost until discharge from MT centre for MT +/- IVT treated patients are, shown in Figure 6 .4. More detailed information for each centre is given in Appendix 6. H.

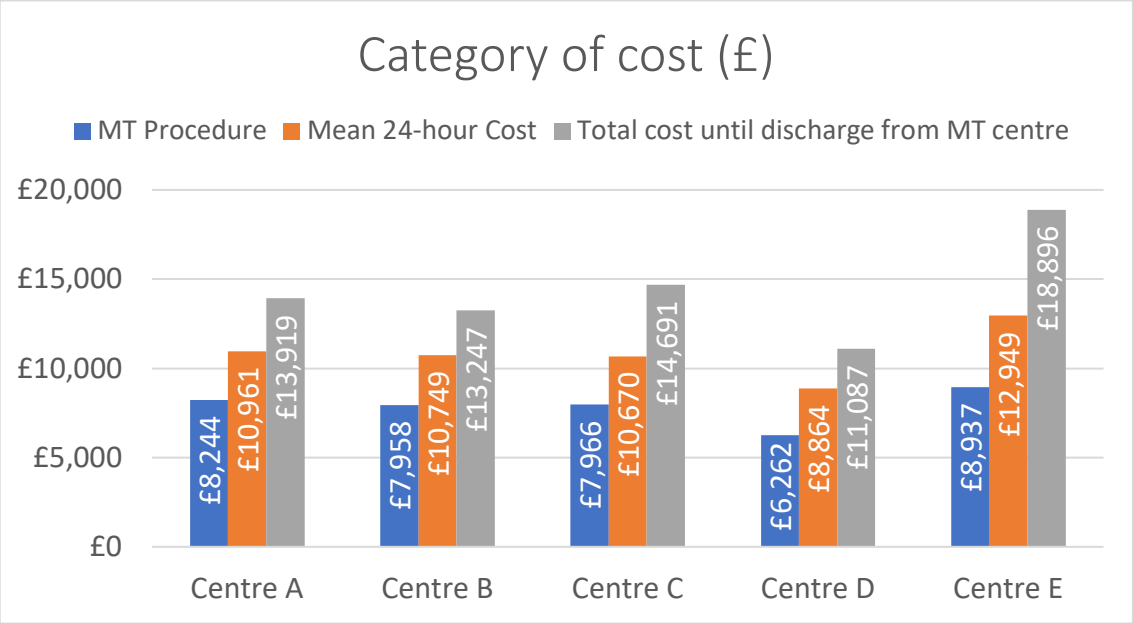


Figure 6.4. Differences in cost for MT+IVT across centres

6.4.2.5 IPD costs for different time horizons at all MT Centres

The mean total cost of providing MT +/- IVT and subsequent inpatient care over the first 24 hours for all 310 patients for whom individual patient data were collected across the five centres, was £10,866 (95% CI £10,547 to £11,185; subsequent inpatient care up to 72 hours was £12,447 (95% CI £10,635 to £14,259). The total cost up to final discharge to different destinations from the MT centres was £14,369, (95% CI £13,609 to £15,128). The components of costs are summarised in Table 6.12.

6.4.2.6 Drivers of cost

The main cost driver for patients treated with MT +/- IVT was the procedure cost, which accounted for 73% [(£7,943 (£2,631), 95% CI £7,649 to £8,237)] of the cost. Table 6.13 shows some key factors that appear to strongly influence cost, for all the 310 patients treated with MT +/- IVT from the five centres combined, including: whether or not patients had local or general anaesthesia; whether stenting or angioplasty was used during thrombectomy; and whether they were admitted to ICU/HDU. There were statistically significant differences between the costs of patient treated with GA compared with LA with a mean difference of £1,229, those needing carotid stenting during thrombectomy with a mean difference of £1,768. The cost was higher for admission to ICU/HDU for more than 24 hours, with a mean difference of £7,556. The median length of stay on ICU/HDU was two days (range 0 to 29 days). Patients treated under GA were more likely to be admitted to ICU/HDU than those treated with LA.

Table 6.12. IPD cost analysis: costs along the treatment pathway for all patients

Item (description of each component)	Costs	(SD)	95% CI
Pre-hospital notification [Mean cost (SD)]	£6.53	£1.76	£6.33 to £6.72
Transportation [Mean cost (SD)]	£422	£268	£392 to £452
Emergency Hospital Attendance [Mean cost (SD)]	£564	£124	£550 to £577
Imaging costs [Mean cost (SD)]	£393	£173	£374 to £413
Thrombectomy procedure	£7,943	£2,631	£7,649 to £8,237
• Thrombectomy Devices [Mean cost (SD)]	£5,176	£2,614	£4,884 to £5,468
• Staffing [Mean cost (SD)]	£1,777	£413	£1,731 to £1,823
• Anaesthesia [Mean cost (SD)]	£130	£96	£119 to £141
• Venue [Mean cost (SD)]	£810	£0	£810 to £810
• Post-MT Recovery Area [Mean cost (SD)]	£50	£45	£45 to £55
Post-op Care [Mean cost (SD)]	£614	£76	£ 606 to £623
ICU/HDU [Mean cost (SD)]	£1,576	£3,408	£1,195 to £1,957
Hospital stay (24hrs) [Mean cost (SD)]	£1,247	£672	£1,172 to £1,322
Total costs +IVT (Hospital stay 24 [Mean cost (SD)]	£10,866	£2,800	£10,547 to £11,185
Total costs (up to 72 HOURS) [Mean cost (SD)]	£12,447	£5,275	£10,635 to £14,259
Total costs (up to repatriation) [Mean cost (SD)]	£11,758	£3,285	£10,402 to £13,114
Hospital stay (Discharge Home from MT) [Mean cost (SD)]	£13,436	£3,490	£11,848 to £15,025
Total cost until discharge from MT Centre to different destinations [Mean cost (SD)]	£14,369	£6,664	£13,609 to £15,128

Table 6.13. Drivers of cost for all MT centres

Drivers of Cost within 24 hours				
	Cost (SD)	**Mean difference**	**95% CI**	**P value**
Anaesthesia				
Local anaesthesia (LA) (n=138) General anaesthesia (GA) (n=134)	£10,344 (£2,743) £11,572 (£2,812)	£1,229	£551 to £1,906	p <0001
Carotid Stenting and angioplasty				
No stenting/angioplasty during MT (n=273) Carotid stenting/angioplasty during MT (n=27)	£10,712(£2,801) £12,480 (£2,281)	£1,768	£794 to 2,742	p=0.001
ICU/HDU				
No admission to ICU (n=203) Admission to ICU (n=107)	£10,186 (£2,415) £12,219 (£3,028)	£2,033	£1,346 to £2,719	p=0.005
Driver of cost after 24 hours until discharge				
ICU/HDU				
No admission to ICU (n= 203) Admission to ICU (n= 58)	£11,833 (£3,574) £19,389 (£8,337)	£7,556	£5,830 to £9,282	p <0001

6.4.2.7 Model of care costs: Mothership versus Drip-and-Ship

Of the 310 patients in the IPD analysis, 192 were treated using a Mothership (MS) model of care, and 118 were treated by Drip-and-Ship (DS). The mean 24-hour costs were £10,787 (SD £2,786) for the MS and £10,996 (SD £2,832) for DS, a mean difference of -£209 (95% CI -£871 to 452), p=0.53 in favour of Mothership. There were also statistically significant differences between MS compared with DS in prehospital transportation costs: £333 (SD £234) vs £568 (SD: £257), with mean difference of £556 (SD: £ 236), p <0.001; in emergency hospital attendance costs: £532 (SD: £94) vs £616 (SD: £148), with mean difference of £85, p<0.001; and in imaging costs: £337 (SD: £97) vs £485 (SD: £148), with mean difference of £148, p<0.001. The difference between the various components of cost between the two groups are reported in Table 6.14.

Table 6.14. Differences between Mothership vs Drip-and-Ship model of care

Variable	Mothership	Drip and ship	Mean difference	95% CI (P-value)
Number of Patients	192	118		
Prenotification [Mean cost (SD)]	£6.23 (£2.19)	£7(0)	£0.7	£0.4to £1 (p=<0.001)
Transportation [Mean cost (SD)]	£333 (£234)	£568 (£257)	£236	£178 to £293 (p=<0.001)
Emergency Hospital Attendance [Mean cost (SD)]	£532 (£94)	£616 (£148)	£85	£54 to £115 (p=<0.001)
Imaging [Mean cost (SD)]	£337 (£97)	£485 (£223)	£148	£104 to £192 (p=<0.000)
MT Procedure cost [Mean cost (SD)]	£,8,067 (£2,658)	£7,742 (£2,585)	£325	£277 to £927 (p=0.29)
Devices [Mean cost (SD)]	£5,251 (£2,680)	£5,053 (£2,508)	£198	-£395 to £791 (p=0.51)
Hospital stay (24hrs) [Mean cost (SD)]	£1,272 (£553)	£1,207 (£832)	£65	- £105 to £235 p= 0.45)
HDU/ICU stay [Mean cost (SD)]	£1,919 (£3,676)	£1,017 (£2,846)	£902	£168-1636 (p=0.29)
Total costs 24 hrs MT only [Mean cost (SD)]	£10,439 (2,751)	£10,644 (2,849)	£204	-£865 to 457 (p=0.54)
Total costs 24 hrs MT +/- IVT [Mean cost (SD)]	£10,787 (£2,786)	£10,996 (£2,832)	£209	- £871 to £452 (p=0.53)
Total costs until discharge from MT [Mean cost (SD)]	£15,149 (£7,284)	£13,073 (£5,262)	£2,075	£639 to £3,512 (p=0.005)

6.4.3 Comparison between total patient data analysis with individual patient data analysis (all centres)

Having conducted both the top-down costing and the bottom-up costing analyses, I compared the costs obtained from both methods. I begin by comparing the average cost per patient at 24 hours for MT +/- IVT treated patients for the TPD with the IPD for individual centres and all centres combined. This is followed by comparison for the MT only group for the TPD with the IPD, again for Centres A to E and all centres**.** No comparison was performed for the IVT only group, because no IVT data was collected for the IPD costing.

The average 24-hour costs for all patients treated with MT + IVT was £10,734 for the TPD costing and £10,866 for IPD costing. The average 24-hour costs for all patients treated with MT only was £11,199 and £10,706 for the TPD and IPD costings respectively (Table 6.15).

The average cost derived from the TPD for both the MT + IVT and MT only groups fell within the confidence interval of the respective IPD cost, as shown in Figures 6.5 and 6.6.

Table 6.15. Total cost and average cost per centre by MT+IVT, MT only and all patients for TPD compared and IPD

	Centre A	Centre B	Centre C	Centre D	Centre E	All (Centres) Patients
MT +/- IVT						
Total cost (24-h)						
TPD	£3,162,141	£3,551,895	£907,127	£660,869	£1,044,841	£9,328,134
IPD	£745,348	£698,685	£640,200	£460,928	£84,1685	£3,368,460
Average cost (24-h)						
TPD	£10,615	£10,997	£10,308	£8,696	£12,439	£10,734
IPD	£10,961	£10,749	£10,670	£8,864	£12,949	£10,866
Confidence interval	£10,423-11,8500	£101,63-1,335	£9,926-11,413	£8,383-9,345	£12,079-13818	£10,547-11,185
MT only						
Total cost (24-h)						
TPD	£914,337	£215,7014	£415,685	£224,400	£588,854	£4,300,290
IPD	£212,100	£365,874	£271,075	£111,510	£265,776	£1,220484
Average cost (24-h)						
TPD	£10,390	£10,785	£10,114	£8,311	£12,515	£11,199
IPD	£10,605	£10,761	£10,843	£7,965	£12,656	£10,706
Confidence interval	£8,488-11,721	£9,892-11,631	£9,844-11,842	£6,631-9,300	£11,479-13,833	£101,76-112,36

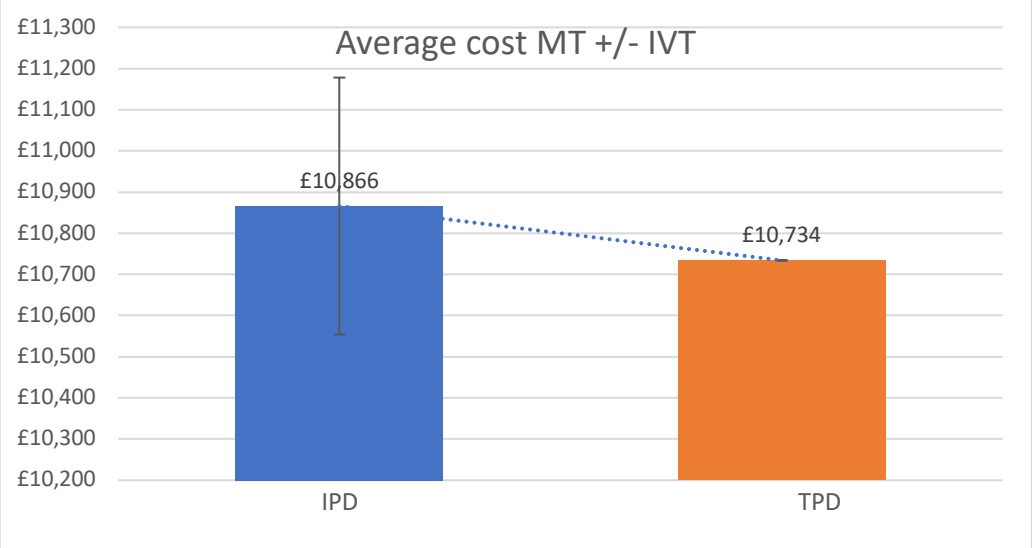


Figure 6.5. Comparison between TPD with IPD (Average cost 24 hours)

MT +/- IVT

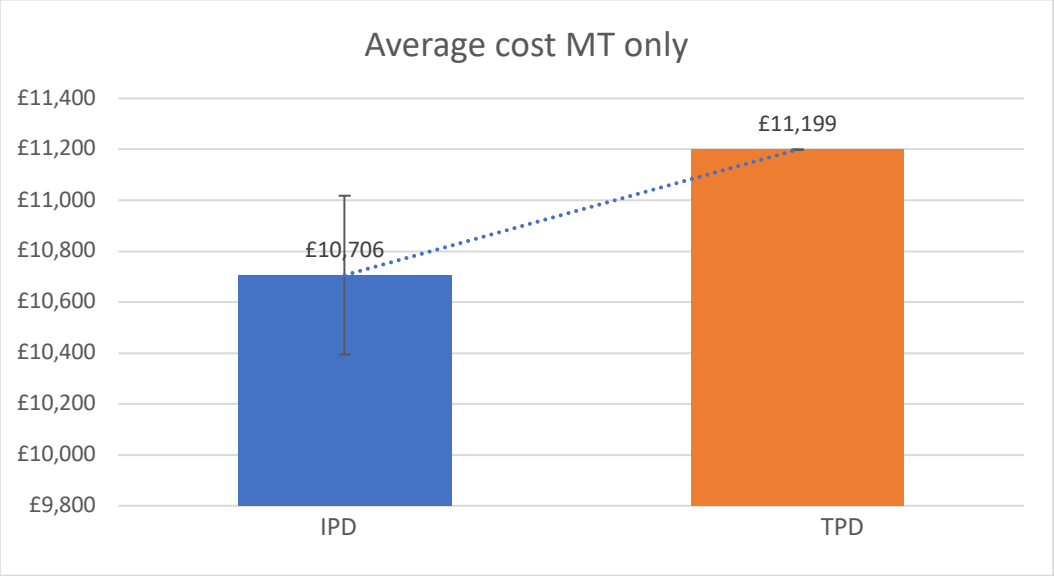


Figure 6.6. Comparison between TPD with IPD (Average cost 24 hours) for MT only

6.4.4 Comparison between individual patient data analysis (all centres) with NHS England Tariff

Finally, I compared the cost for MT +/- IVT obtained from the IPD during the hyper acute phase, up to repatriation and until discharge from the MT centre with the NHS England Tariff for MT +/- IVT (Figure 6.7). It is unclear whether the tariff only covers the intervention, the first 24 hours, hyper acute phase or the whole stay at the MT centre. The mean 24- hour cost and cost up to repatriation were within the Tariff of £11,750, but the other incurred costs at different time horizons were above the Tariff.

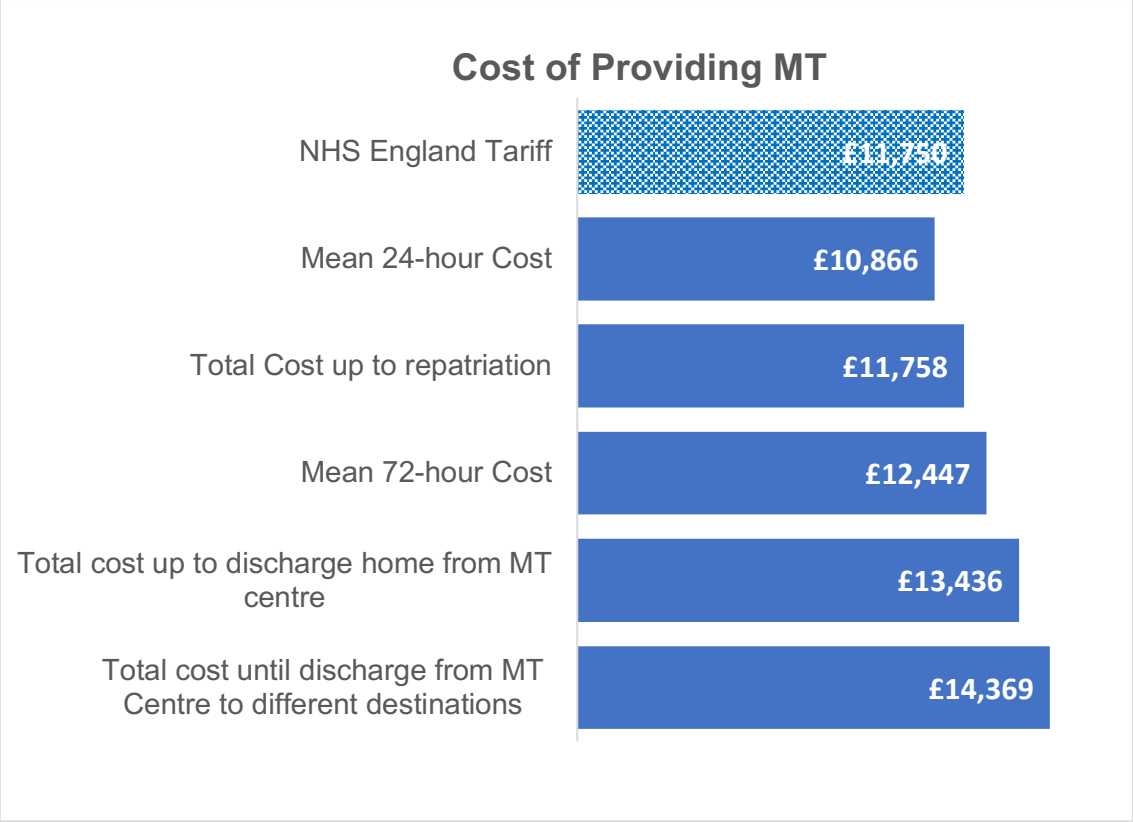


Figure 6.7. Mean costs derived from the Individual Patient Data analysis compared with the NHS England tariff for MT +/- IVT, 2020

6.5 DISCUSSION

This chapter has provided detailed estimates of the cost, from an NHS perspective, of providing MT in a range of routine clinical settings across five MT centres in the UK. A comprehensive, mixed-method approach - –sing top-down and bottom-up techniques - –as used to measure the true cost of delivering MT. While the top-down costing could be beneficial to finance directors and managers making business cases for service provision, the micro-costing could be useful to clinicians for optimising the effectiveness and efficiency of clinical pathways, and to researchers examining heterogeneity across patients. The individual patient and the whole patient populations were treated using similar treatment pathways. The main difference was patient level resource use and costs and the smaller sample size of the IPD compared with the TPD.

Owing to the procedural cost of MT, which accounted for three- quarters of the total cost, the total for patients treated with MT with or without IVT was higher than for those receiving IVT only. The main components contributing to the costs of MT were: thrombectomy devices and other consumables; staffing; use of GA or conscious sedation, with subsequent admission to ICU/HDU and post-op care. Additionally, carotid stenting during MT procedures also contributed significantly to costs.

The primary cost driver of the total costs of providing MT is the use of devices, accounting for 65% of the procedural costs. There are huge differences in the costs of devices ranging from £550 to £1,349 for AC and £1,500 to £5,000 for SR per unit, which can impact the total cost.

The average cost of £10,734 from TPD costing and £10,866 from the IPDA costing within 24 hours post MT, falls within the current NHS England tariff of £11,750.00 for most of the centres. This is omitting any allowance for further costs that could arise from ICU/HDU admissions or carotid stenting. From the IPD analysis, the cost of care for the first 72 hours post-MT, particularly for patients admitted to ICU/HDU for more than 24 hours, is outside the current allocated current NHS England tariff.

The study has also provided insights into the variability between patient groups and across centres. The observed wide variation in the costs of providing MT across the five MT centres arises mainly from a combination of differences in: imaging costs, where, for Drip-and-Ship patients, scans were repeated at MT centres; the type of devices used; use of GA and ICU/HDU admissions. Additionally, the use of carotid stenting during MT was associated with higher costs. Variations might also be explained in part by differences in available resources and pathway organisation. Local structures of pathways will variously send all patients straight to ED, SU or Radiology Department (RD). Moreover, repeat scans for some-Drip-and-Ship patients; whether or not all facilities are on one neuroscience site; performing immediate, post-MT imaging and 24-hr scans, as opposed to only 24-hr post-MT scans, all affect the total cost.

There were variations across the centres. In particular, there was a significant disparity between Centres D and E, with Centre D having the lowest costs overall and Centre E, the highest costs. The high cost for Centre E was due to duplication

of structural organisations and ICU admissions for all patients. The lower cost for Centre D was due to a simpler structure which was based upon direct admission to the Stroke Unit from 9 am to 8 pm, thus bypassing ED. The predominant use of thrombo-aspiration instead of SR also reduced expenditure.

The heterogeneity across the two centres could be of interest in identifying where cost reductions might be made in other MT centres and in future expansion of MT centres.

Compared with other studies, this study captured the resource use and unit costs along the whole pathway. The cost of MT within 24 hours falls within the NHS England tariff, but the cost will exceed the tariff whenever patients are admitted to ICU/HDU or have had additional carotid stenting or had hospital care for longer than 24 hours.

6.5.1 Strengths and limitations

A strength of this study is that both top-down and bottom-up analyses were used to obtain a clear estimate of the totality of costs in each hospital and to get insight into variability between patients and MT centres. This is in addition to comparing the costs obtained from both methods. Furthermore, the fact that the data come from five MT centres in different regions increases its representativeness and provides a firmer basis for wider extrapolation.

Lastly, the data were collected from patients treated in routine clinical settings and therefore represent real-life data.

However, the study has some limitations. First, is the small sample size for the IPD from the individual MT centre. Second, whilst data were available for the IPD up to the time of discharge, they were limited to only 24hrs for the TPD, which restricted the breadth of the comparison. Third, the intervention time was not measured because centres did not consistently record this, and it would have required looking at individual patient records. The fourth limitation is the unavailability of resource use data, after repatriation or discharge from the MT centres into the community, hence it was not possible to calculate the costs after repatriation or rehabilitation. Similarly, it was not possible to capture the total LOS in hospital for the repatriated patients.

6.5.2 Conclusion

This study provides an example of a pragmatic, but comprehensive, approach to measuring the costs of new technologies during their roll-out, which can be incorporated into economic evaluations and budget impact estimates in lower middle-income country (LMIC) settings. The clarity gained from being explicit about bottom-up and top-down approaches, together with a moderate sample size, process study, observation and discussion with laboratory staff, can support policy makers and planners to make more accurate estimates of the resource requirements of the scale-up of new technologies in settings where resources are extremely scarce.

This study has estimated the true cost of delivering MT, through a comprehensive approach to measuring costs. The main drivers of cost were: thrombectomy devices and other consumables; use of GA or conscious sedation; carotid

stenting and admission to ICU/HDU. The variations across the five MT centre were shown to arise from the following factors: imaging, devices, GA and ICU/HDU admission costs. These findings should be of value to policymakers for the strategic planning of stroke services, to clinicians and to other researchers.

6.5.3 Implications for future research

The study estimated the true cost of MT delivery in just five MT centres out of the 24 neuroscience centres in England and the total of 28 across the whole of the UK. There is a clear need for a larger study to involve significantly more regions in the UK. Future studies could also evaluate the costs after discharge from MT centres for patients repatriated to their primary hospitals, or for those transferred to community hospitals pending further rehabilitation. Furthermore, there is a need to establish the cost of the different models of care.

The next section focuses on comparing the comprehensive costs with those collected from published literature. From the comparison, it might be determined how widely the results from the other studies differ or might change, if those studies had used detailed, representative, micro-costing data.

CHAPTER SEVEN

7 Economic Evaluation of Mechanical Thrombectomy for Treatment of Acute Ischaemic Stroke Compared with Intravenous Thrombolysis or Standard Care

7.1 INTRODUCTION

The National Institute for Health and Care Excellence (NICE) recommended mechanical thrombectomy (MT) for the treatment of acute ischaemic stroke (AIS) in 2016 (NICE, 2016) and published prices for stent retrievers and thrombo-aspirators thrombectomy devices in 2018 (NICE, 2018b). Economic analyses of thrombectomy alongside IVT have been conducted to determine the cost-effectiveness of MT and IVT compared with IVT alone for AIS and to assess the budget impact of adopting and implementing thrombectomy services (Health Information and Quality Authority, 2017 , Heggie et al., 2019). In the UK, a modelling study has been used to estimate the optimal number of comprehensive stroke centres (Allen et al., 2018) and more recently, economic modelling has informed the expansion of MT services from 24 to 30 (McMeekin et al., 2019). Economic considerations, including cost-effectiveness and budget impact have also been instrumental in providing evidence for the implementation of MT in other countries (Health Information and Quality Authority, 2017 , Ontario Health Technology Assessment, 2016).

Costing methods are now a key part of the NICE guidelines on technology appraisals (NICE, 2018a). Technology appraisal processes are increasingly being used to support decision making, through NICE guidance, on the adoption

and use of new devices and new technologies in the UK National Health Service (NHS).

The use of economic evaluation is currently recommended by NICE within its reference case, which provides guidance on how to calculate the cost-effectiveness of an intervention. Economic evaluation is defined as, "*the comparative analysis of alternative courses of action in terms of both their cost and consequences"* (Drummond 4th edition. NY ; OUP 2015) (Drummond et al., 2015). Drummond, 2005. It aims to compare the 'opportunity costs' with benefits and is used as an explicit decision tool for making choices about efficient distribution of health care resources (Drummond 4th) (Drummond et al., 2015).

Economic evaluations are commonly based on either patient-level data from clinical trials and observational studies, or on decision-analytical modelling. For economic evaluations conducted alongside an RCT (i.e. trial-based economic evaluation (TBEE) (Ramsey et al., 2015), the economic data can be collected prospectively as part of the clinical study. Patient-level studies, however, may not have a sufficiently long-time horizon to capture all the relevant effects and costs associated with an intervention, depending on the follow-up period of the trial.

This is a particular problem for acute stroke interventions as most of the health utility gains and reduction in costs occur after the trial follow- up period. In health economic evaluation studies of intravenous thrombolysis, for example, with effect data extracted from a meta-analysis of six RCTs, it was shown that thrombolysis might not be cost-effective in the short time. It became cost-effective after the 2nd year and the dominant strategy compared with conservative long term (Ehlers et

al., 2007) hence suggestive of large-scale health economic savings in the long term.

Similarly, a modelling study using the ECASS trial data of patients treated within 3 to 4.5-hour timeframe was cost-effective long term for all patients (Boudreau et al., 2013). Other limitations of TBEE include an inability to address some or all questions, due to a trial being unethical or impractical to carry out, a lack of ge230eneralizabilityo ~~a~~ wider or different population, or the failure to consider all the relevant comparators.

Decision Analytical Modelling (DAM) on the other hand, is a mathematical framework that estimates costs and health outcomes through the integration of evidence from multiple sources (Sun et al., 2006). It can be used to extrapolate effects and costs over a long-time horizon but may be limited by the quality of available data, and the results can be subject to a high degree of uncertainty concerning data and sources and modelling methods (Health Information and Quality Authority, 2017).

This chapter ls divided into two sections, first, a literature review of the economic evaluation studies and second, a modelling of MT for AIS using an already developed model. The first section begins by conducting a systematic review of the published economic evaluations and cost analyses of MT, in order to amalgamate and synthesise the current evidence base on the cost and cost-effectiveness of MT (with or without IVT) compared with IVT or standard

treatment in patients with AIS. The review will contribute to the current knowledge base and identify research gaps.

The second section of this chapter focuses on a simulation using the Candio 2021 decision model (Candio et al., 2021) with more granular data from the micro-costing data presented in Chapter 6. From the output it can be determined, in an exploratory way, how the results of applying the developed model using existing cost data might have differed or changed if the detailed cost analysis data presented in this thesis had been used.

The chapter aims to determine whether the economic conclusions drawn in previous economic evaluations change with the use of higher quality and granular costs.

The aims and objectives of the study can therefore be summarised as follows:

1. To collate the current economic evidence from the existing literature on the costs and cost-effectiveness of MT with or without IVT, compared with IVT or medical treatment of AIS.
2. To determine how the introduction of a more detailed costing into a developed model might affect the estimated incremental cost-effectiveness ratio (ICER) and the probability of MT intervention being cost-effective.
3. To explore the key components underpinning the cost-effectiveness estimate of MT.
4. To explore for heterogeneity in models of care practices across different hospitals and regional care policies.

7.2 LITERATURE REVIEW

The initial step in establishing what is known from the existing literature about the costs and cost-effectiveness of MT compared to IVT was to conduct a semi-structured systematic review. This systematic review of the literature provided information on what is already known on the costs and cost-effectiveness of MT and identified the key research gaps in the literature. Following this, the present study sought to provide more accurate, detailed and up-to-date estimates of the costs of MT in routine clinical practice in the UK.

7.2.1 LITERATURE REVIEW Methods

The research question for the systematic review was formulated as “What are the costs and cost-effectiveness of MT for the treatment of AIS?”

The review was guided by established review protocols of the Cochrane Collaboration (Higgins and Green, 2009) and national guidelines on the retrieval and interpretations of economic evaluations of health technologies (Health Information and Quality Authority, 2014), the Centre for Reviews and Dissemination’s (CRD) guidance for undertaking reviews in health care (University of York, 2008) and followed the PRISMA standard (Moher et al., 2009) for reporting the findings of such studies.

7.2.1.1 Inclusion criteria

The final selection of full-text articles was based on the Population, Intervention, Control Outcomes and Study Design (PICO) criteria presented in Table 7.1.

Table 7.1. Selection Criteria

PICO Protocol	
Population	Stroke patients (>18 years) with documented large vessel occlusion stroke using either computed tomography angiography (CTA) or Magnetic resonance angiography (MRA).
Intervention	Endovascular mechanical therapy using thrombectomy devices (new generation devices) with or without IVT.
Comparator	Best medical treatment with or without intravenous thrombolysis with tissue plasminogen activator (rt-PA).
Outcomes	Economic outcomes, resource use, costs, measures of cost-effectiveness (incremental cost-effectiveness ratios, disaggregated total costs and effects) associated with the use of MT for AIS, and quality-adjusted life year (QALY).
Study Designs	Economic evaluation studies (cost analyses studies, cost effectiveness, cost-utility, cost-minimisation, cost benefit analysis) budget impact analysis, business cases of MT for ischaemic stroke and Health technology assessments. RCTs, systematic reviews, observational studies, economic modelling studies and guidelines. Cost analysis reported in any currency and study follow-up (time horizon over which costs and benefits are considered or modelled) greater than three months.

7.2.1.2 Exclusion criteria

Articles were excluded if they did not meet the PICO criteria, were non-comparative studies of MT with or without IVT, were published prior to 2015, unpublished studies, published in abstract form only, or were letters or editorials.

7.2.1.3 Search strategy

Literature searching was conducted using a combination of Medical Subject Headings (MeSH) terms and keywords in the following databases: Ovid Medline, Ovid EMBASE; Cochrane Database of Systematic Reviews and the Cochrane Central Registry of Controlled Trials; Stroke Trials Registry; Clinicaltrials.gov and Current Controlled Trials; Health Technology Assessment Database (HTA); the Cost-Effectiveness Analysis Registry; EBSCOhost (EconLIT, Academic Search and CINAHL); Reviews and Dissemination (CRD) databases; and the National Health Service Economic Evaluation Database (*NHS EED) (discontinued in March 2015, now via Cochrane*). Cross-referencing and hand-searching of reference lists of relevant articles and conference proceedings was also conducted. Papers published in any language between January 2015 and July 2020 (based on all new generation devices) were included. Studies with English abstracts were included, and no restrictions were placed on country of origin. The search was regularly updated with an automated alert set on Medline and EMBASE.

The search terms used were ‘brain isch(a)emia’, ‘acute isch(a)emic stroke’, ‘cerebral infarction’, ‘cerebrovascular accident’, ‘CVA’, AND ‘mechanical thrombolysis’, ‘endovascular therapy’, ‘endovascular treatment’, ‘endovascular embolectomy’, ‘endovascular thrombectomy’, ‘intra(-)arterial intervention’, ‘intra(-)arterial treatment’, ‘intra(-)arterial therapy’, ‘intra(-)arterial thrombolysis’, ‘neuro(-) thrombectomy’, AND ‘Cost-effectiveness analysis’, ‘cost-effectiveness’, ‘cost-utility analysis’, ‘cost utility’, ‘cost-benefit analysis’, ‘cost benefit’, ‘cost analysis’, ‘cost estimates’, ‘ cost , benefit’ AND “randomised controlled trial‘ (where parentheses indicate terms that were searched with and without the bracketed text). Search strategy in Appendix 7.A.

7.2.1.4 Study selection

The titles followed by abstracts of identified studies were examined and then full texts were scrutinized for inclusion. Once eligibility had been assessed, data from each study were extracted and entered a spreadsheet using a standard format designed specifically for the review. A PRISMA flow chart of study selection is shown in Figure 7.1.

7.2.1.5 Data extraction

The following information was extracted from the included primary studies, as well as from published supplementary material where relevant:

1) Background characteristics of the included studies (first author, publication year, country of study, types of interventions and comparators, patient population, study design [cost-effectiveness analysis, cost-utility analysis]; economic evaluation model [Markov model, decision tree model]; perspective [health care payer, health care system, society], time horizon; discount rate, currency, year of cost and data sources).

6) 2) Main study characteristics (cost components; costs and benefits, effectiveness; health outcome measures [QALY]; incremental cost-effectiveness ratio [ICER], sensitivity analysis results with the approached used (multivariate, univariate or threshold analysis) and study conclusions. The details of extracted information are in Appendix 7.B.

7.2.1.6 Outcome measures

The primary outcomes of interest were the costs, cost-effectiveness, cost–utility and cost benefit associated with the use of MT for the treatment of AIS. Other outcomes of interest included the reported incremental costs, incremental effectiveness, and incremental cost-effectiveness ratios, quality adjusted life years gained, willingness to pay (WTP) and disaggregated components of total costs.

7.2.1.7 Assessment of study quality

Using the NICE Economic Evaluation Checklist, the quality of the identified published economic evaluations of MT studies was assessed for their relevance and limitations of methodology (NICE, 2015). The studies are rated as: “Directly Applicable”, “Partially Applicable (fails to meet one criterion)” and “Not Applicable (fails to meet more than one criterion)”. The overall quality of the study methodology is classified with “Minor Limitation”, “Potentially Serious Limitation” or “Very serious limitations”. This is based on whether a study meets all or fails to meet one or more, quality criteria.

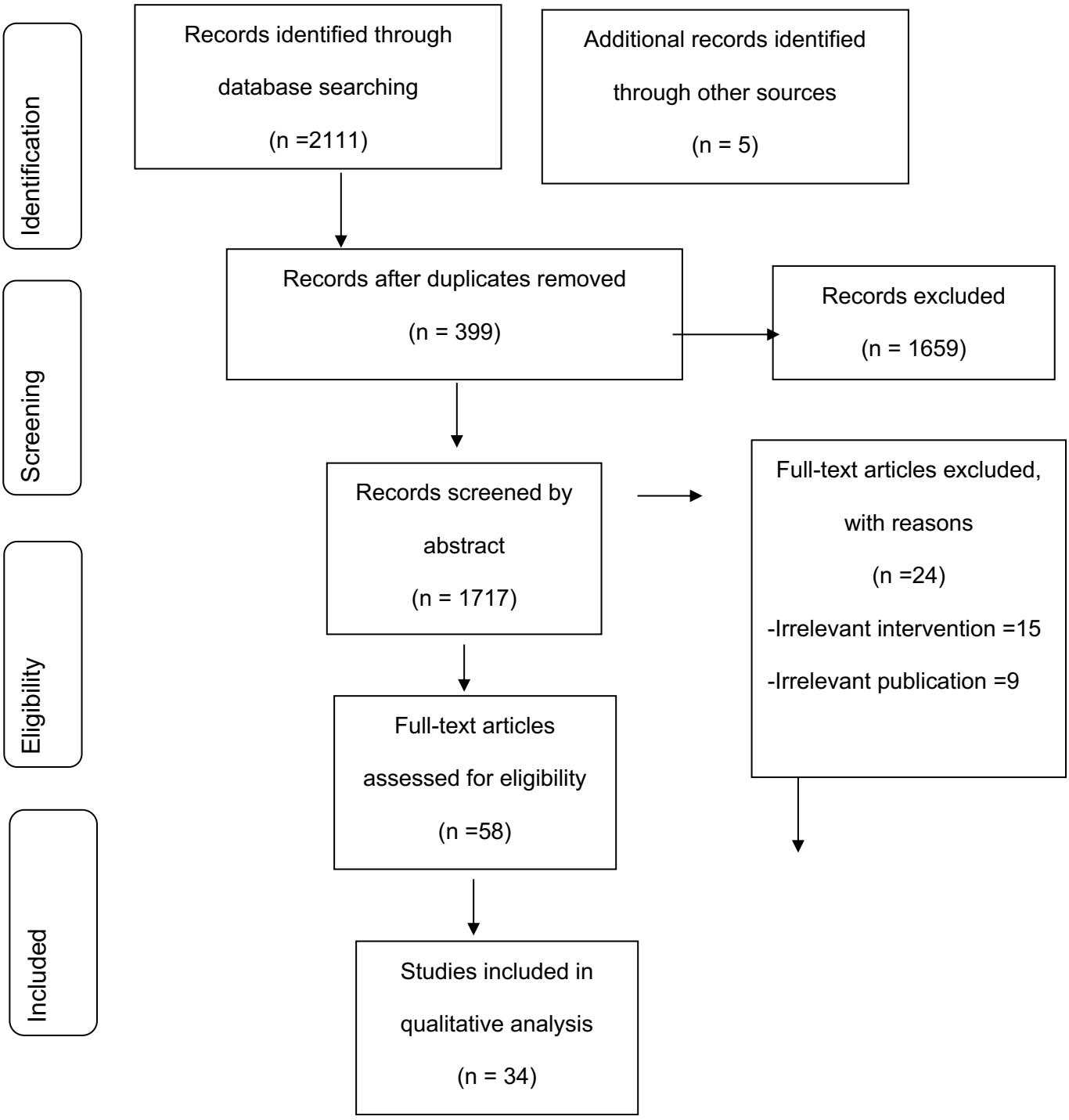


Figure 7.1. PRISMA flow chart of study selection

Adapted from Moher, 2009 (Moher et al., 2009).

7.2.2 LITERATURE REVIEW Results

7.2.2.1 Study characteristics

Overall, 2116 articles were identified, of which 2082 were excluded and 34 articles were included (Table 6.1). Among the included studies, six were cost analyses studies (Vega-Valdes et al., 2018, Campbell et al., 2017, Rai and Evans, 2015, Comai et al., 2015, Kass-Hout et al., 2015, Vidal and Milburn, 2016), one was a cost benefit analysis (Mangla et al., 2016) and 23 were cost utility studies (Kabore et al., 2019, Arora et al., 2018, Ruggeri et al., 2018, Pan et al., 2018, Frønsdai et al., 2016, Heggie et al., 2019, Trippoli et al., 2018, Kunz et al., 2018, Achit et al., 2017, de Andres-Nogales et al., 2017, Simpson et al., 2017, Shireman et al., 2017, Steen Carlsson et al., 2017, Ganesalingam et al., 2015, Leppert et al., 2015, Aronsson et al., 2016, Kunz et al., 2016, Lobotesis et al., 2016, Xie et al., 2016, Pizzo et al., 2019, Thurman, 2015). Among the cost-utility studies, two were conducted alongside a clinical trial (THRACE) (Achit et al., 2017, Shireman et al., 2017), four were HTAs (Ontario Health Technology Assessment, 2016, Frønsdai et al., 2016, MSAC Australia, 2016, Health Information and Quality Authority, 2017) and the rest were model based analyses. There were four systematic reviews of CEA studies (Teljeur et al., 2019, Boudour et al., 2018, Ryu et al., 2018, Sevick et al., 2017). Details of the different study characteristics are in Appendix 7.B. and detailed study findings in Appendices 7 C-E.

7.2.2.2 Cost analysis studies

Out of the six cost analyses studies, one was from Spain (Vega-Valdes et al., 2018), one from Australia (Campbell et al., 2017), one from Sweden (Comai et

al., 2015) and three from the USA (Vidal and Milburn, 2016, Rai and Evans, 2015, Kass-Hout et al., 2015). These cost studies reported on various components of costs. Vega-Valdes and colleagues (Vega-Valdes et al., 2018) included the costs of emergency admissions; imaging; physician consultations; admissions up to 24 hours after intervention; rehabilitation sessions and 90-day outpatient follow-up. The estimated cost of MT was €6,574.14 and IVT-tPA was €636.76 per patient. The average final total cost of patients treated with MT was €16,059 ± 7,209 and IVT-tPA was € 8,169 ± 3,734.30. The study, however, did not cover the costs of transportation or other peri-procedural staff costs associated with MT. Notably, Campbell (2017) reported the cost of inter-hospital transfer for MT at US$ 576 per patient (Campbell et al., 2017).

Five studies reported on the costs of devices (Campbell et al., 2017, Vidal and Milburn, 2016, Comai et al., 2015, Turk et al., 2015) and three studies compared the costs of different devices (Comai et al., 2015, Vidal and Milburn, 2016, Turk et al., 2015). Campbell 2017 reported on the procedural costs of MT and staffing costs (Campbell et al., 2017). Vidal 2016 (Vidal and Milburn, 2016) reported the average cost of Penumbra 5MAX ACE per case to be $4,916 per case compared with the cost of stent-retriever (SR) estimated at $9,620 with potential savings of 49% in favour of 5MAX ACE. Comai and colleagues (Comai et al., 2015) compared the cost differences between the use of direct aspiration first-pass technique (ADAPT) with stent-retrievers for MT and found a cost difference of €−2,748 with an estimated cost savings of €32,226 in favour of the ADAPT Technique. Similarly, Turk and colleagues (Turk et al., 2015) reported on the average total costs of three thrombectomy devices for the treatment of LAO stroke. The average total costs were: $31,716 for the ADAPT technique; $46,735

for stent-retrievers with local aspiration (SRLA); and $47,673, for the Penumbra system (PS). The average cost for patients treated with the ADAPT technique was significantly lower than for those treated with PS (p <0.0001) and also for patients treated with SRLA (p=0.0008). There was, however, no significant difference in the average total costs between the PS and SRLA treated patients (p=0.6228).

Two studies (Campbell et al., 2017, Rai and Evans, 2015) looked at hospitalisation costs. Campbell (2017) reported inpatient care post MT up to 90 days at $15,689 (95% CI-$10,774–$20,605) and $30,569 (95% CI $21,575–$39,564) for IVT.

Rai and colleagues (Rai and Evans, 2015) reported $23,698 (favourable outcome) for MT compared with $13,688 (favourable outcome) for the control group and $31,500 (poor outcome) vs $20,934 (poor outcome). This is in addition to a net financial gain of $476 for the MT treated group compared with a net financial loss of $1,752 for the IVT treated group.

7.2.2.3 Cost utility studies

The countries of origin of the cost-utility studies were: four from the UK (Heggie et al., 2019, Pizzo et al., 2019, Lobotesis et al., 2016, Ganesalingam et al., 2015); two from Italy (Ruggeri et al., 2018, Trippoli et al., 2018); two from France (Kabore et al., 2019, Achit et al., 2017); one from Spain (de Andres-Nogales et al., 2017); two from Canada (Xie et al., 2016, Ontario Health Technology Assessment, 2016); three from Sweden (Steen Carlsson et al., 2017, Aronsson et al., 2016, Thurman, 2015); one from Norway (Frønsdai et al., 2016); two from Australia

(Arora et al., 2018, MSAC Australia, 2016); three from USA (Kunz et al., 2018, Shireman et al., 2017, Kunz et al., 2016) and one from China (Pan et al., 2018). All but one study had patients treated with MT within a 6-24 hrs window of symptom onset (Pizzo et al., 2019) and the rest (presumably) within 0-6 hrs of symptom onset. Six studies (Ganesalingam et al., 2015, Lobotesis et al., 2016, Arora et al., 2018, Kabore et al., 2019, Heggie et al., 2019, Health Information and Quality Authority, 2017) had additional micro-costing components.

7.2.2.3.1 Perspective

The perspective adopted was that of the healthcare systems in 17 studies (MSAC Australia, 2016, Heggie et al., 2019, Pizzo et al., 2019, Kabore et al., 2019, Arora et al., 2018, Ruggeri et al., 2018, Pan et al., 2018, de Andres-Nogales et al., 2017, Frønsdal et al., 2016, Achit et al., 2017, Simpson et al., 2017, Shireman et al., 2017, Ganesalingam et al., 2015, Aronsson et al., 2016, Kunz et al., 2016, Xie et al., 2016, Lobotesis et al., 2016) with discount rates between 3% and 6% and societal perspective in three (Leppert et al., 2015, Steen Carlsson et al., 2017, Thurman, 2015). Both healthcare and societal perspectives were used in three studies (Health Information and Quality Authority, 2017 , Ontario Health Technology Assessment, 2016, Kunz et al., 2018).

7.2.2.3.2 Time horizon

The time horizon was one year in three studies (Pan et al., 2018, Achit et al., 2017, Simpson et al., 2017); five years in four studies (Ruggeri et al., 2018, Health Information and Quality Authority, 2017 , Ontario Health Technology Assessment, 2016, Xie et al., 2016); 10 years in one study (Kabore et al., 2019);

20-30 years-long in six studies (Aronsson et al., 2016, Kunz et al., 2016, Ganesalingam et al., 2015, Pizzo et al., 2019, Frønsdai et al., 2016, Thurman, 2015); and lifetime/long-term in nine studies (Leppert et al., 2015, Steen Carlsson et al., 2017, MSAC Australia, 2016, de Andres-Nogales et al., 2017, Lobotesis et al., 2016, Shireman et al., 2017, Kunz et al., 2018, Arora et al., 2018, Heggie et al., 2019).

7.2.2.3.3 Data source

Effectiveness data were derived from different sources including: analyses of single RCTs such as MR CLEAN (Leppert et al., 2015); SWIFT PRIME (Shireman et al., 2017, Lobotesis et al., 2016); THRACE (Achit et al., 2017); PISTE (Heggie et al., 2019), use of pooled individual-level data from the five RCTs (Arora et al., 2018, Kunz et al., 2016) and literature reviews (Ganesalingam et al., 2015, Aronsson et al., 2016, Xie et al., 2016). Some of the studies also obtained data from six trials (pooled analysis of five RCTs) plus THRACE (Kabore et al., 2019) and from seven trials (pooled analysis of five RCTs plus THRACE and PISTE (Heggie et al., 2019).

Efficacy outcomes were extracted from five RCT trails in 13 studies:(Frønsdai et al., 2016, Trippoli et al., 2018, Kunz et al., 2018, Kunz et al., 2016, Steen Carlsson et al., 2017, Aronsson et al., 2016, Xie et al., 2016, Health Information and Quality Authority, 2017 , Ontario Health Technology Assessment, 2016, MSAC Australia, 2016, Ganesalingam et al., 2015, Mangla et al., 2016, Arora et al., 2018, Thurman, 2015).

Outcomes were also collected from single RCTs in seven studies (Ruggeri et al., 2018, Achit et al., 2017, Lobotesis et al., 2016, de Andres-Nogales et al., 2017, Simpson et al., 2017, Shireman et al., 2017, Leppert et al., 2015).

7.2.2.3.4 Utilities

Utility values were derived from IPD of RCTs in four studies (Shireman et al., 2017, Simpson et al., 2017, Leppert et al., 2015, Achit et al., 2017), and the remaining cost-utility studies drew utility values from observational studies and other sources (Luengo-Fernandez et al., 2013, Dorman et al., 1997, Sandercock et al., 2002, Rivero-Arias et al., 2010, Dorman et al., 2000, Morris et al., 2011).

The outcome data sources were heterogenous, but most were from the thrombectomy trials and the cost sources from the published literature available in most studies. In two of the UK studies (Ganesalingam et al., 2015, Pizzo et al., 2019), utility scores were obtained from published literature (Dorman et al., 1997, Sandercock et al., 2002) and from the NICE technology assessment on Alteplase for AIS (NICE, 2012) and one from the Oxford Vascular Study (Lobotesis et al., 2016).

In two of the RCTs, Stent-retriever was dominant (less expensive and more effective); SWIFT PRIME was dominant (saving $2,996) and REVASCAT was dominant (saving $7,793), while in the other three trials, the savings were cost effective but non-dominant: MR CLEAN achieved $1,662; ESCAPE $2,780 and EXTEND-IA $256. Furthermore, in the probability analysis of the pooled data there was a 53% probability of MT being both cost-saving and QALY increasing (Aronsson et al., 2016).

7.2.2.4 Study findings

The cost of an MT procedure ranged from £5,641 to £10,929 with a mean cost of £8, 688 (SD £1,526). The mean incremental cost over 1 year was £6,603 (SD £4,632); over 5 years £3,106 (SD £1,819), 20-30 years mean £3,841 (£3,668) and lifetime/long-term £4,829 (£13,576). The estimated additional benefit in QALYs varied between 0.04 and 2.51 for different time horizon. Furthermore, the estimated mean incremental cost-effectiveness ratios (ICERs) per QALY ranged through £108,680 (£89,855) over I year; £3,106 (£1,819) over 5 years; £4,467 (£3,924) over 20-30 years and £16,604 (£23,392) over a patient's lifetime.

For treatment with MT beyond 6 hours from onset, the incremental cost per QALY of MT over a 20-year period was £1,219; when treated after 12 hours, £4,096; after 16 hours and £2,894; after 24 hours from symptom onset (Pizzo et al., 2019). The ICER for MT performed at different time windows were: £1,227/QALY within 12 hours, £4,103/QALY within 16 hours and £2,984/QALY gained within 24 hours of stroke onset (Pizzo et al., 2019).

Whilst MT was found to be dominant in seven studies (Arora et al., 2018, Ruggeri et al., 2018, Shireman et al., 2017, Steen Carlsson et al., 2017, Aronsson et al., 2016, Lobotesis et al., 2016, de Andres-Nogales et al., 2017), it was non-dominant in the five other studies (Achit et al., 2017, Ganesalingam et al., 2015, Leppert et al., 2015, Kunz et al., 2016, Xie et al., 2016), all of which reported higher costs and more QALYs. All studies in this category had a high probability of being cost-effective within the acceptable threshold.

For treatment beyond 6 hours, the probability of MT being cost-effective for WTP threshold at both £20,000 and £30,000 per QALY was 99.9% (Pizzo et al., 2019). Using individual-level cost data from the perspective of the National Health Insurance Scheme (NHIS) in France and outcome data from the THRACE trial, MT was shown to be more cost-effective than IVT, with an incremental cost per one QALY gained of $14,881 (€13,423) (Achit et al., 2017). Similarly, using data from the SWIFT trial from a payer's perspective and over a lifetime horizon treatment with MT using SR was dominant over IVT alone, with higher QALYs and net savings of US$22,203 (Shireman et al., 2017).

An economic evaluation of MT from a Swedish health care perspective, using data from the initial five positive trials, along with data from registries and published studies, reported that MT alongside IVT was associated with a gain of 0.40 life-years and 0.99 QALYs, with a cost saving of $221 per patient(Aronsson et al., 2016). In the lifelong base case analysis of pooled data (HERMES), the ICER per QALY was Australian $12,880 with an incremental cost of Australian $10,666 (Arora et al., 2018).

The use of Stent-retriever device was dominant (less expensive and more effective) in the SWIFT PRIME and REVASCAT RCTs with savings of $2,996 and $7,793 respectively. On the contrary, in the other three trials, the savings were MR CLEAN $1,662; ESCAPE $2,780 and EXTEND-IA $256. Furthermore, in the probability analysis of the pooled data there was a 53% probability of MT being both cost-saving and gained QALY (Aronsson et al., 2016).

A UK based model study, which also used data from the five trials, but from the UK National Health Service and Personal Social Services perspective, found MT was cost-effective with an average £7,061 per QALY gained and 100% probability of being cost effective at both a £20,000 and £30,000 threshold over the patient's lifetime (Ganesalingam et al., 2015).

In a study based on the landmark Multicentre MR CLEAN trial, MT was cost effective with an average US$14,137 per QALY gained and 97.6% probability of being <US$50,000 per QALY over the patient's lifetime from a societal perspective (Leppert et al., 2015). Another economic analysis alongside the SWIFT PRIME trial demonstrated a saving over the patient's lifetime of $23,203 per patient (Simpson et al., 2017).

7.2.2.*5* Sensitivity analysis

Eight studies analysed uncertainty in the data being used through one-way deterministic sensitivity analysis (Heggie et al., 2019, Leppert et al., 2015, Kunz et al., 2016, Shireman et al., 2017, Ganesalingam et al., 2015, Lobotesis et al., 2016, Xie et al., 2016, Pan et al., 2018, Health Information and Quality Authority, 2017); 2-way analysis was used in one study (Aronsson et al., 2016) and one study used one-way plus multiway sensitivity analyses (Ruggeri et al., 2018).

Probabilistic sensitivity analysis (PSA) was performed in four studies (Health Information and Quality Authority, 2017 , Pan et al., 2018, Kabore et al., 2019, Pizzo et al., 2019), and four studies reported cost-effectiveness acceptability curves (CEACs) as part of PSA (Health Information and Quality Authority, 2017 , Heggie et al., 2019, Aronsson et al., 2016, Pizzo et al., 2019) to illustrate the probability of MT being cost-effective compared with IVT/standard care over a

range of willingness to-pay (WTP) thresholds. For MT performed within the presumed 0- 6 hours window the probability of MT being cost-effective ranged between 70% and 100% (Health Information and Quality Authority, 2017 , Ganesalingam et al., 2015, Heggie et al., 2019, Kabore et al., 2019, Xie et al., 2016, Lobotesis et al., 2016, Leppert et al., 2015, Shireman et al., 2017) at various WTP thresholds of acceptability in different countries.

For MT beyond 6 hrs, it was demonstrated through a one-way sensitivity that the cost of MT should be at least £35,518 from the DAWN trial data at 12 hours and £33,185 using the DEFUSE 3 trial data at 16 hours and in excess of £43,140 from the DAWN trial data at 24 hours and for MT to be borderline cost effective at a threshold of £20,000 per QAL gained (Pizzo et al., 2019).

7.2.2.6 Quality of studies

Using the NICE economic evaluation checklist, the majority of the studies were in the “Partially Applicable with Minor to Moderate Limitations” category for the quality of the methodology. The methodological limitations included using intervention outcome data from multiple data sources, lack of discounting, lack of clarity on the intervention treatment window and uncertainty on which costs were included. The details of quality assessment scores are presented in Appendix 7.F.

7.2.2.7 Cost benefit analysis

The only cost benefit analysis reported the direct benefit of MT valued at $1,788 (€1,518) per patient, and the indirect benefit at $161,836 (€137,370) per patient. Additionally, It valued a financial benefit of treatment with MT (reduced direct and

indirect financial burden from stroke) of $8 billion for 50,000 patients on an annual basis (Mangla et al., 2016).

7.2.2.8 Systematic Reviews of Economic Evaluation studies

Four SRs of economic evaluations were identified, one each from Canada (Sevick et al., 2017), France (Boudour et al., 2018), Ireland (Teljeur et al., 2018) and the USA (Ryu et al., 2018). The review of economic evaluations of 17 studies by Servick and colleagues included those that used first generation devices, which have been shown to have a low recanalisation rate.

Similarly, the review by Teljeur and colleagues (Teljeur et al., 2018), which estimated the cost-utility and cost-benefit of MT relative to standard care involving thirteen studies, dichotomised the evaluations into those that used first and second-generation devices (Appendix 7.E). Boudour and colleagues (Boudour et al., 2018) included eight studies that used only second-generation devices but limited their analysis to the studies that used stent-retrievers, not other thrombectomy devices. The review by Ryu involved all intracranial interventions including MT.

7.2.3 LITERATURE REVIEW Discussion and Conclusions

From the systematic review, 34 studies were identified that estimated the costs and cost effectiveness of MT compared with standard care costs. The studies were dichotomised into “Treatment within 6 hours” and “Treatment beyond 6 hours” of symptom onset. This review evaluated all types of new generation devices and excluded old generation devices. The included studies were of partial applicability with minor limitations. This review was focused on published

economic evaluations that used second generation devices and was not limited to the use of only one type of device. The majority of the MT health economic evaluations were based on decision-analytical modelling (Ruggeri et al., 2018, Pizzo et al., 2019, Simpson et al., 2017, de Andres-Nogales et al., 2017, Lobotesis et al., 2016). Only two were conducted along RCTs (THRACE, SWIFT PRIME) which provided individual patient data for various analyses (Achit et al., 2017, Shireman et al., 2017).

As productivity losses and ongoing care needs, most studies identified were conducted only from the healthcare-payer perspective, with just three studies reporting results from both societal and healthcare-payer perspectives (Kunz et al., 2018, Health Information and Quality Authority, 2017 , Ontario Health Technology Assessment, 2016), and three studies were conducted only from a societal perspective (Leppert et al., 2015, Steen Carlsson et al., 2017, Thurman, 2015). Steen Carlsson and colleagues (Steen Carlsson et al., 2017) took a societal perspective because in the Swedish setting, the main burden of social services costs from the burden of stroke falls on municipalities, financed by income taxation and some financial assistance from the government.

A large number of studies adopted a lifetime horizon (Heggie et al., 2019, Arora et al., 2018, Kunz et al., 2018, Shireman et al., 2017, de Andres-Nogales et al., 2017, Lobotesis et al., 2016, Leppert et al., 2015, Steen Carlsson et al., 2017, MSAC Australia, 2016) with some 20-30 years-long (Frønsdai et al., 2016, Aronsson et al., 2016, Kunz et al., 2016, Pizzo et al., 2019, Ganesalingam et al., 2015, Thurman, 2015). This is reassuring, as a long-time horizon is likely to be required to capture all the potential differences in costs and effectiveness

between MT compared with IVT or standard care. The reported lifetime ICERs for MT varied from being dominant to a range that is considered cost-effective per QALY and within an acceptable WTP threshold for most countries.

Systematic reviews of published evaluations either included both first and second- generation devices or were restricted to only SR. This current review captured only new generation devices and was not restricted to SR but included all MT devices that are not always covered in the existing literature. The costing studies done with old devices may no longer be relevant. Additionally, those reviews restricted to the use of SR may not be generalisable as there are now more devices and the cost may be lower than the cost of SR.

7.2.3.1 Limitations and Strengths

7.2.3.1.1 Limitations of Identified Published Studies

The limitations of the cost analyses' data include: retrospective (Vega-Valdes et al., 2018, Turk et al., 2015); single centre (Vega-Valdes et al., 2018, Turk et al., 2015) and small sample size (Turk et al., 2015, Vega-Valdes et al., 2018, Comai et al., 2015). The studies vary in the components of costs captured along the treatment pathways. Furthermore, none of the cost analyses studies cover all costs accumulated along the treatment pathways for MT in real-world clinical settings. The costs of additional CT/MR angiography performed before MT, costs of drip-and-ship procedures or repatriation to the referring hospital, were not included in these studies. Only one study captured the cost for inter-hospital transfer to an MT centre. Patients transferred to specialist centres for MT will incur cost of transportation. Furthermore, none of the studies included

resource-use related to the type of anaesthesia, carotid stenting, and ICU admission. The cost-utility studies varied in the cost components captured in their micro-costing, which are influenced by the study design, outcome data, perspective and time horizon adopted.

The published studies generally had limited information on costs associated with advanced imaging such as CTA, CTP; additional intervention, such as carotid stenting during the procedure; type of anaesthesia, particularly the cost of local anaesthesia or conscious sedation and admission to ICU. The studies were limited by heterogeneity in methodology, perspectives, sources of data for model inputs and varying time horizons. This is in addition to limited economic evaluations conducted alongside RCTs, which have the advantage of being collected progressively and subsequently provides IPDA for subgroup analyses.

The cost-effectiveness studies were principally based on the use of stent-retrievers (Simpson et al., 2017, de Andres-Nogales et al., 2017, Lobotesis et al., 2016) with only limited information for other thrombectomy devices (Pizzo et al., 2019, Trippoli et al., 2018). The model-based CEA studies used data from the trials where stent retrievers were used predominantly. Stent retrievers, for example were used in 100% of cases in three RCTs: EXTEND-IA, SWIFT PRIME and REVASCAT; with 81.5% in MR CLEAN and 77% in ESCAPE. In the CEA of MT “Beyond 6 hours” conducted using the data from the DEFUSE 3 and DAWN trials, different devices were used. While in DAWN, Trevo® devices were used in all cases, 80% of SR were used in DEFUSE 3. The resource use was from different sources for the various studies. For example, a Swedish study used real-life resources together with pooled outcome data from the five RCTs (Steen

Carlsson et al., 2017) and a US study (Leppert et al., 2015) used Medicare cost estimates and outcomes data from the MR CLEAN trial.

Two UK studies employed hospital resource-use from an NHS perspective (Ganesalingam et al., 2015, Lobotesis et al., 2016).

Another limitation of the included published studies is that few of the studies considered a societal perspective. Of those that adopted a societal perspective, the costs related to loss of productivity and other indirect costs were not fully captured.

Limitations of existing reviews include the inclusion of both first- and second-generation devices or to studies that used only SR, unlike this current study.

7.2.3.1.2 Limitations and Strengths of present review

This current review was limited to economic evaluation studies published in English, therefore studies published in other languages might have missed. The review was also limited by study quality evaluated by one reviewer, which is prone to subjective bias and potential failure to completely summarise the complexity of economic evaluation studies.

The current review, unlike previous reviews, focused on published economic evaluations that used all types of second-generation devices, rather than being limited to the use of only one type.

7.2.3.2 Conclusion

Mechanical thrombectomy has been consistently shown to be cost-effective across all studies, ranging from high quality HTAs, RCTs and systematic reviews of CEA, and has even been found to be dominant (more effective and less expensive) compared with IVT or standard care in a number of studies. MT for treatment of AIS has also been shown to be associated with long-term cost savings, particularly from the healthcare-payer's perspective, despite the studies' limitations.

Based on the established limitations of the studies, particularly regarding the cost components not captured by the published CEA, an already developed model will process cost estimates from my micro-costing of actual treatment pathways for large number of patients with detailed resource use from different centres. The next section will input the comprehensive micro-costing data into the already published model to highlight potential differences.

7.3 Input of cost analysis data into a developed model

7.3.1 Introduction

The systematic review described above in section 7.2 identified a number of limitations in the economic evaluation studies that were identified, notably a focus on old generation devices or only SR, and a lack of full coverage of all the cost components along the treatment pathway. In this section, I use the micro-costing information on the intervention cost of MT presented in Chapter 6 in combination with an existing cost-effectiveness model, with the objective of ascertaining

whether a more accurate and real-life representation of MT treatment costs affects the identification of the optimal treatment strategy from a health economic perspective and the probability of the intervention being cost-effective. My micro-costing can also help to quantify the uncertainty around these cost and cost-effectiveness estimates, and the precision of estimated differences in various policy settings.

The section will assess the economic implications of implementing MT intervention in terms of subsequent (post-event) costs and health-related outcomes (quality of life and survival). It does this by using an existing published economic model (Candio et al., 2021) which was accessed via an academic collaboration with the model developers.

In order to make the analysis consistent with the UK context, the Lobotesis protocol was chosen as being the closest and best estimate for application to the UK setting (Lobotesis et al., 2016). The model fully incorporates the Lobotesis Protocol, which was also used by Ruggeri (Ruggeri et al., 2018). Although all three studies (Ruggeri et al., 2018, Lobotesis et al., 2016, Candio et al., 2021) used the same intervention protocol and based their analyses on the same resources needed to perform MT (namely, staffing, number of devices and consumables (Appendix 7.G), their intervention cost estimates differed as they used different unit costs: Lobotesis (Lobotesis et al., 2016) used NHS-based unit costs (NHS Reference Costs 2014); Ruggeri (Ruggeri et al., 2018) used Italian health care system costs; and Candio (Candio et al., 2021) used macro-level weights to adjust for country-level differences. In this analysis, I use information collected from my micro-costing study in terms of resource use and unit costs

related to the MT procedure, to assess how this changes the MT procedure cost, affects the economic results and therefore, the cost-effectiveness of MT, and how it compares with those reported in the economic analysis by (Candio et al., 2021).

7.3.2 Methods and data

To conduct the analysis, the cost components generated via my micro-costing study were matched with the Lobotesis MT intervention protocol as implemented in the Candio Model. For the base case analysis, I considered four main categories of resource use: devices, consumables, venue and staffing. The cost components already included in the intervention protocol were identified within the micro-costing dataset to avoid duplication and each category was expanded or narrowed to include only the relevant components. The unit costs reported in the previous section for each of the different hospitals were also applied.

In the second phase, once the micro-costing-derived intervention cost estimates were incorporated in the Candio economic model, it was run to generate incremental cost-effectiveness ratios and assess the probability of MT treatment being cost-effective. Comparisons were also made between the cost-effectiveness results based on my micro-costing data, with results based on other cost estimates. Lastly, different scenarios were explored, representing different hospital settings and policy options, including a sub-group analysis.

7.3.2.1 Resource use and costs

Here I used the resource and cost information obtained from the micro-costing analysis conducted across 5 UK treatment centres and presented in Chapter 6 (hereafter referred to as the Balami micro-costing).

Detailed similarities and differences between the Lobotesis cost framework and the Balami micro-costing are summarised in Appendix 7.G. In the Lobotesis cost framework, resource use for MT was collected: for the venue of MT; stent retrievers (SR); catheters and other thrombectomy consumables and staffing. Resource use was also collected for IVT and non-thrombolytic therapy, such as the pre-intervention CT imaging (non-contrast CT head) and blood test in ED. Similarly, in the Balami micro-costing, resource use for venue of MT and for staffing was collected. This is in addition to resource collection for SR, catheters and other thrombectomy consumables. Resource use was also collected for other devices like thrombo-aspirators (TA).

In contrast to the Lobotesis protocol, which was used by both Ruggeri (2018) and Candio (2021), the Balami micro-costing collected resource use for other thrombectomy devices including TA, in addition to SR. Resource use was also collected for ED attendance; imaging including CT, CT angiogram and CT perfusion; use of anaesthesia (either general, local anaesthesia, or conscious sedation); carotid stenting during MT; immediate post MT care; ICU/HDU admission and 24-hour post intervention care. Resource use was also captured for post-intervention scans (CT and MRI). Notably, the Balami micro-costing captured detailed resource use along the individual patient's whole treatment pathway, commencing with the pre-hospital notification phone call and ending with repatriation or discharge from the MT Centre. Additionally, resource use was also captured for patients transferred from non-MT Centres to MT Centres known as the Drip-and-Ship. Resources used in the acute phase and up to discharge from the MT Centre were similarly captured.

While the Lobotesis Protocol estimated 1.2 stent retrievers, the Balami micro-costing collected the actual number of devices used per patient, which was usually a mixture of devices and at a ratio of 1.1. Further differences were found in the number of hours allocated to the use of IRS or theatre for MT; three hours for Lobotesis protocol and two hours for the Balami micro-costing; four hours for a consultant anaesthetist in the Lobotesis protocol, compared with three hours in the Balami micro-costing. The Balami micro-costing allocated three hours to the Stroke Team, consisting of stroke nurse, stroke consultant, registrar and foundation doctor or core trainee, in some cases. The Balami micro-costing also allocated one hour each for use of GA and the Recovery Area post MT.

The Balami study provided information on resource use in the post-operation recovery stage which was not covered in the Lobotesis protocol. Importantly, the micro-costing study also provided standard error estimates of key parameters of the MT procedure (see Table 7.2 and Appendix 7.G) which allowed for an exploration of the related decision uncertainty in the cost-effectiveness analysis (see results section below). However, due to data limitations, it was assumed that the cost for IVT and non-thrombolytic treatments would be the same as that used in the Lobotesis study.

7.3.2.2 Description of the Candio model

The recently published model by Candio and colleagues (Candio et al., 2021), hereafter referred to as the Candio model, is a mathematical model that was adapted from the Lobotesis model. The model design is a Markov model with an embedded decision tree. In the published analysis, the authors adopted a societal cost perspective, including health and social care costs, informal care costs, and

productivity losses. The decision tree component illustrates the potential differences in long-term disability and mortality at three months post stroke, as defined by the modified Rankin Scale (mRS), comparing MT treatment in combination with intravenous thrombolysis (IVT), compared to standard care defined as IVT alone. The Markov Model then analysed the impact of interventions on costs and survival, and quality of life over a 5-year time horizon. Based on the criteria used in previous RCT studies (see Analysis section below), eligible ischaemic stroke patients were assumed to either undergo a MT procedure (MT + standard care) or receive standard care only. For patients aged 80 years old or over, standard care was defined as the non-thrombolytic treatment. For patients below the age of 80 years, standard care was defined as IVT+ non-thrombolytic treatment.

The effectiveness of MT and the baseline (that of the comparator/s) 0-6 mRS score distribution were derived from IPDA of five trials (HERMES) (Goyal et al., 2016). The cohort data drawn from the Oxford Vascular Study (OXVASC) (Rothwell et al., 2005) was used to derive and calculate resource use and therefore costs, survival and quality of life parameters for each of the six mRS scores (stroke survivors, 0-5 mRS score) states and six follow-up points up to 5 years (i.e. 3 months, 1, 2, 3, 4, 5 years after the event). In terms of extrapolation, the difference in terms of costs and outcomes between the intervention (MT) and the comparator arms in the model is solely given by the difference in the 3-month mRS score distribution. Therefore, for instance, because of a reduction in the proportion of patients with an mRS score of 5 at 3 months due to MT, fewer costs and better survival/quality of life outcomes will gradually accumulate over the 5-year time horizon, relative to the comparator.

The main modelling outcome was the 3-month modified Rankin Scale (0-6) distribution from effects on costs and outcomes were projected. Probabilistic sensitivity analysis was used to obtain the probability of MT being cost-effective. Further details of the model have been published elsewhere (Candio et al., 2021).

7.3.2.3 Model parameters

In order to allow for comparability between the results of this study and Candio's analysis, decision analytical model parameters and baseline settings were aligned with those used to undertake Candio's analysis (Candio et al., 2021). These include parameters relating to post-treatment events and effects (e.g., post-treatment health and social care costs, mortality and quality of life) and target population. As for the latter, the population was the UK population 2017 including individuals aged 20 years or over, based on three identified selection criteria: stroke severity defined as NIHSS score of ≥ 5; time to symptom onset within 6 hours and not disabled before event as defined as modified Rankin Scale (mRS) of <3.

Model simulations were run for 28 age group /gender combinations (14 five-year age groups, i.e., 20-24, 25-29 up to >=85 years old, and defined for both gender groups, female/male) over a five-year time horizon. Results were subsequently combined based on group proportions.

Two perspectives for economic evaluation were considered at a cost-effectiveness threshold of £20,000 per QALY gained; a societal perspective including informal care costs, and productivity losses, as well as health and social care costs, and a health and social care perspective only. Quality-adjusted life

years, defined as the survival time weighted by the quality of life experienced by patients, was defined as the primary health benefit (Appendix 7.G). The price year was 2017/18, and all costs and outcomes were discounted at an annual 3.5% rate, in line with official guidance.

7.3.2.4 Model Outcomes

The main outputs of interest from the simulation were: differences in incremental costs in the incremental cost-effectiveness ratio (ICER) of MT vs. standard care, which was estimated by dividing the difference in mean costs by the difference in mean QALYs for MT compared to standard care, and probability of MT of being cost-effective. The latter is illustrated using a cost-effectiveness acceptability curve (Figure 7.1) which shows the probability that an intervention is cost-effective for a range of WTP for an additional QALY gain (Fenwick and Byford, 2005).

The primary, secondary and sub-group analyses performed were as follows:

7.3.2.4.1 Primary analysis

The primary analysis was a comparison of the model outputs using the Candio model defaults of Lobotesis resource use and NHS Reference Costs, with outputs when the micro-costing results were used.

7.3.2.4.2 Secondary analysis

The main secondary analysis was to repeat the primary analysis for each of the five treatment centres in the micro-costing study, so introducing differences between their specific costs and the 5-centre average used in the baseline.

7.3.2.4.3 Subgroup analyses

Seven subgroups were also considered, based on type of anaesthesia, admission to ICU, and model of care: 1) General anaesthesia (GA) 2) Local anaesthesia (LA) 3) conscious sedation (CS) 4) ICU/HDU admission 5) direct admission to HASU 6) Mothership model of care 7) Drip-and-Ship model of care.

The anaesthesia and ICU admission subgroups are single points on the treatment pathway and so are most likely to have effects on procedure and treatment costs. However, the model of care (Mothership and Drip-and-Ship) subgroups involve the whole treatment pathway, and so may impact on total costs. In addition, all subgroups could have an impact on the probability of MT being cost-effective. Additionally, there could be variation across the 5 individual UK centres from the type of anaesthesia used or admission to ICU by individual centre. Subgroup analysis was not considered in the Lobotesis protocol or in the Ruggeri and Candio model analyses (Ruggeri et al., 2018, Lobotesis et al., 2016, Candio et al., 2021).

Table 7.2. Extracted baseline data from the Lobotesis protocol and from the five UK centres collectively

Resource use items and costs	Lobotesis Protocol	Balami micro-costing (All Patients) N=310
Primary intervention device		
Stent-retrievers		
Unit (mean)	1.2	0.57
Std error	NA	0.028
95% CI	NA	0.52 - –.63
Unit cost	£3,190	£3,120
Total cost	£3,828	£1,778
Thrombo-Aspirators		
Unit (mean)	NA	0.72
Std error	NA	0.026
95% CI	NA	0.67 - –.77

Unit cost	**NA**	**£921**
Total cost	**£0**	**£663**
Total cost of Primary intervention devices	**£3,828**	**£2,442**
Catheters and support kits		
Catheter/support kit		
Unit (mean)	**1**	**NA**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**NA**
Total cost	**£920**	**£0**
Direct Access Catheter		
Unit (mean)	**NA**	**0.42**
Std error	**NA**	**0.028**
95% CI	**NA**	**0.37 - –.48**
Unit cost	**NA**	**£595**
Total cost	**£0**	**£250**
Proximal Balloon Flow Arrest Guide Catheter		
Unit (mean)	**NA**	**0.08**
Std error	**NA**	**0.015**
95% CI	**NA**	**0.05 - –.11**
Unit cost	**NA**	**£595**
Total cost	**£0**	**£48**
Carotid Stent		
Unit (mean)	**NA**	**0.09**
Std error	**NA**	**0.016**
95% CI	**NA**	**0.06 -0.12**
Unit cost	**NA**	**£800**
Total cost	**£0**	**£72**
Total cost of Catheters and supportive kits	**£920**	**£370**
Consumables		
Procedure Pack		
Unit (mean)	**1**	**NA**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**£35**	**NA**
Total cost	**£35**	**£0**
Drapes/Gowns/Gloves		
Unit (mean)	**1**	**NA**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**NA**
Total cost	**£80**	**£0**
Sheath		
Unit (mean)	**1**	**NA**
Std error	**NA**	**NA**

95% CI	**NA**	**NA**
Unit cost	**NA**	**NA**
Total cost	**£15**	**£0**
Drapes/Gowns/Gloves, procedure pack and others		
Unit (mean)	**NA**	**1**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**NA**
Total cost	**£0**	**£191**
Total cost of Consumables	**£130**	**£191**
Venue		
Interventional Suite		
Unit (mean)	**3**	**2**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**£150**	**£405**
Total cost of Venue	**£450**	**£810**
Recovery post-MT		
Recovery Area		
Unit (mean)	**NA**	**0.60**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**90.2**
Total cost	**£0**	**£54**
Recovery Nurse		
Unit (mean)	**NA**	**0.4**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**£49**
Total cost	**£0**	**£20**
Total cost of Recovery post-MT	**£0**	**£74**
Resource use items and costs	**Lobotesis protocol**	**Balami Micro-costing (All Patients) N=310**
Staffing		
Anaesthetist (Consultant)		
Unit (mean)	**4**	**3**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**£157**	**£157**
Total cost	**£628**	**£471**
Anaesthetist assistant		
Unit (mean)	**4**	**3**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**£58**	**£58**

Total cost	**£232**	**£174**
Anaesthetist SpR		
Unit (mean)	**NA**	**0.40**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**£60**
Total cost	**£0**	**£24**
Radiographer Band (1)		
Unit (mean)	**3**	**2**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**£58**	**£58**
Total cost	**£174**	**£116**
Radiographer Band (2)		
Unit (mean)	**NA**	**0.6**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**£58**
Total cost	**£0**	**£35**
Consultant INR		
Unit (mean)	**3**	**3**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**£140**	**£140**
Total cost	**£420**	**£420**
Registrar		
Unit (mean)	**3**	**0.4**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**£60**	**£60**
Total cost	**£180**	**£24**
Nurse Band 7		
Unit (mean)	**3**	**3**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**£58**	**£58**
Total cost	**£174**	**£174**
Scrub Nurse Band 5		
Unit (mean)	**3**	**3**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**£49**	**£49**
Total cost	**£147**	**£147**
Scrub Nurse Band 6		
Unit (mean)	**NA**	**0.4**

Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**£58**
Total cost	**£0**	**£23**
Stroke Consultant		
Unit (mean)	**NA**	**3**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**£140**
Total cost	**£0**	**£420**
Stroke Nurse		
Unit (mean)	**NA**	**3**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**£58**
Total cost	**£0**	**£174**
Stroke SpR		
Unit (mean)	**NA**	**0.6**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**£60**
Total cost	**£0**	**£36**
FY2/CTI**		
Unit (mean)	**NA**	**0.2**
Std error	**NA**	**NA**
95% CI	**NA**	**NA**
Unit cost	**NA**	**£58**
Total cost	**£0**	**£12**
Total cost of Staffing	**£1,955**	**£2,250**
Total cost of MT intervention	**£7,283**	**£6,135**

7.3.3 RESULTS

The results are presented first for the primary and secondary analyses and then for the sub-group analyses. The primary analysis is the baseline Lobotesis vs Balami micro-costing analysis for all centres combined, and the secondary analysis is for the individual five centres. Finally, results are presented for sub-groups by type of anaesthesia, ICU admission and model of care.

7.3.3.1 Primary analysis (Lobotesis vs Balami micro-costing)

The overall treatment costs including IVT and non-thrombolytic therapy, were £7,859 (95 % CI £7,859 - £7,859) for Lobotesis and £6,711 (95% CI £6,537 - £6,894), based on Balami micro-costing for all centres. Similarly, the mean costs of MT procedure were £7,283 (95% CI £7,283 - £7,283) for Lobotesis and £6,135 (95% CI £ 5,961 - £6,318) based on the Balami micro-costing analysis for all centres. The MT intervention cost accounted for more than 90% of the total treatment cost in both groups.

Mechanical thrombectomy was found to be dominant (negative ICER, less costly and more effective than the comparator) both when the Lobotesis protocol and the Balami micro-costing data were used. The probability of being cost-effective at a £20,000 NICE WTP threshold per extra QALY was 100% in both cases (Figure 7.2). As shown in Figure 7.1, MT would be 40% likely to be cost-effective if a QALY was valued at zero (MT generates cost-savings), with this probability increasing up to 100% at around £15,000.

Converting these results into total costs for all patients included in the micro-costing, the Candio model shows that using the micro-costing data resulted in a total cost saving from MT versus IVT from the health care perspective over 5 years, of £52,625,411 (£2,297 per treated patient), compared with £26,334,323 (£1,150 per treated patient) using the Lobotesis data and Reference Costs. From a wider societal perspective, these differences increased to £105,941,395 (£4,625 per treated patient) using the micro-costing data and £79,650,306 (£3,477 per patient treated) using the Lobotesis protocol and reference costs. Table 7.3 shows the results of the primary analysis.

7.3.3.2 Secondary Analysis

Table 7.4 reports the results of the secondary analysis.

The overall treatment costs including IVT and non-thrombolytic therapy varied between £5,938 (95% CI £5,531 - £6,386) and £7,722 (95% CI £ 7,374 - £ 8,061) for the individual centres. Similarly, the MT intervention cost for the individual five centres also varied between £ 5,362 (95% CI £4,955 - £ 5,810) and £7,146 (95% CI £6,798 - £7,485).

In all centres, MT was found to dominant compared to standard care. The probability of being cost-effective at £20,0000 per extra QALY (NICE's'lower WTP threshold) was 100% for all centres. The cost savings varied from £29,473,923 (£1,287 per treated patient) up to £70,353,328 (£3,071 per patient) from a healthcare perspective. Similarly, from a wider societal perspective these differences also varied with increased savings from £82,789,906 (£3,614 per treated patient) to £123,669,312 (£5,398 per treated patient) for the individual centres.

Table 7.3. Primary Analysis (Lobotesis vs Balami micro-costing data)

Treatment combination*		**Lobotesis et al., 2016**	**Balami micro-costing (All 5 centres)**
MT+IVT	52%		
MT only	48%		
MT intervention cost		£ 7,283	£ 6,135
2.50%		£ 7,283	£ 5,961
97.50%		£ 7,283	£ 6,318
Treatment cost		£ 7,859	£ 6,711
2.50%		£ 7,859	£ 6,537
97.50%		£ 7,859	£ 6,894
Health and Social care perspective			
Deterministic ICER		MT dominates	MT dominates
Total cost-savings to health and social care sector		£ 26,334,323	£ 52,625,411
2.50%		-£ 149,278,171	-£ 122,583,403
97.50%		£ 138,333,202	£ 179,008,161
Per patient treat cost-saving		£ 1,150	£ 2,297
Probability cost-effective at a £20,0000 (€ 22,727) NICE's'WTP threshold per extra QALY		100%	100%
Societal perspective			
Deterministic ICER		MT dominates	MT dominates
Total cost-savings to society		£ 79,650,306	£ 105,941,395
2.50%		-£ 125,352,489	-£ 104,175,980
97.50%		£ 194,124,997	£ 241,901,916
Per patient treated cost-saving		£ 3,477	£4,625
Probability cost-effective at a £20,0000 (€ 22,727) NICE's'WTP threshold per extra QALY		100%	100%

5-year time horizon; year of analysis=2017; MT=mechanical thrombectomy; IVT=intravenous thrombolysis.
ICER=incremental cost-effectiveness ratio; NICE=National Institute of Health and Care Excellence.
WTP=willingness to pay. *based on the proportion of >=80 yers old within the treated group of patients.

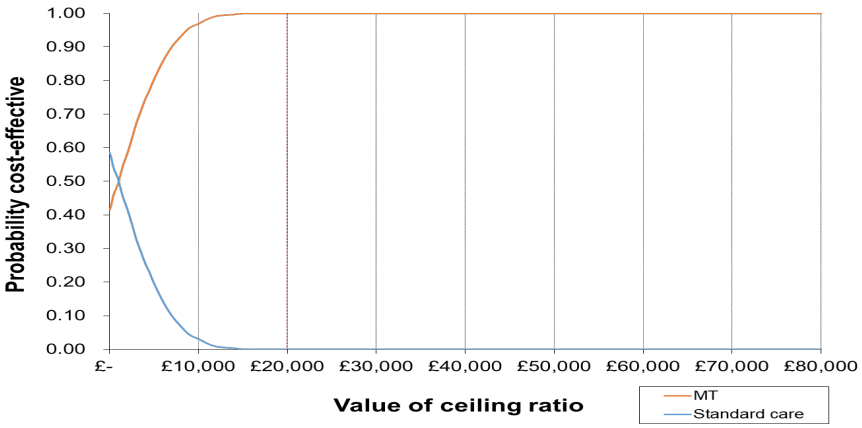


Figure 7.2. Cost-effectiveness acceptability curve

Table 7.4. Secondary Analysis (Lobotesis, Balami micro-costing All centres and individual centres A-E)

Treatment combination* MT+IVT 52% MT only 48%	**Lobotesis et al., 2016**	**Balami micro-costing (All Centres)**	**Balami micro-costing (Centre A)**	**Balami micro-costing (Centre B)**	**Balami micro-costing (Centre C)**	**Balami micro-costing (Centre D)**	**Balami micro-costing (Centre E)**
MT intervention cost	£ 7,283	£ 6,135	£ 7,146	£ 6,656	£ 5,724	£ 5,362	£ 6,841
2.50%	£ 7,283	£ 5,961	£ 6,798	£ 6,427	£ 5,331	£ 4,956	£6,456
97.50%	£ 7,283	£ 6,318	£ 7,485	£ 6,890	£ 6,084	£ 5,810	£ 7,226
Treatment cost	£ 7,859	£ 6,711	£ 7,722	£ 7,232	£ 6,300	£ 5,938	£ 7,416
2.50%	£ 7,859	£ 6,537	£ 7,374	£ 7,003	£ 5,907	£ 5,531	£7,031
97.50%	£7,859	£6,894	£ 8,061	£ 7,4669	£ 6,660	£ 6,386	£ 7,802
Health and Social care perspective							
Deterministic ICER	MT dominates	MT dominates	MT dominates	MT dominates	MT dominates	MT dominates	MT dominates
Total cost-savings to health and social care sector	£ 26,334,323	£ 52,625,411	£ 29,473,923	£ 40,694,472	£ 62,052,001	£ 70,353,328	£36,471,532
2.50%	-£ 149,278,171	-£ 122,583,403	-£ 153,197,303	-£128,789,394	-£ 120,933,484	-£ 100,488,158	-£139,702,369
97.50%	£ 138,333,202	£ 179,008,161	£136,689,062	£ 166,251,956	£ 175,560,497	£ 186,531,624	£ 150,961,559
Per patient treat cost-saving	£ 1,150	£ 2,297	£ 1,287	£ 1,776	£ 2,709	£ 3,071	£ 1,592
Probability cost-effective at a £20,0000 (€ 22,727) NICE's'WTP threshold per extra QALY	100%	100%	100%	100%	100%	100%	100%
Societal perspective							
Deterministic ICER	MT dominates	MT dominates	MT dominates	MT dominates	MT dominates	MT dominates	MT dominates

Total cost-savings to society	£79,650,306	£105,941,395	£ 82,789,906	£94,010,455	£ 115,367,984	£123,669,312	£89,787,515
2.50%	-£125,352,489	-£ 104,175,980	-£110,635,245	-£108,995,140	-£87,556,296	-£ 72,149,334	-£107,998,531
97.50%	£ 194,124,997	£ 241,901,916	£ 208,863,246	£223,974,752	£257,440,799	£ 244,703,700	£ 215,572,951
Per patient treated cost-saving	£ 3,477	£ 4,625	£ 3,614	£4,104	£ 5,036	£ 5,398	£ 3,919
Probability cost-effective at a £20,0000 (€ 22,727) NICE's'WTP threshold per extra QALY	100%	100%	100%	100%	100%	100%	100%

7.3.3.3 Subgroup Analysis

Table 7.5 reports the results of the analyses by sub-groups based on anaesthesia pre and peri-operatively, ICU/HDU admission post MT operation, and overall model of care.

7.3.3.3.1 Anaesthesia

The treatment cost using LA was £6,801 (95% CI £6,626 - £6,977), £6,939 (95% CI £6,767 -£7,114) using GA and £6,879 (95% CI £6,699- £7,059) using CS and for MT intervention cost, LA, £6,226 (95% ££ 6,050 - £ 6,402), GA £6,363 (95% CI £6,191 - £ 6,538) and CS £6,303 (95% CI £6,123 - £6,483).

MT intervention remained the dominant strategy and the probability of being cost-effective at a £20,0000 NICE WTP threshold per extra QALY was 100% with any forms/combinations of anaesthesia. While MT using all forms of anaesthesia was associated with cost savings, the savings were greater with LA than with GA or CS. MT intervention using LA was associated with a cost savings of £2,207 per patient from both a health and a social care perspective and £4,534 per patient from a societal perspective. Table 7.5 shows the output from the type of anaesthesia.

7.3.3.3.2 ICU admission

Admission to ICU post MT was £7,728 (95% CI £7,282- £8,254) and despite the additional cost compared with £6,135 (95% CI £5,961 - £6,318) for Balami micro-costing baseline with no ICU admission, the cost-effectiveness resultsremained unchanged from the base-case scenario. Table 7.6 shows the output from ICU admission.

7.3.3.3.3 ICU admission and Anaesthesia

While ICU admission following MT with any form of anaesthesia was associated with cost savings, it was more marked in the LA group admitted to ICU. The costs saving was £2,207 per patient from both the health and social care perspective and £4,534 from a purely societal perspective.

Table 7.5. Type of Anaesthesia (General anaesthesia, Local anaesthesia and Conscious sedation)

ANAESTHESIA	Micro-costing data (All 5 centres)	Balami micro-costing (All 5 centres) LOCAL anaesthesia- only	Balami micro-costing (All 5 centres) GENERAL only	Balami micro-costing (All 5 centres) CONSCIOUS only
MT intervention cost	£ 6,294	£ 6,226	£ 6,363	£6,303
2.50%	£ 6,107	£ 6,050	£ 6,191	£ 6,123
97.50%	£6,471	£ 6,402	£ 6,538	£6,483
Treatment cost	£ 6,870	£ 6,801	£ 6,939	£ 6,879
2.50%	£ 6,683	£ 6,626	£ 6,767	£ 6,699
97.50%	£ 7,047	£ 6,977	£ 7,114	£ 7,059
Health and Social care perspective				
Deterministic ICER	MT dominates	MT dominates	MT dominates	MT dominates
Total cost-savings to health and social care sector	£48,983,680	£50,559,071	£47,416,034	£ 48,790,540
2.50%	-£ 117,203,927	-£125,531,152	-£118,423,015	-£111,400,949
97.50%	£174,359,256	£157,821,793	£164,641,719	£ 157,646,580
Per patient treat cost-saving	£2,138	£ 2,207	£2,070	£2,130
Probability cost-effective at a £20,0000 (€ 22,727) NICE's'WTP threshold per extra QALY	100%	100%	100%	100%

Societal perspective				
Deterministic ICER	MT dominates	MT dominates	MT dominates	MT dominates
Total cost-savings to society	£102,299,664	£ 103,875,054	£ 100,732,018	£102,106,523
2.50%	-£ 101,691,114	-£98,825,058	-£ 93,103,310	-£112,576,754
97.50%	£ 233,738,888	£ 221,815,445	£ 225,761,362	£ 225,275,132
Per patient treated cost-saving	£4,466	£ 4,534	£ 4,397	£ 4,457
Probability cost-effective at a £20,0000 (€ 22,727) NICE's'WTP threshold per extra QALY	100%	100%	100%	100%

Table 7.6. ICU admissions (ICU admission with type of anaesthesia)

ICU / ANAESTHESIA	Balami micro-costing (All 5 centres) ICU ONLY	Balami micro-costing (All 5 centres) ICU + ANAESTHESIA	Balami micro-costing (All 5 centres) ICU + LOCAL	Balami micro-costing (All 5 centres) ICU + GENERAL	Balami micro-costing (All 5 centres) ICU + CONSCIOUS
MT intervention Cost	£ 7,728	£ 7,886	£ 818	£ 955	£,895
2.50%	£ 7,282	£430	£ 7,337	£ 7,493	£ 7,435
97.50%	£ 8,254	£ 8,404	£ 8,354	£ 8,485	£ 8,422
Treatment cost	£ 8,303	£ 8,462	£ 8,394	£8,531	£8,471
2.50%	£ 7,857	£8,006	£ 7,913	£8,069	£8,011
97.50%	£ 8,830	£8,980	£8,930	£9,061	£8,998

Health and Social care perspective					
Deterministic ICER	MT dominates	MT dominates	MT dominates	MT dominates	MT dominates
Total cost-savings to health and social care sector	£ 16,152,298	£12,510,567	£14,085,958	£ 10,942,921	£12,317,427
2.50%	-£151,138,181	-£167,921,100	-£163,184,460	-£161,639,158	-£167,436,368
97.50%	£129,406,802	£120,501,362	£121,098,174	£119,735,226	£143,122,921
Per patient treat cost-saving	£705	£546	£615	£478	£538
Probability cost-effective at a £20,0000 (€ 22,727) NICE's'WTP threshold per extra QALY	100%	100%	100%	100%	100%
Societal perspective					
Deterministic ICER	MT dominates	MT dominates	MT dominates	MT dominates	MT dominates
Total cost-savings to society	£69,468,282	£65,826,551	£67,401,941	£64,258,905	£65,633,411
2.50%	-£148,695,909	-£131,438,717	-£133,150,693	-£131,250,593	-£141,225,901
97.50%	£187,535,105	£188,005,357	£185,497,049	£200,840,705	£193,105,006
Per patient treated cost-saving	£3,032	£2,873	£2,942	£2,805	£2,865
Probability cost-effective at a £20,0000 (€ 22,727) NICE's'WTP threshold per extra QALY	100%	100%	100%	100%	100%

7.3.3.3.4 Model of care (MS and DS)

The treatment cost in the MS was £7,913 (95% CI £7,735 -£8,097) and £8,380 (95% CI £8,200- £ 8,573) for DS. The MT intervention cost was £ 7,337 (95% CI £7,159 -£ 7,521) and £7,804 (95% CI £7,997-£7,997) for MS and DS respectively with MT being dominant in both groups. However, the cost savings from both health and social care was higher in the MS group £25,089,478 (£1,095 per patient treated) than the £14,391,242 (£628 per patient treated) in the DS group. The savings from a societal perspective were also higher in the MS model of care compared with the DS, at £78,405,462 (£3,423 per patient treated) vs £67,707,225 (£2,956 per patient treated).

Table 7.7. Model of care (Mothership and Drip-and-Ship)

MODE OF CARE	Balami micro-costing (All 5 centres)	Balami micro-costing (All 5 centres) MOTHERSHIP only	Balami micro-costing (All 5 centres) DRIP-N-SHIP only
MT intervention cost	£7,515	£ 7,337	£ 7,804
2.50%	£ 7,312	£7,159	£ 7,624
97.50%	£ 7,745	£ 7,521	£ 7,997
Treatment cost	£ 8,091	£ 7,913	£ 8,380
2.50%	£ 7,888	£7,735	£ 8,200
97.50%	£ 8,321	£8,097	£ 8,573
Health and Social care perspective			
Deterministic ICER	MT dominates	MT dominates	MT dominates
Total cost-savings to health and social care sector	£21,017,246	£ 25,089,478	£14,391,242
2.50%	-£ 156,034,988	-£ 147,045,145	-£ 151,928,062
97.50%	£143,634,773	£140,245,596	£ 116,899,534
Per patient treat cost-saving	£917	£1,095	£628
Probability cost-effective at a £20,0000 (€ 22,727) NICE's'WTP threshold per extra QALY	100%	100%	100%
Societal perspective			
Deterministic ICER	MT dominates	MT dominates	MT dominates
Total cost-savings to society	£74,333,230	£78,405,462	£67,707,225
2.50%	-£ 135,989,297	-£ 122,236,166	-£ 140,307,055
97.50%	£ 208,619,248	£195,650,006	£186,579,562
Per patient treated cost-saving	£3,245	£3,423	£ 2,956
Probability cost-effective at a £20,0000 (€ 22,727) NICE's'WTP threshold per extra QALY	100%	100%	100%

7.3.3.4 Sensitivity Analysis

The analysis using the Candio model involved a set of probabilistic sensitivity and scenario analyses which aimed to ascertain whether those changes in assumptions regarding the cost of the intervention / pathway affected the cost-effectiveness conclusions.

7.3.4 Discussion

In the analysis reported above I have shown that, when using more granular and up-to-date cost information from my micro-costing analysis rather than the costs and assumptions used in previous studies, a comparison of MT with IVT results in substantially higher cost savings from both a health and social care and a societal perspective, than the savings suggested when using the Lobotesis resource use data. Using the Candio model to simulate 5-year costs and outcomes from MT and IVT, the type of anaesthesia and ICU admission – neither of which were explicitly considered in the Lobotesis Protocol – are associated with very wide variations in costs and cost savings across the five MT centres. The simulations shed some light on the implications that heterogeneity of treatment protocols and associated costs in actual clinical practice can have for decision making.

While the economic conclusions remain unchanged from previous studies (i.e.MT dominates IVT), the use of more accurate data regarding the MT intervention and pathway costs from my micro-costing data confirms that MT is highly likely to provide good value for money in UK settings, with potentially substantially larger cost savings than previously estimated, both from a health and social care and from a societal perspective. The cost savings from a wider societal perspective will impact not only on the patients but also on the families and the economy in terms of the impact on informal carers and losses in productivity.

Mechanical thrombectomy was found to be dominant in both the new model and the Lobotesis protocol, a result similar to other CE studies (Arora et al., 2018,

Ruggeri et al., 2018, Shireman et al., 2017, Steen Carlsson et al., 2017, Aronsson et al., 2016, de Andres-Nogales et al., 2017). There were cost savings from using stent retrievers and other devices from both the societal and healthcare perspectives. Unlike the Lobotesis Protocol in which only stent-retrievers were used, the Balami micro-costing reflects the real-life setting where a mixture of devices is used routinely. The Balami micro-costing also captures explicitly the type and number of devices employed. New trials used a mixture of devices; exceptionally EXTEND-IA, SWIFT PRIME and REVASCAT(Campbell et al., 2015a, Saver et al., 2015, Jovin et al., 2015) mainly used stent retrievers. Studies that compare devices have reported potential savings compared with SR through the use of Penumbra 5MAX ACE (Vidal and Milburn, 2016) and Direct Aspiration First-Pass Technique (ADAPT) (Comai et al., 2015).

The output from the new model also provides new insights into variations in cost savings across the individual centres. The variations can be explained by differences in how services are organised, their available resources and facilities, types of devices and method of anaesthesia. On arrival at hospital, patients may be directed straight to the Stroke Unit or to the Radiology Department, bypassing the ED. Cost savings are also affected depending on neuroscience facilities being on one or more sites. Scanning costs were calculated differently in different hospitals. They variously included or excluded capital depreciation, use of SR, or other devices and the proportion of MT cases requiring ICU admission. Centres using general anaesthesia and ICU admission more often had significantly higher costs. Repeated scans for all Drip-and-Ship patients or for selected cases, post MT 24-hour scans as opposed to only 24-hour post MT scans were additional

drivers of costs. The use of LA was associated with more cost savings than GA and CS.

Examining the whole treatment pathway, there were more cost savings in the MS compared with the DS model of care. The higher costs in the DS were due to: the additional emergency hospital attendance (EHA); imaging costs from the repeat EHA and CT scans at MT Centre; inter-hospital transportation and repatriations. This has implications for policy makers as to whether or not there should be an expansion of thrombectomy centres. Allen and colleagues' model (Allen et al., 2019) projected that the optimal number of MT centres in England should be 30, necessitating an increase from the current 24 centres.

The analysis shows that if patients are not transferred (MS), it is more cost-effective. However, it is essential to clarify that it is not a comparison of whether moving to an MS model of care for all suspected LAO patients who would otherwise go to the local hospital (DS), is cost-effective. That would include costs on non-LAO stroke and mimics having to be repatriated to the local hospital, which would be increased costs with no benefit.

Further modelling by the same group estimated that the additional six new centres would generate 190 QALYs (95%CI − – to 399) with a resultant net saving to the healthcare system of £1,864,000 per year (95% CI -£1,204,000 to £5,017,000). From their estimated budget impact, there would be a saving of £980,000 in the first year and £7.07 million in years 2 to 5 (McMeekin et al., 2019). The McMeekin used costs data from multiple sources, including cost associated with each level of mRS from a longitudinal study of patients in Belgium (Dewilde et al., 2017), cost of MT from my initial published micro-costing data on only 80

patients treated in the MS and DS model of care (Balami et al., 2018a) and ambulance costs from the Personal Social Services Research Unit (PSSRU).The results might have been different particularly in terms of the cost savings if my recent micro-costing data involving 310 patients (Balami et al., 2020) had been applied.

It is unlikely that all centres now providing IVT could become MT centres. Another option could require restructuring the pathway. The direct transfer model of care, where patients are transferred directly to an MT Centre for imaging and treatment before repatriation to their primary hospital, could be practised more widely. This model can save the costs of additional scans and transportation in the DS model. A limitation with the direct transfer, as shown in the modelling work by Allen and colleagues(Allen et al., 2018), is that MT centres could be overwhelmed with non-LAO stroke and mimics and non-MT primary stroke centres could lose the volume of patients necessary to sustain high quality IVT services. The direct transfer pathway already exists in some parts of the country. A similar structure which was practised for thrombolysis in London and Manchester following the reorganisation of services in 2010, was shown to reduce both length of stay and costs (Bray et al., 2013, Morris et al., 2014). However, the recent RACECAT trial showed no difference in clinical outcomes between direct transfer to Mothership and Drip and Ship models (Desai et al., 2021). A cost-effectiveness analysis of this trial has yet to be presented or published.

This study, unlike others, captured the whole treatment pathway. Arora and colleagues (Arora et al., 2018) incorporated the use of anaesthesia and interhospital transfer in their Australian cost effectiveness model adapted from the Lobotesis Protocol. Another CE study from a Swedish Perspective, using real

life registry data (Riksstroke), captured costs of transportation (interhospital transfer and repatriation), ICU admission, post-acute hospital costs and long-term costs, but did not include the type of anaesthesia used nor considered Model of Care factors (Steen Carlsson et al., 2017). This study is, therefore, more comprehensive as it characterises the heterogeneity of treatment across different settings.

7.3.4.1 Strengths and limitations

There are some limitations to the new simulation from using the Candio model. An inability to develop a new customised model means that the inherent limitations remain, potentially affecting the outcome.

The main limitation of the Candio model is the five-year time horizon, which may not capture all long-term costs and outcomes. A further limitation concerns the utility estimates.

While the difference in utility, and therefore QALYs, is time-dependent, as it accumulates over time as the two cohorts (the intervention and comparator arms) progress, a main structural assumption of Candio's model is that it assumes that stroke patients will not change their mRS score assigned at 3 months (i.e. the 3-month mRS score is a permanent state). Although this may impact on the precision of the economic estimates, these assumptions align with previous similar models by Lobotesis and Ruggeri.

There are also notable strengths to the Candio model when combined with the micro-costing data. Firstly, more granular data, for example the actual number of devices and catheters per patient, was used in the simulation. Secondly, using

the micro-costing data offers an opportunity to use the Candio model to explore: heterogeneity in type of anaesthesia, ICU admission, model of care and variations across individual centres. None of these could be explored in the Candio model using the Lobotesis Protocol. Lastly, both health and social care and societal perspectives are considered. The societal perspective also takesinto account informal care and productivity losses.

7.3.4.2 Conclusions

The micro-costing study used in this chapter to model the cost-effectiveness of MT vs IVT, is based on real-life data from high output MT centres, and has added new evidence to the limited, procedure-only economic evaluation studies that have predominated in the literature. It provides a more realistic estimate of the true cost savings and hence the viability of business cases for expansion of MT in the UK. This study has further confirmed the short and long-term cost savings of treatment with MT, both from a health and social care and a societal perspective. It has helped to identify the primary drivers of cost, including the use of GA and admission to ICU. It has also evaluated the cost/benefit variations in models of care. Significantly, it has added new economic evidence to the existing literature concerning stroke treatment pathways in the UK and beyond.

7.3.4.3 Implications for future research

Future studies should model different imaging selection strategies and the use of new devices to determine if they will impact on cost. Similarly, studies could collect data to validate the conclusion drawn in this study that wider use of LA will produce significant cost savings and better functional outcomes for patients.

Furthermore, studies could explore heterogeneity in other country settings where the uncertainty surrounding the investment decision may be higher: for example, in lower income countries, cost savings may be reduced as the value of health and social care resources is lower.

CHAPTER EIGHT

8 Discussion and Conclusion

8.1 Introduction

This thesis explored issues relating to the clinical and cost-effectiveness of MT in routine clinical setting and the cost of delivering MT within the NHS. The overall thesis aims were to establish the clinical effectiveness of MT for AIS through analysis of up to date estimates of efficacy of MT from RCTs and a UK registry**,** and to provide reliable and comprehensive estimates of the costs of providing MT in the UK NHS through a cost analysis study. The results and their implications are discussed at the end of each substantive chapter, but this final chapter provides an overview of the study findings and considers the limitations and challenges that arose when conducting the study. The contributions to the literature generated by this thesis are summarised, and the generalisability of the findings and their policy implications. The chapter concludes by identifying areas for further research.

8.2 Overview of thesis findings

This thesis has explored several aspects of MT in detail and in terms of clinical benefits, variations in treatment pathways in the different centres and the comprehensive costs of providing MT within the UK NHS.

The systematic review (SR) and meta-analysis (MA) of the clinical effectiveness of MT alongside IVT for AIS undertaken and conducted in Chapter 3,

demonstrated clear evidence of the benefits and safety of MT when used alongside IVT, in comparison with standard medical treatment (with or without IVT) for the treatment of AIS.

The empirical study in Chapter 4, of the extent to which the positive findings from the SR and MA of the thrombectomy trials are transferable to routine clinical practice, using prospective observational registry data, further confirmed the evidence for the clinical effectiveness and safety of MT outside the research setting. However, there were significant limitations due to missing and incomplete data, particularly for recanalisation rates and the 90-day follow-up records, so that any interpretations drawn must be duly qualified.

The systematic review of the treatment pathways of MT and IVT for AIS undertaken and conducted in Chapter 5, identified wide variability in the flow pathways for MT provision across several countries. Considerable differences in treatment pathways for delivering MT and IVT in routine clinical practice across a range of thrombectomy centres in the UK, Germany, Italy and Canada were also identified. The study captured the number of patients passing through every phase of the pathways; the type of imaging used; the form of treatment through to final discharge destinations, both for the individual centres and also collectively. Effective treatment pathways are critical for improving delivery of stroke care, particularly for an efficient delivery of MT.

The resources used and unit costs along the identified treatment pathways were established in Chapter 6. Through a comprehensive approach to measuring costs, the true cost of delivering MT and the main drivers were also determined.

The main drivers of cost are thrombectomy devices and other consumables; use of general anaesthesia (GA) or conscious sedation; carotid stenting and admission to Intensive Care Unit/ High dependency Unit (ICU/HDU). The variations in costs across the five MT centres arose mainly from: imaging; type of devices used; use of GA and ICU/HDU admission. These findings, which should be of value to policymakers for strategic planning of stroke services, provide detailed estimates of the cost, from an NHS perspective, of providing MT in a range of routine clinical settings across five MT centres in the UK.

The SR of economic evaluation studies was conducted in Chapter 7. It established the cost-effectiveness conclusions of MT compared to standard practice reported in previous studies. Running a simulation using an existing cost-effectiveness model with more granular data from the micro-costing study, identified the short and long-term cost-savings of treatment with MT, both from a health and social care and a societal perspective. Chapter 7 also evaluated the cost/benefit variations in models of care.

8.3 Limitations and strengths this research

The UK SITS Database findings of the clinical and safety benefits of MT in clinical practices compared with those revealed in the MT cannot be considered reliable because of the amount of missing data. The data were not robust enough to answer the questions regarding the efficacy and safety of the utilisation of MT in the UK, cannot be definitively answered due to missing and incomplete data, particularly for recanalisation rates and the 90-day follow-up records.

The thesis revealed variations in the treatment pathways in four regions (Greater London, North East and West Midlands of England and Northern Ireland) that were studied, out of the 12 regions in the UK. The lack of wider regional coverage was another limitation. Ideally, all the regions in the UK should have been included to give a comprehensive picture of the various treatment pathways currently in use. It was, however, not possible to study centres from all regions due to resource constraints.

The micro-costing study in Chapter 6, addressing the costs of delivering MT, was conducted at five hospitals in four regions. While findings from each hospital are reliable since a significant amount of primary data was collected, the generalizability of the findings would be stronger if more hospitals had been studied covering wider regions of the UK.

Furthermore, whilst data were available for the Individual Patient Data (IPD) up to the time of discharge, they were limited to only 24hrs for the Total Patient Data (TPD), which restricted the breadth of the comparison. Another limitation was the unavailability of resource-use data after repatriation or discharge from the MT centres into the community. It was therefore not possible to calculate the costs after repatriation or rehabilitation.

There are some limitations to the new simulation from using the recently published Candio mathematical model. The inability to develop a new, customised model for the economic model simulation, means that the limitations inherent in Candio's model are embedded in and potentially affect the conclusions. The main limitation arising from the use of Candio's model is the

five-year time horizon; this prevents capture of all long-term costs and outcomes beyond five years.

The main strengths of this thesis include: first, the identification of clinical pathways in multiple centres and variations across the centres involved; second, the granular data, for example the actual number of devices and catheters per patient used in the simulation; third, the micro-costing data that enabled exploration of heterogeneity in type of anaesthesia, ICU/HDU admission, model of care and variations across MT centres.

8.4 Challenges of this research

This thesis provided some interesting challenges to address. In the early stages of the study, there were practical challenges of getting some of the high output centres to participate in the study, especially those in the London region. Most of the participating centres initially did not collect or have comprehensive data. They started collecting the data after agreeing to participate in the study. Another huge challenge was obtaining detailed individual patient datasets in sufficient quantity to use for the micro-costing study. Lastly, the Covid-19 pandemic imposed further challenges and pressures. One significant consequence, for example, was that complete records of data from international sources within the defined time horizon became unobtainable.

Besides the undoubted benefits of newly acquired team-work skills, the positive relationships established with other professionals working in this field across the

UK and overseas, provide a foundation for future collaborative studies to advance stroke treatment in the years ahead.

Nonetheless, future teams planning to emulate or update this wide and deep collection of data should be aware of the complex, time-consuming and labour-intensive nature of this work and the stresses that can be imposed upon the team.

Having contextualised the findings of the thesis and described the challenges, limitations and strengths, the following section describes the contribution it makes to the literature.

8.5 Contribution to the literature

Despite the limitations and challenges described in the previous section, this thesis has contributed to the literature in the following ways:

1. **by generating new evidence from the SR and MA of MT for the treatment of LAO AIS**

   Mechanical thrombectomy for the treatment of LAO AIS in the MT trials was conducted at well-established MT centres with experienced INRs. The SR & MA of MT trials for the treatment of AIS demonstrated clear evidence of the benefits of MT in terms of significantly helping to restore patients' functional independence. This SR demonstrated how the improved clinical function (modified Rankin Scale score of 0–2) at 90 days poststroke, became more pronounced in the subgroup analysis of MT trials where >50% of patients were treated with thrombectomy devices. The new evidence generated from the SR & MA on the use of MT for the treatment of MT in Chapter 3 formed the basis for NICE to recommend MT to the NHS in 2016. This is in addition to other supporting evidence.

2. **by establishing the treatment pathway and variations in the pathways across the UK and international centres**

   This study has also contributed to the literature by confirming the clinical benefits and safety of MT for the treatment of AIS outside the research setting. Additionally, the study established the different and varied pathways for the treatment of MT and IVT in different centres in the UK, Germany, Italy and Canada.

3. **by determining the true costs of MT and the drivers of those costs**

The thesis has further provided evidence of the true cost of MT within the NHS, in addition to establishing the drivers of costs including GA and admission to ICH/HDU. The mean 24-hour cost and cost up to repatriation per patient treated with MT +/- IVT, were within the NHS Tariff, but the other incurred costs at different time horizons were above the Tariff. Thrombectomy procedure accounted for 73% of the 24-hour cost and devices accounted for 65% of the procedure costs. Among the drivers of costs are the use of devices, particularly if multiple devices are used in one procedure.

This thesis provided detailed understanding of the costs associated with AIS patients progressing through the established treatment pathways, the various resources that might be used and their costs. Since the standard treatment for patients with LAO stroke is now MT and being a new treatment, it is vital to understand how much it costs to deliver the service within the NHS. The transparent breakdown of the costs of delivering MT allows for other centres or researchers to apply these specific costs within their own studies.

Given the detailed data collected with resources used and unit costs along the whole treatment pathway that was undertaken - –rom pre-hospital notification to hospital discharge from MT centre – users of the data such as service planners, modellers and other researchers, can have confidence in the evidence generated.

4. **by providing the health economic evidence around cost-savings and the drivers of associated costs.**

The economic evaluation of MT vs IVT is based on the simulation using a recently published model that utilises micro-costing data from real-life settings. These were aligned with the identified clinical pathways from high output MT centres and have consequently added new evidence to the more limited, procedure-only, economic evaluation studies that have to date predominated in the literature. The micro-costing study has provided a more realistic estimate of the true cost savings and hence, the viability of business cases for expansion of MT in the UK. This aspect provides new evidence on the primary drivers of cost, including the use of GA and admission to ICU and the cost/benefit variations in models of care. Finally, the study has significantly added new economic evidence to the existing literature concerning stroke treatment pathways in the UK and beyond. Based on the differences between the UK and other countries, there is probably valuable potential for the UK and some of the MT centres in Germany and Canada, to benefit from each other's research in this field.

8.6 Generalisability of the findings

Mechanical thrombectomy in combination with IVT is now both the standard treatment and also the recommended treatment for patients with AIS stroke due to LAO. The evidence from the SR and MA of the trials are transferable outside the research setting and generalisable to clinical centres with the facilities and the interventionists to perform the intervention.

The established true cost of delivering MT in routine clinical settings from five UK centres can reasonably be applied in other hospitals in the UK and beyond. Even if pathways in other hospitals are very different, further costing studies might be of value in such centres. Arguably, there could be variations in costs, depending on flow pathway, the types of devices and anaesthesia used. Similarly, the cost-savings from treatment with MT are also generalisable, albeit the variations in the amount of cost savings depend on the model of care, type of anaesthesia and devices used.

In contrast, the treatment pathways with the variations identified in just four regions of the UK (Greater London, North East and West Midlands of England, and in Northern Ireland) may not be generalisable to the other nine regions in the UK.

Having established, the main findings and their limitations, in addition to the contribution to the literature and generalisability, the policy implications will be discussed next.

8.7 Policy implications

Despite the robust clinical efficacy and cost-effectiveness of MT with IVT for the treatment of AIS with the recommendation by NICE and several guidelines, there are challenges to the full implementation of thrombectomy services within the NHS. Not all hospitals have the infrastructure and manpower to offer the treatment and even some of the large comprehensive stroke centres are not providing a 24/7 MT service. The results from this thesis may be of value when considering future service reconfiguration in terms of helping to support the development of wide-ranging business cases and being the catalyst for the establishment of more thrombectomy centres throughout the UK. These cost estimates can be used by hospital managers and decision makers to assess the budget impact of policies to use MT efficiently.

The establishment of main drivers of cost include: thrombectomy devices and other consumables; the use of GA or conscious sedation; carotid stenting and admission to ICU/HDU. The variations in cost across the five MT centres were shown to arise mainly from the costs of imaging, devices, GA and ICU/HDU admissions. The detailed examination of the whole treatment pathway revealed there are certainly more cost savings to be made by using the MS compared with the DS model of care and more potential cost-savings through using LA compared with GA. Such a comprehensive assembly of data costs should be invaluable to policymakers for the strategic planning of stroke services. Notably, the pandemic has influence treatment pathways with higher costs due to the use of Personal Protective Equipment (PPE) and other safety measures such as air cycling after each MT intervention.

8.8 Future research

There is a clear need for a larger study to involve significantly more regions in the UK to better capture the regional variations in costs of MT delivery for meaningful comparison with the potential for eventual standardisation.

Similarly, there is need for a study to evaluate how the pandemic has influenced IVT and MT treatment pathways, the additional costs of Personal Protective Equipment (PPE), and air cycling leading to longer delays between cases etc. This should optimise the standard of care for stroke patients throughout the country during future pandemics.

Future studies could also evaluate the costs after discharge from MT Centres for patients repatriated to their primary hospitals and for those transferred to community hospitals, pending further rehabilitation. There is, moreover, a need to establish the cost for different models of care, such as motherships, drip-and-ship and direct transfer, including costs relating to non-LAO stroke patients affected by such service changes to help identify the costs and clinical efficacy of each for future planning of thrombectomy services.

Future studies should model different imaging selection strategies and the use of new devices to determine if they will impact on cost. Similarly, studies could collect data to validate the probability shown in this study that wider use of LA will produce significant cost savings and better functional outcomes for patients.

Subsequent studies could explore heterogeneity in other country settings where the uncertainty surrounding the investment decision may be higher as, for

example, in lower income countries where cost savings may be reduced as the funding for the health and social care resources is lower.

Finally, future research could explore the use of robotic surgery, particularly in view of the shortage of INRs. There is a potential for future application of the robotically-assisted endovascular interventions for AIS in remote areas where there are no INRs.

The safety and feasibility of robotically assisted percutaneous coronary intervention in coronary lesions have been established in the PRCISE and the CORA-PCI Studies (Mahmud et al., 2017, Weisz et al., 2013) and in case series in which tele-stenting procedures of type A lesions achieved good angiographic results with no peri-procedural complications (Patel et al., 2019).

Robotic-assisted brain aneurysm embolization using the CoroPath GRX System has only recently been explored (ClinicalTrials.gov Identifier: NCT04236856, 2020). The ongoing, prospective, single-arm, multi-centre, non-inferiority GRX neuro-study, designed to evaluate the effectiveness and safety of the CoroPath GRX System for endovascular cerebral aneurysm embolisation compared to historical controls (ClinicalTrials.gov Identifier: NCT04236856, 2020), when completed, could pave the way for Robotic-assisted cerebral endovascular therapy.

8.9 Concluding remarks

Mechanical thrombectomy with IVT is now a standard treatment for LAO stroke with demonstrated clinical and cost-effectiveness, and yet the full implementation of MT in the UK has been limited. Furthermore, there has been a lack of reliable information on the true costs of delivering MT in routine clinical practice within the NHS. Through this detailed micro-costing study, the true cost of MT within the clinical setting has been established. It is hoped that the findings from the study will influence future policy and contribute to a more efficient and effective implementation of MT services.

Through a mapping exercise, different treatment pathways and variations in pathways were identified. Effective treatment pathways are critical for improving delivery of stroke care, particularly for the efficient delivery of MT.

The evidence presented here will be disseminated to clinicians, researchers, health economists and decision-makers primarily through future peer reviewed journal articles and presentations at stroke and health economic conferences and symposia. The evidence generated here seeks to inform practice and, ultimately, to lead to more efficient and wider use of MT for the estimated 10,000 eligible NHS patients with AIS due to LAO that could benefit from the intervention.

Word Counts by Chapter

Word count excluding bibliography, declarations, tables and figures

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Chapter 9 References

ABILLEIRA, S., CARDONA, P., RIBÓ, M., MILLÁN, M., OBACH, V., ROQUER, J., CÁNOVAS, D., MARTÍ-FÀBREGAS, J., RUBIO, F., ALVAREZ-SABÍN, J., DÁVALOS, A., CHAMORRO, A., DE MIQUEL, M. A., TOMASELLO, A., CASTAÑO, C., MACHO, J. M., RIBERA, A. & GALLOFRÉ, M. 2014. Outcomes of a contemporary cohort of 536 consecutive patients with acute ischemic stroke treated with endovascular therapy. *Stroke,* 45**,** 1046-52.

ABILLEIRA, S., PEREZ DE LA OSSA, N., JIMENEZ, X., CARDONA, P., COCHO, D., PURROY, F., SERENA, J., ROMAN, L. S., URRA, X., VILARO, M., CORTES, J., GONZALEZ, J. A., CHAMORRO, A., GALLOFRE, M., JOVIN, T., MOLINA, C., COBO, E., DAVALOS, A. & RIBO, M. 2019. Transfer to the Local Stroke Center versus Direct Transfer to Endovascular Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory (RACECAT): Study protocol of a cluster randomized within a cohort trial. *Int J Stroke***,** 1747493019852176.

ACHIT, H., SOUDANT, M., HOSSEINI, K., BANNAY, A., EPSTEIN, J., BRACARD, S. & GUILLEMIN, F. 2017. Cost-Effectiveness of Thrombectomy in Patients With Acute Ischemic Stroke: The THRACE Randomized Controlled Trial. *Stroke,* 48**,** 2843-2847.

ADAMS, H. P., JR., BENDIXEN, B. H., KAPPELLE, L. J., BILLER, J., LOVE, B. B., GORDON, D. L. & MARSH, E. E., 3RD 1993. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke,* 24**,** 35-41.

AGOSTONI, E., CAROLEI, A., MICIELI, G., PROVINCIALI, L., TONI, D. & VIDALE, S. 2018. The organisation of the acute ischemic stroke management: key notes of the Italian Neurological Society and of the Italian Stroke Organization. *Neurol Sci,* 39**,** 415-422.

AGUIAR DE SOUSA, D., VON MARTIAL, R., ABILLEIRA, S., GATTRINGER, T., KOBAYASHI, A., GALLOFRÉ, M., FAZEKAS, F., SZIKORA, I., FEIGIN, V., CASO, V. & FISCHER, U. 2019. Access to and delivery of acute ischaemic stroke treatments: A survey of national scientific societies and stroke experts in 44 European countries. *European Stroke Journal,* 4**,** 13-28.

ALBERS, G. W., MARKS, M. P., KEMP, S., CHRISTENSEN, S., TSAI, J. P., ORTEGA-GUTIERREZ, S., MCTAGGART, R. A., TORBEY, M. T., KIM-TENSER, M., LESLIE-MAZWI, T., SARRAJ, A., KASNER, S. E., ANSARI, S. A., YEATTS, S. D., HAMILTON, S., MLYNASH, M., HEIT, J. J., ZAHARCHUK, G., KIM, S., CARROZZELLA, J., PALESCH, Y. Y., DEMCHUK, A. M., BAMMER, R., LAVORI, P. W., BRODERICK, J. P. & LANSBERG, M. G. 2018. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N Engl J Med,* 378**,** 708-718.

ALBERTA HEALTH SERVICES. 2016. *Endovascular Reperfusion Alberta (ERA). Alberta Health Services. December* [Online]. Available: https://albertahealthservices.ca/scns/Page13274.aspx [Accessed 15 March 2019].

ALEXANDROV, A. V. & GROTTA, J. C. 2002. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. *Neurology,* 59**,** 862-7.

ALLEN, M., PEARN, K., JAMES, M., FORD, G. A., WHITE, P., RUDD, A. G., MCMEEKIN, P. & STEIN, K. 2018. Maximising access to thrombectomy services for stroke in England: A modelling study. *European Stroke Journal,* 4**,** 39-49.

ALLEN, M., PEARN, K., JAMES, M., FORD, G. A., WHITE, P., RUDD, A. G., MCMEEKIN, P. & STEIN, K. 2019. Maximising access to thrombectomy services for stroke in England: A modelling study. *Eur Stroke J,* 4**,** 39-49.

ALMEKHLAFI, M., KUNZ, W., MENON, B., MCTAGGART, R., JAYARAMAN, M., BAXTER, B., HECK, D., FREI, D., DERDEYN, C. & TAKAGI, T. 2019. Imaging of patients with suspected large-vessel occlusion at primary stroke centers: available modalities and a suggested approach. *American Journal of Neuroradiology,* 40**,** 396-400.

ALMEKHLAFI, M. A., KUNZ, W. G., MCTAGGART, R. A., JAYARAMAN, M. V., NAJM, M., AHN, S. H., FAINARDI, E., RUBIERA, M., KHAW, A. V., ZINI, A., HILL, M. D., DEMCHUK, A. M., GOYAL, M. & MENON, B. K. 2020. Imaging Triage of Patients with Late-Window (6–24 Hours) Acute Ischemic Stroke: A Comparative Study Using Multiphase CT Angiography versus CT Perfusion. *American Journal of Neuroradiology,* 41**,** 129-133.

ALMEKHLAFI, M. A., MISHRA, S., DESAI, J. A., NAMBIAR, V., VOLNY, O., GOEL, A., EESA, M., DEMCHUK, A. M., MENON, B. K. & GOYAL, M. 2014. Not all "successful" angiographic reperfusion patients are an equal validation of a modified TICI scoring system. *Interv Neuroradiol,* 20**,** 21-7.

ANGERMAIER, A., LANGNER, S., KIRSCH, M., KESSLER, C., HOSTEN, N. & KHAW, A. 2011. CT-angiographic collateralization predicts final infarct volume after intra-arterial thrombolysis for acute anterior circulation ischemic stroke. *Cerebrovascular diseases,* 31**,** 177-184.

ARONSSON, M., PERSSON, J., BLOMSTRAND, C., WESTER, P. & LEVIN, L. A. 2016. Cost-effectiveness of endovascular thrombectomy in patients with acute ischemic stroke. *Neurology,* 86**,** 1053-9.

ARORA, N., MAKINO, K., TILDEN, D., LOBOTESIS, K., MITCHELL, P. & GILLESPIE, J. 2018. Cost-effectiveness of mechanical thrombectomy for acute ischemic stroke: an Australian payer perspective. *J Med Econ,* 21**,** 799-809.

ARSAVA, E. M., BALLABIO, E., BENNER, T., COLE, J. W., DELGADO-MARTINEZ, M. P., DICHGANS, M., FAZEKAS, F., FURIE, K. L., ILLOH, K., JOOD, K., KITTNER, S., LINDGREN, A. G., MAJERSIK, J. J., MACLEOD, M. J., MEURER, W. J., MONTANER, J., OLUGBODI, A. A., PASDAR, A., REDFORS, P., SCHMIDT, R., SHARMA, P., SINGHAL, A. B., SORENSEN, A. G., SUDLOW, C., THIJS, V., WORRALL, B. B., ROSAND, J. & AY, H. 2010. The Causative Classification of Stroke system: an international reliability and optimization study. *Neurology,* 75**,** 1277-84.

ASTRUP, J., SIESJÖ, B. K. & SYMON, L. 1981. Thresholds in cerebral ischemia - the ischemic penumbra. *Stroke,* 12**,** 723-5.

AVIV, R. I., MANDELCORN, J., CHAKRABORTY, S., GLADSTONE, D., MALHAM, S., TOMLINSON, G., FOX, A. J. & SYMONS, S. 2007. Alberta Stroke Program Early CT Scoring of CT perfusion in early stroke visualization and assessment. *AJNR Am J Neuroradiol,* 28**,** 1975-80.

AY, H., FURIE, K. L., SINGHAL, A., SMITH, W. S., SORENSEN, A. G. & KOROSHETZ, W. J. 2005. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol,* 58**,** 688-97.

BADHIWALA, J. H., NASSIRI, F., ALHAZZANI, W., SELIM, M. H., FARROKHYAR, F., SPEARS, J., KULKARNI, A. V., SINGH, S., ALQAHTANI, A., ROCHWERG, B., ALSHAHRANI, M., MURTY, N. K., ALHAZZANI, A., YARASCAVITCH, B., REDDY, K., ZAIDAT, O. O. & ALMENAWER, S. A. 2015. Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis. *Jama,* 314**,** 1832-43.

BALAMI, J., MCMEEKIN, P., WHITE, P., FLYNN, D., WIGGAM, I., FLYNN, P., CHEMBALA, J., NATARAJAN, I., DIXIT, A. & HUNTER, A. 2018a. Case costing of mechanical thrombectomy for acute ischaemic stroke in routine clinical setting:: cost differences between mothership vs drip and ship. *International Journal of Stroke,* 13**,** 45-46.

BALAMI, J. S., COUGHLAN, D., WHITE, P. M., MCMEEKIN, P., FLYNN, D., ROFFE, C., NATARAJAN, I., CHEMBALA, J., NAYAK, S., WIGGAM, I., FLYNN, P., SIMISTER, R., SAMMARAIEE, Y., SIMS, D., NADER, K., DIXIT, A., CRAIG, D., LUMLEY, H., RICE, S., BURGESS, D., FODDY, L., HOPKINS, E., HUDSON, B., JONES, R., JAMES, M. A., BUCHAN, A. M., FORD, G. A. & GRAY, A. M. 2020. The cost of providing mechanical thrombectomy in the UK NHS: a micro-costing study. *Clin Med (Lond),* 20**,** e40-e45.

BALAMI, J. S., HADLEY, G., SUTHERLAND, B. A., KARBALAI, H. & BUCHAN, A. M. 2013. The exact science of stroke thrombolysis and the quiet art of patient selection. *Brain,* 136**,** 3528-53.

BALAMI, J. S., SUTHERLAND, B. A., EDMUNDS, L. D., GRUNWALD, I. Q., NEUHAUS, A. A., HADLEY, G., KARBALAI, H., METCALF, K. A., DELUCA, G. C. & BUCHAN, A. M. 2015. A systematic review and meta-analysis of randomized controlled trials of endovascular thrombectomy compared with best medical treatment for acute ischemic stroke. *Int J Stroke,* 10**,** 1168-78.

BALAMI, J. S., WHITE, P. M., MCMEEKIN, P. J., FORD, G. A. & BUCHAN, A. M. 2018b. Complications of endovascular treatment for acute ischemic stroke: Prevention and management. *Int J Stroke,* 13**,** 348-361.

BANDETTINI DI POGGIO, M., FINOCCHI, C., BRIZZO, F., ALTOMONTE, F., BOVIS, F., MAVILIO, N., SERRATI, C., MALFATTO, L., MANCARDI, G. & BALESTRINO, M. 2019. Management of acute ischemic stroke, thrombolysis rate, and predictors of clinical outcome. *Neurol Sci,* 40**,** 319-326.

BANKS, J. L. & MAROTTA, C. A. 2007. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke,* 38**,** 1091-6.

BARBER, P. A., DEMCHUK, A. M., ZHANG, J. & BUCHAN, A. M. 2000. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet,* 355**,** 1670-4.

BARON, J. C. 1999. Mapping the ischaemic penumbra with PET: implications for acute stroke treatment. *Cerebrovasc Dis,* 9**,** 193-201.

BASSLER, D., BRIEL, M., MONTORI, V. M., LANE, M., GLASZIOU, P., ZHOU, Q., HEELS-ANSDELL, D., WALTER, S. D., GUYATT, G. H., FLYNN, D. N., ELAMIN, M. B., MURAD, M. H., ABU ELNOUR, N. O., LAMPROPULOS, J. F., SOOD, A., MULLAN, R. J., ERWIN, P. J., BANKHEAD, C. R., PERERA, R., RUIZ CULEBRO, C., YOU, J. J., MULLA, S. M., KAUR, J., NERENBERG, K. A., SCHÜNEMANN, H., COOK, D. J., LUTZ, K., RIBIC, C. M., VALE, N., MALAGA, G., AKL, E. A., FERREIRA-GONZALEZ, I., ALONSO-COELLO, P., URRUTIA, G., KUNZ, R., BUCHER, H. C., NORDMANN, A. J., RAATZ, H., DA SILVA, S. A., TUCHE, F., STRAHM, B., DJULBEGOVIC, B., ADHIKARI, N. K., MILLS, E. J., GWADRY-SRIDHAR, F., KIRPALANI, H., SOARES, H. P., KARANICOLAS, P. J., BURNS, K. E., VANDVIK, P. O., COTO-YGLESIAS, F., CHRISPIM, P. P. & RAMSAY, T. 2010. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *Jama,* 303**,** 1180-7.

BERGE, E., WHITELEY, W., AUDEBERT, H., DE MARCHIS, G. M., FONSECA, A. C., PADIGLIONI, C., DE LA OSSA, N. P., STRBIAN, D., TSIVGOULIS, G. & TURC, G. 2021. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J,* 6**,** I-lxii.

BERKHEMER, O. A., FRANSEN, P. S., BEUMER, D., VAN DEN BERG, L. A., LINGSMA, H. F., YOO, A. J., SCHONEWILLE, W. J., VOS, J. A., NEDERKOORN, P. J., WERMER, M. J., VAN WALDERVEEN, M. A., STAALS, J., HOFMEIJER, J., VAN OOSTAYEN, J. A., LYCKLAMA À NIJEHOLT, G. J., BOITEN, J., BROUWER, P. A., EMMER, B. J., DE BRUIJN, S. F., VAN DIJK, L. C., KAPPELLE, L. J., LO, R. H., VAN DIJK, E. J., DE VRIES, J., DE KORT, P.

L., VAN ROOIJ, W. J., VAN DEN BERG, J. S., VAN HASSELT, B. A., AERDEN, L. A., DALLINGA, R. J., VISSER, M. C., BOT, J. C., VROOMEN, P. C., ESHGHI, O., SCHREUDER, T. H., HEIJBOER, R. J., KEIZER, K., TIELBEEK, A. V., DEN HERTOG, H. M., GERRITS, D. G., VAN DEN BERG-VOS, R. M., KARAS, G. B., STEYERBERG, E. W., FLACH, H. Z., MARQUERING, H. A., SPRENGERS, M. E., JENNISKENS, S. F., BEENEN, L. F., VAN DEN BERG, R., KOUDSTAAL, P. J., VAN ZWAM, W. H., ROOS, Y. B., VAN DER LUGT, A., VAN OOSTENBRUGGE, R. J., MAJOIE, C. B. & DIPPEL, D. W. 2015. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med,* 372**,** 11-20.

BEUMER D, S. G., FONVILE S, ET AL 2013. Intra-arterial occlusion in acute ischemic stroke: relative frequency in an unselected population.

. *Cerebrovasc Diseases* 66-66.

BHATIA, R., HILL, M. D., SHOBHA, N., MENON, B., BAL, S., KOCHAR, P., WATSON, T., GOYAL, M. & DEMCHUK, A. M. 2010. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. *Stroke,* 41**,** 2254-8.

BIVARD, A., LEVI, C., SPRATT, N. & PARSONS, M. 2013. Perfusion CT in acute stroke: a comprehensive analysis of infarct and penumbra. *Radiology,* 267**,** 543-50.

BNF: BRITISH NATIONAL FORMULARY. Available: NICE. https://bnf.nice.org.uk [Accessed].

BOSE, A., HENKES, H., ALFKE, K., REITH, W., MAYER, T. E., BERLIS, A., BRANCA, V. & SIT, S. P. 2008. The Penumbra System: a mechanical device for the treatment of acute stroke due to thromboembolism. *AJNR Am J Neuroradiol,* 29**,** 1409-13.

BOUDOUR, S., BARRAL, M., GORY, B., GIROUDON, C., AULAGNER, G., SCHOTT, A. M., TURJMAN, F., VIPREY, M. & ARMOIRY, X. 2018. A systematic review of economic evaluations on stent-retriever thrombectomy for acute ischemic stroke. *J Neurol,* 265**,** 1511-1520.

BOUDREAU, D. M., GUZAUSKAS, G., VILLA, K. F., FAGAN, S. C. & VEENSTRA, D. L. 2013. A model of cost-effectiveness of tissue plasminogen activator in patient subgroups 3 to 4.5 hours after onset of acute ischemic stroke. *Ann Emerg Med,* 61**,** 46-55.

BOULANGER, J. M., LINDSAY, M. P., GUBITZ, G., SMITH, E. E., STOTTS, G., FOLEY, N., BHOGAL, S., BOYLE, K., BRAUN, L., GODDARD, T., HERAN, M., KANYA-FORSTER, N., LANG, E., LAVOIE, P., MCCLELLAND, M., O'KELLY, C., PAGEAU, P., PETTERSEN, J., PURVIS, H., SHAMY, M., TAMPIERI, D., VANADEL, B., VERBEEK, R., BLACQUIERE, D., CASAUBON, L., FERGUSON, D., HEGEDUS, Y., JACQUIN, G. J., KELLY, M., KAMAL, N., LINKEWICH, B., LUM, C., MANN, B., MILOT, G., NEWCOMMON, N., POIRIER, P., SIMPKIN, W., SNIEDER, E., TRIVEDI, A., WHELAN, R., EUSTACE, M., SMITKO, E. & BUTCHER, K. 2018. Canadian Stroke Best Practice Recommendations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018. *Int J Stroke,* 13**,** 949-984.

BRACARD, S., DUCROCQ, X., MAS, J. L., SOUDANT, M., OPPENHEIM, C., MOULIN, T. & GUILLEMIN, F. 2016. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol,* 15**,** 1138-47.

BRAY, B. D., AYIS, S., CAMPBELL, J., HOFFMAN, A., ROUGHTON, M., TYRRELL, P. J., WOLFE, C. D. & RUDD, A. G. 2013. Associations between the organisation of stroke services, process of care, and mortality in England: prospective cohort study. *Bmj,* 346**,** f2827.

BREKENFELD, C., GOEBELL, E., SCHMIDT, H., HENNINGSEN, H., KRAEMER, C., TEBBEN, J., FLOTTMANN, F., THOMALLA, G. & FIEHLER, J. 2018. 'Drip-and-

drive': shipping the neurointerventionalist to provide mechanical thrombectomy in primary stroke centers. *J Neurointerv Surg,* 10**,** 932-936.
BRODERICK, J. P., BROTT, T., TOMSICK, T., MILLER, R. & HUSTER, G. 1993. Intracerebral hemorrhage more than twice as common as subarachnoid hemorrhage. *J Neurosurg,* 78**,** 188-91.
BRODERICK, J. P., PALESCH, Y. Y., DEMCHUK, A. M., YEATTS, S. D., KHATRI, P., HILL, M. D., JAUCH, E. C., JOVIN, T. G., YAN, B., SILVER, F. L., VON KUMMER, R., MOLINA, C. A., DEMAERSCHALK, B. M., BUDZIK, R., CLARK, W. M., ZAIDAT, O. O., MALISCH, T. W., GOYAL, M., SCHONEWILLE, W. J., MAZIGHI, M., ENGELTER, S. T., ANDERSON, C., SPILKER, J., CARROZZELLA, J., RYCKBORST, K. J., JANIS, L. S., MARTIN, R. H., FOSTER, L. D. & TOMSICK, T. A. 2013. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med,* 368**,** 893-903.
BROUWERS, M. C., KHO, M. E., BROWMAN, G. P., BURGERS, J. S., CLUZEAU, F., FEDER, G., FERVERS, B., GRAHAM, I. D., GRIMSHAW, J., HANNA, S. E., LITTLEJOHNS, P., MAKARSKI, J. & ZITZELSBERGER, L. 2010. AGREE II: advancing guideline development, reporting and evaluation in health care. *Cmaj,* 182**,** E839-42.
BURGOS, A. M. & SAVER, J. L. 2019. Evidence that Tenecteplase Is Noninferior to Alteplase for Acute Ischemic Stroke: Meta-Analysis of 5 Randomized Trials. *Stroke,* 50**,** 2156-2162.
BYRNE, D., SUGRUE, G., STANLEY, E., WALSH, J. P., MURPHY, S., KAVANAGH, E. C. & MACMAHON, P. J. 2017. Improved Detection of Anterior Circulation Occlusions: The "Delayed Vessel Sign" on Multiphase CT Angiography. *AJNR Am J Neuroradiol,* 38**,** 1911-1916.
BYRNE, D., WALSH, J. P., SUGRUE, G., NICOLAOU, S. & ROHR, A. 2020. CT Imaging of Acute Ischemic Stroke. *Canadian Association of Radiologists Journal,* 71**,** 266-280.
CADTH. 2019. *Grey Matters: A practical tool for searching health-related grey literature. The Canadian Agency for Drugs and Technologies in Health (CADTH) Research Information Services.* [Online]. Available: https://www.cadth.ca/resources/finding-evidence/grey-matters [Accessed 15 July 2019].
CALGARY STROKE PROGRAM. 2021. *mCTA Collateral flow assessment in Acute Stroke. Calgary Stroke Program, University of Calgary, Canada* [Online]. Available: http://www.aspectsinstroke.com/collateral-scoring [Accessed 03 March 2021].
CAMPBELL, B. C., CHRISTENSEN, S., LEVI, C. R., DESMOND, P. M., DONNAN, G. A., DAVIS, S. M. & PARSONS, M. W. 2011. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. *Stroke,* 42**,** 3435-40.
CAMPBELL, B. C., HILL, M. D., RUBIERA, M., MENON, B. K., DEMCHUK, A., DONNAN, G. A., ROY, D., THORNTON, J., DORADO, L., BONAFE, A., LEVY, E. I., DIENER, H. C., HERNÁNDEZ-PÉREZ, M., PEREIRA, V. M., BLASCO, J., QUESADA, H., REMPEL, J., JAHAN, R., DAVIS, S. M., STOUCH, B. C., MITCHELL, P. J., JOVIN, T. G., SAVER, J. L. & GOYAL, M. 2016. Safety and Efficacy of Solitaire Stent Thrombectomy: Individual Patient Data Meta-Analysis of Randomized Trials. *Stroke,* 47**,** 798-806.
CAMPBELL, B. C., MITCHELL, P. J., CHURILOV, L., KESHTKARAN, M., HONG, K.-S., KLEINIG, T. J., DEWEY, H. M., YASSI, N., YAN, B. & DOWLING, R. J. 2017. Endovascular thrombectomy for ischemic stroke increases disability-free survival, quality of life, and life expectancy and reduces cost. *Frontiers in neurology,* 8**,** 657.
CAMPBELL, B. C., MITCHELL, P. J., KLEINIG, T. J., DEWEY, H. M., CHURILOV, L., YASSI, N., YAN, B., DOWLING, R. J., PARSONS, M. W., OXLEY, T. J., WU, T. Y., BROOKS, M., SIMPSON, M. A., MITEFF, F., LEVI, C. R., KRAUSE, M.,

HARRINGTON, T. J., FAULDER, K. C., STEINFORT, B. S., PRIGLINGER, M., ANG, T., SCROOP, R., BARBER, P. A., MCGUINNESS, B., WIJERATNE, T., PHAN, T. G., CHONG, W., CHANDRA, R. V., BLADIN, C. F., BADVE, M., RICE, H., DE VILLIERS, L., MA, H., DESMOND, P. M., DONNAN, G. A. & DAVIS, S. M. 2015a. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med,* 372**,** 1009-18.

CAMPBELL, B. C. V., DE SILVA, D. A., MACLEOD, M. R., COUTTS, S. B., SCHWAMM, L. H., DAVIS, S. M. & DONNAN, G. A. 2019. Ischaemic stroke. *Nat Rev Dis Primers,* 5**,** 70.

CAMPBELL, B. C. V., DONNAN, G. A., LEES, K. R., HACKE, W., KHATRI, P., HILL, M. D., GOYAL, M., MITCHELL, P. J., SAVER, J. L., DIENER, H. C. & DAVIS, S. M. 2015b. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. *Lancet Neurol,* 14**,** 846-854.

CANDIO, P., VIOLATO, M., LEAL, J. & LUENGO-FERNANDEZ, R. 2021. Cost-Effectiveness of Mechanical Thrombectomy for Treatment of Nonminor Ischemic Stroke Across Europe. *Stroke,* 52**,** 664-673.

CASAUBON, L. K., BOULANGER, J. M., GLASSER, E., BLACQUIERE, D., BOUCHER, S., BROWN, K., GODDARD, T., GORDON, J., HORTON, M., LALONDE, J., LARIVIÈRE, C., LAVOIE, P., LESLIE, P., MCNEILL, J., MENON, B. K., MOSES, B., PENN, M., PERRY, J., SNIEDER, E., TYMIANSKI, D., FOLEY, N., SMITH, E. E., GUBITZ, G., HILL, M. D. & LINDSAY, P. 2016. Canadian Stroke Best Practice Recommendations: Acute Inpatient Stroke Care Guidelines, Update 2015. *Int J Stroke,* 11**,** 239-52.

CASP. 2014. *Critical Appraisal Skills Programme (CASP). CASP Randomised Controlled Trial Standard Checklist:* [Online]. Available: www.casp-uk.net/checklists [Accessed].

CHIA, N. H., LEYDEN, J. M., NEWBURY, J., JANNES, J. & KLEINIG, T. J. 2016. Determining the Number of Ischemic Strokes Potentially Eligible for Endovascular Thrombectomy: A Population-Based Study. *Stroke,* 47**,** 1377-80.

CHRISTIANA CARE HEALTH SYSTEM. 2016. *Acute Ischaemic stroke- Christiana Care Clinical Pathways.10 May* [Online]. Available: http://pathways.christianacare.org/wp-content/uploads/2016/05/Acute-Ischemic-Stroke-Pathway.pdf [Accessed 15 March 2019].

CICCONE, A., BERGE, E. & FISCHER, U. 2019. Systematic review of organizational models for intra-arterial treatment of acute ischemic stroke. 14**,** 12-22.

CICCONE, A., VALVASSORI, L., NICHELATTI, M., SGOIFO, A., PONZIO, M., STERZI, R. & BOCCARDI, E. 2013. Endovascular treatment for acute ischemic stroke. *N Engl J Med,* 368**,** 904-13.

CLERY, A., BHALLA, A., BISQUERA, A., SKOLARUS, L. E., MARSHALL, I., MCKEVITT, C., RUDD, A., SACKLEY, C., MARTIN, F. C., MANTHORPE, J., WOLFE, C. & WANG, Y. 2020. Long-Term Trends in Stroke Survivors Discharged to Care Homes. *Stroke,* 51**,** 179-185.

CLIFTON, A. 2017. Mechanical thrombectomy services: can the UK meet the challenge? *Pract Neurol,* 17**,** 250-251.

CLINICALTRIALS.GOV IDENTIFIER: NCT04236856. 2020. *National Institutes of Health (NIH). CorPath® GRX Neuro Study,CorPath® GRX Neuro Study. Clinical Trials.gov website* [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT04236856 [Accessed 16 December 2020].

COMAI, A., HAGLMULLER, T., FERRO, F., DALL'ORA, E., CURRO DOSSI, R. & BONATTI, G. 2015. Sequential endovascular thrombectomy approach (SETA) to acute ischemic stroke: preliminary single-centre results and cost analysis. *Radiologia Medica,* 120**,** 655-61.

CÔTÉ, R., HACHINSKI, V. C., SHURVELL, B. L., NORRIS, J. W. & WOLFSON, C. 1986. The Canadian Neurological Scale: a preliminary study in acute stroke. *Stroke,* 17**,** 731-7.

COUGHLAN, D., MCMEEKIN, P., FLYNN, D., FORD, G. A., LUMLEY, H., BURGESS, D., BALAMI, J., MAWSON, A., CRAIG, D., RICE, S. & WHITE, P. 2021. Secondary transfer of emergency stroke patients eligible for mechanical thrombectomy by air in rural England: economic evaluation and considerations. *Emerg Med J,* 38**,** 33-39.

CURTIS, A. & BURNS, A. 2017. Unit cost of health and social care. Canterbury, UK: Personal Social Services Research Unit.

D'ESTERRE, C. D., TRIVEDI, A., PORDELI, P., BOESEN, M., PATIL, S., HWAN AHN, S., NAJM, M., FAINARDI, E., SHANKAR, J. J. S. & RUBIERA, M. 2017. Regional comparison of multiphase computed tomographic angiography and computed tomographic perfusion for prediction of tissue fate in ischemic stroke. *Stroke,* 48**,** 939-945.

DARGAZANLI, C., CONSOLI, A., BARRAL, M., LABREUCHE, J., REDJEM, H., CICCIO, G., SMAJDA, S., DESILLES, J. P., TAYLOR, G., PREDA, C., COSKUN, O., RODESCH, G., PIOTIN, M., BLANC, R. & LAPERGUE, B. 2017. Impact of Modified TICI 3 versus Modified TICI 2b Reperfusion Score to Predict Good Outcome following Endovascular Therapy. *AJNR Am J Neuroradiol,* 38**,** 90-96.

DE ANDRES-NOGALES, F., ALVAREZ, M., DE MIQUEL, M. A., SEGURA, T., GIL, A., CARDONA, P., CASADO, M. A., NOGUEIRA, R. G. & DAVALOS, A. 2017. Cost-effectiveness of mechanical thrombectomy using stent retriever after intravenous tissue plasminogen activator compared with intravenous tissue plasminogen activator alone in the treatment of acute ischaemic stroke due to large vessel occlusion in Spain. *Eur Stroke J,* 2**,** 272-284.

DEL ZOPPO, G. J., POECK, K., PESSIN, M. S., WOLPERT, S. M., FURLAN, A. J., FERBERT, A., ALBERTS, M. J., ZIVIN, J. A., WECHSLER, L., BUSSE, O. & ET AL. 1992. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol,* 32**,** 78-86.

DESAI, S. M., LESLIE-MAZWI, T. M., HIRSCH, J. A. & JADHAV, A. P. 2021. Optimal transfer paradigm for emergent large vessel occlusion strokes: recognition to recanalization in the RACECAT trial. *Journal of NeuroInterventional Surgery,* 13**,** 97-99.

DEWILDE, S., ANNEMANS, L., PEETERS, A., HEMELSOET, D., VANDERMEEREN, Y., DESFONTAINES, P., BROUNS, R., VANHOOREN, G., CRAS, P., MICHIELSENS, B., REDONDO, P. & THIJS, V. 2017. Modified Rankin scale as a determinant of direct medical costs after stroke. *Int J Stroke,* 12**,** 392-400.

DIBIASIO, E., JAYARAMAN, M., GOYAL, M., YAGHI, S., TUNG, E., HIDLAY, D., TUNG, G., BAIRD, G. & MCTAGGART, R. A. 2019. Dismantling the ability of CT and MRI to identify the target mismatch profile in patients with anterior circulation large vessel occlusion beyond six hours from symptom onset. *Emergency radiology,* 26**,** 401-408.

DILL, T. 2008. Contraindications to magnetic resonance imaging: non-invasive imaging. *Heart,* 94**,** 943-8.

DIRECT-NCT03192332, S. *Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke (SWIFT DIRECT) ClinicalTrials.gov Identifier: NCT03192332* [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT03192332 [Accessed 20 July 2018].

DIRECT-SAFE, N. *DIRECT-SAFE: A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval. ClinicalTrials.gov Identifier: NCT03494920* [Online]. Available: https://clinicaltrials.gov/ct2/show/NCT03494920 [Accessed 20 July 2018].

DORMAN, P., DENNIS, M. & SANDERCOCK, P. 2000. Are the modified "simple questions" a valid and reliable measure of health related quality of life after stroke? *Journal of Neurology, Neurosurgery & Psychiatry,* 69**,** 487-493.

DORMAN, P. J., WADDELL, F., SLATTERY, J., DENNIS, M. & SANDERCOCK, P. 1997. Is the EuroQol a valid measure of health-related quality of life after stroke? *Stroke,* 28**,** 1876-82.

DRUMMOND, M., SCULPHER, M., CLAXTON KP, STODDART, G. & TORRANCE, G. 2015. *Methods for the economic evaluation of health care programmes,* Oxford, UK, Oxford University Press.

EHLERS, L., ANDERSEN, G., CLAUSEN, L. B., BECH, M. & KJØLBY, M. 2007. Cost-Effectiveness of Intravenous Thrombolysis With Alteplase Within a 3-Hour Window After Acute Ischemic Stroke. *Stroke,* 38**,** 85-89.

ELIJOVICH, L., GOYAL, N., MAINALI, S., HOIT, D., ARTHUR, A. S., WHITEHEAD, M. & CHOUDHRI, A. F. 2016. CTA collateral score predicts infarct volume and clinical outcome after endovascular therapy for acute ischemic stroke: a retrospective chart review. *J Neurointerv Surg,* 8**,** 559-62.

ELOFUKE, P., REID, J. M., RANA, A. & MACLEOD, M. J. 2016. Disappearance of the hyperdense MCA sign after stroke thrombolysis: implications for prognosis and early patient selection for clot retrieval. *J R Coll Physicians Edinb,* 46**,** 81-86.

EMBERSON, J., LEES, K. R., LYDEN, P., BLACKWELL, L., ALBERS, G., BLUHMKI, E., BROTT, T., COHEN, G., DAVIS, S., DONNAN, G., GROTTA, J., HOWARD, G., KASTE, M., KOGA, M., VON KUMMER, R., LANSBERG, M., LINDLEY, R. I., MURRAY, G., OLIVOT, J. M., PARSONS, M., TILLEY, B., TONI, D., TOYODA, K., WAHLGREN, N., WARDLAW, J., WHITELEY, W., DEL ZOPPO, G. J., BAIGENT, C., SANDERCOCK, P. & HACKE, W. 2014. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet,* 384**,** 1929-35.

EUNETHTA. 2016. *European Network For Health Technology Assessement (EUnetHTA) Endovascular therapy using mechanical thrombectomy devices for acute ischaemic stroke.* [Online]. Available: https://www.eunethta.eu/wp-content/uploads/2018/01/Mechanical-thrombectomy-devices-for-acute-ischaemic- stroke_Rapid-REA_Updated-and-Final-Feb-2016.pdf. [Accessed 11 October 2018].

EUROPEAN STROKE ORGANISATION. 2009. *Guidelines for Management of Ischaemic Stroke Update.European Stroke Organisation (ESO)* [Online]. Available: http://www.eso-stroke.org/pdf/ESO_Guideline_Update_Jan_2009.pdf [Accessed 10 December 2019].

EVANS, J., GRAHAM, B., PORDELI, P., AL-AJLAN, F., WILLINSKY, R., MONTANERA, W., REMPEL, J., SHUAIB, A., BRENNAN, P. & WILLIAMS, D. 2018. Time for a time window extension: insights from late presenters in the ESCAPE trial. *American Journal of Neuroradiology,* 39**,** 102-106.

FARGEN, K. M., NEAL, D., FIORELLA, D. J., TURK, A. S., FROEHLER, M. & MOCCO, J. 2015. A meta-analysis of prospective randomized controlled trials evaluating endovascular therapies for acute ischemic stroke. *J Neurointerv Surg,* 7**,** 84-9.

FARZIN, B., FAHED, R., GUILBERT, F., POPPE, A. Y., DANEAULT, N., DUROCHER, A. P., LANTHIER, S., BOUDJANI, H., KHOURY, N. N., ROY, D., WEILL, A., GENTRIC, J. C., BATISTA, A. L., LÉTOURNEAU-GUILLON, L., BERGERON, F., HENRY, M. A., DARSAUT, T. E. & RAYMOND, J. 2016. Early CT changes in patients admitted for thrombectomy: Intrarater and interrater agreement. *Neurology,* 87**,** 249-56.

FEIGIN, V. L., FOROUZANFAR, M. H., KRISHNAMURTHI, R., MENSAH, G. A., CONNOR, M., BENNETT, D. A., MORAN, A. E., SACCO, R. L., ANDERSON, L., TRUELSEN, T., O'DONNELL, M., VENKETASUBRAMANIAN, N., BARKER-COLLO, S., LAWES, C. M., WANG, W., SHINOHARA, Y., WITT, E., EZZATI, M., NAGHAVI, M. & MURRAY, C. 2014. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet,* 383**,** 245-54.

FEIGIN, V. L., LAWES, C. M. M., BENNETT, D. A., BARKER-COLLO, S. L. & PARAG, V. 2009. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *The Lancet Neurology,* 8**,** 355-369.

FEIGIN, V. L., NGUYEN, G., CERCY, K., JOHNSON, C. O., ALAM, T., PARMAR, P. G., ABAJOBIR, A. A., ABATE, K. H., ABD-ALLAH, F., ABEJIE, A. N., ABYU, G. Y., ADEMI, Z., AGARWAL, G., AHMED, M. B., AKINYEMI, R. O., AL-RADDADI, R., AMINDE, L. N., AMLIE-LEFOND, C., ANSARI, H., ASAYESH, H., ASGEDOM, S. W., ATEY, T. M., AYELE, H. T., BANACH, M., BANERJEE, A., BARAC, A., BARKER-COLLO, S. L., BÄRNIGHAUSEN, T., BARREGARD, L., BASU, S., BEDI, N., BEHZADIFAR, M., BÉJOT, Y., BENNETT, D. A., BENSENOR, I. M., BERHE, D. F., BONEYA, D. J., BRAININ, M., CAMPOS-NONATO, I. R., CASO, V., CASTAÑEDA-ORJUELA, C. A., RIVAS, J. C., CATALÁ-LÓPEZ, F., CHRISTENSEN, H., CRIQUI, M. H., DAMASCENO, A., DANDONA, L., DANDONA, R., DAVLETOV, K., DE COURTEN, B., DEVEBER, G., DOKOVA, K., EDESSA, D., ENDRES, M., FARAON, E. J. A., FARVID, M. S., FISCHER, F., FOREMAN, K., FOROUZANFAR, M. H., GALL, S. L., GEBREHIWOT, T. T., GELEIJNSE, J. M., GILLUM, R. F., GIROUD, M., GOULART, A. C., GUPTA, R., GUPTA, R., HACHINSKI, V., HAMADEH, R. R., HANKEY, G. J., HARERI, H. A., HAVMOELLER, R., HAY, S. I., HEGAZY, M. I., HIBSTU, D. T., JAMES, S. L., JEEMON, P., JOHN, D., JONAS, J. B., JÓŹWIAK, J., KALANI, R., KANDEL, A., KASAEIAN, A., KENGNE, A. P., KHADER, Y. S., KHAN, A. R., KHANG, Y. H., KHUBCHANDANI, J., KIM, D., KIM, Y. J., KIVIMAKI, M., KOKUBO, Y., KOLTE, D., KOPEC, J. A., KOSEN, S., KRAVCHENKO, M., KRISHNAMURTHI, R., KUMAR, G. A., LAFRANCONI, A., LAVADOS, P. M., et al. 2018. Global, Regional, and Country-Specific Lifetime Risks of Stroke, 1990 and 2016. *N Engl J Med,* 379**,** 2429-2437.

FEIGIN, V. L., NORRVING, B. & MENSAH, G. A. 2017. Global Burden of Stroke. *Circ Res,* 120**,** 439-448.

FENWICK, E. & BYFORD, S. 2005. A guide to cost-effectiveness acceptability curves. *British Journal of Psychiatry,* 187**,** 106-108.

FIESCHI, C., ARGENTINO, C., LENZI, G. L., SACCHETTI, M. L., TONI, D. & BOZZAO, L. 1989. Clinical and instrumental evaluation of patients with ischemic stroke within the first six hours. *J Neurol Sci,* 91**,** 311-21.

FLYNN, D., FRANCIS, R., HALVORSRUD, K., GONZALO-ALMOROX, E., CRAIG, D., ROBALINO, S., MCMEEKIN, P., CORA, A., BALAMI, J., FORD, G. A. & WHITE, P. 2017. Intra-arterial mechanical thrombectomy stent retrievers and aspiration devices in the treatment of acute ischaemic stroke: A systematic review and meta-analysis with trial sequential analysis. *Eur Stroke J,* 2**,** 308-318.

FONAROW, G. C., SMITH, E. E., SAVER, J. L., REEVES, M. J., BHATT, D. L., GRAU-SEPULVEDA, M. V., OLSON, D. M., HERNANDEZ, A. F., PETERSON, E. D. & SCHWAMM, L. H. 2011. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. *Circulation,* 123**,** 750-8.

FONAROW, G. C., ZHAO, X., SMITH, E. E., SAVER, J. L., REEVES, M. J., BHATT, D. L., XIAN, Y., HERNANDEZ, A. F., PETERSON, E. D. & SCHWAMM, L. H. 2014. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *Jama,* 311**,** 1632-40.

FRANSEN, P. S., BERKHEMER, O. A., LINGSMA, H. F., BEUMER, D., VAN DEN BERG, L. A., YOO, A. J., SCHONEWILLE, W. J., VOS, J. A., NEDERKOORN, P. J., WERMER, M. J., VAN WALDERVEEN, M. A., STAALS, J., HOFMEIJER, J., VAN OOSTAYEN, J. A., LYCKLAMA À NIJEHOLT, G. J., BOITEN, J., BROUWER, P. A., EMMER, B. J., DE BRUIJN, S. F., VAN DIJK, L. C., KAPPELLE, L. J., LO, R. H., VAN DIJK, E. J., DE VRIES, J., DE KORT, P. L.,

VAN DEN BERG, J. S., VAN HASSELT, B. A., AERDEN, L. A., DALLINGA, R. J., VISSER, M. C., BOT, J. C., VROOMEN, P. C., ESHGHI, O., SCHREUDER, T. H., HEIJBOER, R. J., KEIZER, K., TIELBEEK, A. V., DEN HERTOG, H. M., GERRITS, D. G., VAN DEN BERG-VOS, R. M., KARAS, G. B., STEYERBERG, E. W., FLACH, H. Z., MARQUERING, H. A., SPRENGERS, M. E., JENNISKENS, S. F., BEENEN, L. F., VAN DEN BERG, R., KOUDSTAAL, P. J., VAN ZWAM, W. H., ROOS, Y. B., VAN OOSTENBRUGGE, R. J., MAJOIE, C. B., VAN DER LUGT, A. & DIPPEL, D. W. 2016. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. *JAMA Neurol,* 73**,** 190-6.

FRØNSDAI, K., SKÅR Å, STOINSKA-SCHNEIDER A, ORMSTAD SS & B, F. 2016. *Mechanicalthrombectomy for acute ischemic stroke [Internet]. Oslo (Norway): Norwegian. Mechanical thrombectomy for acute ischemic stroke [Internet]. Os lo (Norway): Norwegian Institute of Public Health; 2016 Dec* [Online]. Available: https://www.fhi.no/en/publ/2016/mekanisk-trombektomi-ved-akutt-hjerneinfarkt/. [Accessed 30 July 2019 2019].

FRØNSDAL, K., SKÅR, Å., STOINSKA-SCHNEIDER, A., ORMSTAD, S. & FURE, B. 2016. Mechanical Thrombectomy for Acute Ischemic Stroke. Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH), Oslo, Norway.

FURLAN, A., HIGASHIDA, R., WECHSLER, L., GENT, M., ROWLEY, H., KASE, C., PESSIN, M., AHUJA, A., CALLAHAN, F., CLARK, W. M., SILVER, F. & RIVERA, F. 1999. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *Jama,* 282**,** 2003-11.

GANESALINGAM, J., PIZZO, E., MORRIS, S., SUNDERLAND, T., AMES, D. & LOBOTESIS, K. 2015. Cost-Utility Analysis of Mechanical Thrombectomy Using Stent Retrievers in Acute Ischemic Stroke. *Stroke,* 46**,** 2591-8.

GAO, J., PARSONS, M. W., KAWANO, H., LEVI, C. R., EVANS, T.-J., LIN, L. & BIVARD, A. 2017. Visibility of CT early ischemic change is significantly associated with time from stroke onset to baseline scan beyond the first 3 hours of stroke onset. *Journal of stroke,* 19**,** 340.

GOLD , M., SIEGEL , S., RUSSELL , L. & WEINSTEIN , M., EDITORS 1996. *Cost-Effectiveness in Health and Medicine,* New York, Oxford University Press.

GOLDSTEIN, E. D., SCHNUSENBERG, L., MOONEY, L., RAPER, C. C., MCDANIEL, S., THORPE, D. A., FRANKE, M. T., ANDERSON, L. K., MCCLURE, L. L., OGLESBY, M. M., LEWIS, C. Y., VELICHKO, C., BRADLEY, B. G., HORN, W. W., JR., REID, A. N., SIEGEL, J. L., CANNISTRARO, R., BECHTLE, P., BARBOSA, M. T., SILVERS, S. M., BROWN, B. L., FREEMAN, W. D., MILLER, D. A., BARRETT, K. M. & HUANG, J. F. 2018. Reducing Door-to-Reperfusion Time for Mechanical Thrombectomy With a Multitiered Notification System for Acute Ischemic Stroke. *Mayo Clin Proc Innov Qual Outcomes,* 2**,** 119-128.

GONZÁLEZ, R. G., SCHAEFER, P. W., BUONANNO, F. S., SCHWAMM, L. H., BUDZIK, R. F., RORDORF, G., WANG, B., SORENSEN, A. G. & KOROSHETZ, W. J. 1999. Diffusion-weighted MR Imaging: Diagnostic Accuracy in Patients Imaged within 6 Hours of Stroke Symptom Onset. *Radiology,* 210**,** 155-162.

GOYAL, M., DEMCHUK, A. M., MENON, B. K., EESA, M., REMPEL, J. L., THORNTON, J., ROY, D., JOVIN, T. G., WILLINSKY, R. A., SAPKOTA, B. L., DOWLATSHAHI, D., FREI, D. F., KAMAL, N. R., MONTANERA, W. J., POPPE, A. Y., RYCKBORST, K. J., SILVER, F. L., SHUAIB, A., TAMPIERI, D., WILLIAMS, D., BANG, O. Y., BAXTER, B. W., BURNS, P. A., CHOE, H., HEO, J. H., HOLMSTEDT, C. A., JANKOWITZ, B., KELLY, M., LINARES, G., MANDZIA, J. L., SHANKAR, J., SOHN, S. I., SWARTZ, R. H., BARBER, P. A., COUTTS, S. B., SMITH, E. E., MORRISH, W. F., WEILL, A., SUBRAMANIAM, S., MITHA, A. P., WONG, J. H., LOWERISON, M. W., SAJOBI, T. T. & HILL, M. D. 2015.

Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med,* 372**,** 1019-30.
GOYAL, M., FARGEN, K. M., TURK, A. S., MOCCO, J., LIEBESKIND, D. S., FREI, D. & DEMCHUK, A. M. 2014. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. *J Neurointerv Surg,* 6**,** 83-6.
GOYAL, M., MENON, B. K., VAN ZWAM, W. H., DIPPEL, D. W., MITCHELL, P. J., DEMCHUK, A. M., DAVALOS, A., MAJOIE, C. B., VAN DER LUGT, A., DE MIQUEL, M. A., DONNAN, G. A., ROOS, Y. B., BONAFE, A., JAHAN, R., DIENER, H. C., VAN DEN BERG, L. A., LEVY, E. I., BERKHEMER, O. A., PEREIRA, V. M., REMPEL, J., MILLAN, M., DAVIS, S. M., ROY, D., THORNTON, J., ROMAN, L. S., RIBO, M., BEUMER, D., STOUCH, B., BROWN, S., CAMPBELL, B. C., VAN OOSTENBRUGGE, R. J., SAVER, J. L., HILL, M. D. & JOVIN, T. G. 2016. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet,* 387**,** 1723-31.
GROTTA, J. C., WELCH, K. M., FAGAN, S. C., LU, M., FRANKEL, M. R., BROTT, T., LEVINE, S. R. & LYDEN, P. D. 2001. Clinical deterioration following improvement in the NINDS rt-PA Stroke Trial. *Stroke,* 32**,** 661-8.
GRUNWALD, I. Q., PHILLIPS, D. J., SEXBY, D., WAGNER, V., LESMEISTER, M., BACHHUBER, M., MATHUR, S., GUYLER, P., FISHER, J., PERERA, S., HELWIG, S. A., SCHOTTEK, A., EWART, I., MENON, N., INAM UL HAQ, M., GRÜN, D., MERZOU, F., HOWARD, C., MAPPLEBECK, S., DOMMETT, D., ALAM, S., CHAKRABARTI, A., GERRY, S., WILTSHIRE, C., BAILEY, M., BERTSCH, T., FOSTER, T., DAVIS, T., REITH, W., FASSBENDER, K. & WALTER, S. 2020. Mobile Stroke Unit in the UK Healthcare System: Avoidance of Unnecessary Accident and Emergency Admissions. *Cerebrovasc Dis,* 49**,** 388-395.
HACKE, W. 2018. A New DAWN for Imaging-Based Selection in the Treatment of Acute Stroke. *N Engl J Med,* 378**,** 81-83.
HACKE, W., KASTE, M., BLUHMKI, E., BROZMAN, M., DÁVALOS, A., GUIDETTI, D., LARRUE, V., LEES, K. R., MEDEGHRI, Z., MACHNIG, T., SCHNEIDER, D., VON KUMMER, R., WAHLGREN, N. & TONI, D. 2008. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med,* 359**,** 1317-29.
HANTSON, L., DE WEERDT, W., DE KEYSER, J., DIENER, H. C., FRANKE, C., PALM, R., VAN ORSHOVEN, M., SCHOONDERWALT, H., DE KLIPPEL, N., HERROELEN, L. & ET AL. 1994. The European Stroke Scale. *Stroke,* 25**,** 2215-9.
HAVENON, A. D., MLYNASH, M., KIM-TENSER, M. A., LANSBERG, M. G., LESLIE-MAZWI, T., CHRISTENSEN, S., MCTAGGART, R. A., ALEXANDER, M., ALBERS, G., BRODERICK, J., MARKS, M. P. & HEIT, J. J. 2019. Results From DEFUSE 3. *Stroke,* 50**,** 632-638.
HEALTH IMPROVEMENT SCOTLAND. 2016. *Health Improvement Scotland. Endovascular therapy using mechanical thrombectomy devices for patients with acute ischaemic stroke: Advice Statement 004-16 (PDF)* [Online]. Available: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/topics_assessed/shtg_004-16.aspx [Accessed 10 January 2019].
HEALTH INFORMATION AND QUALITY AUTHORITY. 2014. *Guidelines for the Retrieval and Interpretation of Economic Evaluations of Health Technologies in Ireland September 2014. Health Information and Quality Authority* [Online]. Available: https://www.hiqa.ie/sites/default/files/2017-01/Guidelines-Retrieval-and-Interpretation-of-Econ-Lit.pdf [Accessed 15 January 2019].
HEALTH INFORMATION AND QUALITY AUTHORITY. 2017 *Health Information and Quality Authority. Health technology assessment (HTA) of a national emergency*

endovascular service for mechanical thrombectomy in the management of acute ischaemic stroke. Published 25 January [Online]. Available: https://www.hiqa.ie/sites/default/files/2017-02/Mechanical-Thrombectomy-technical-report.pdf [Accessed 15 January 2019].

HEGGIE, R., WU, O., WHITE, P., FORD, G. A., WARDLAW, J., BROWN, M. M., CLIFTON, A. & MUIR, K. W. 2019. Mechanical thrombectomy in patients with acute ischemic stroke: A cost-effectiveness and value of implementation analysis. *Int J Stroke*, 1747493019879656.

HEIT, J. J., ZAHARCHUK, G. & WINTERMARK, M. 2018. Advanced Neuroimaging of Acute Ischemic Stroke: Penumbra and Collateral Assessment. *Neuroimaging Clin N Am,* 28, 585-597.

HELDNER, M. R., ZUBLER, C., MATTLE, H. P., SCHROTH, G., WECK, A., MONO, M. L., GRALLA, J., JUNG, S., EL-KOUSSY, M., LÜDI, R., YAN, X., ARNOLD, M., OZDOBA, C., MORDASINI, P. & FISCHER, U. 2013. National Institutes of Health stroke scale score and vessel occlusion in 2152 patients with acute ischemic stroke. *Stroke,* 44, 1153-7.

HEUSCHMANN, P. U., WIEDMANN, S., WELLWOOD, I., RUDD, A., DI CARLO, A., BEJOT, Y., RYGLEWICZ, D., RASTENYTE, D. & WOLFE, C. D. 2011. Three-month stroke outcome: the European Registers of Stroke (EROS) investigators. *Neurology,* 76, 159-65.

HIGASHIDA, R. T., FURLAN, A. J., ROBERTS, H., TOMSICK, T., CONNORS, B., BARR, J., DILLON, W., WARACH, S., BRODERICK, J., TILLEY, B. & SACKS, D. 2003. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke,* 34, e109-37.

HIGGINS, J. & GREEN, S. 2009. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0. 2 [updated September 2009] ed: The Cochrane Collaboration; 2009. *Available from www. cochrane-handbook. org*.

HIGGINS, J. P., ALTMAN, D. G., GØTZSCHE, P. C., JÜNI, P., MOHER, D., OXMAN, A. D., SAVOVIC, J., SCHULZ, K. F., WEEKS, L. & STERNE, J. A. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj,* 343, d5928.

HILL, M. D., ROWLEY, H. A., ADLER, F., ELIASZIW, M., FURLAN, A., HIGASHIDA, R. T., WECHSLER, L. R., ROBERTS, H. C., DILLON, W. P., FISCHBEIN, N. J., FIRSZT, C. M., SCHULZ, G. A. & BUCHAN, A. M. 2003. Selection of acute ischemic stroke patients for intra-arterial thrombolysis with pro-urokinase by using ASPECTS. *Stroke,* 34, 1925-31.

HIRANO, T., SASAKI, M., MORI, E., MINEMATSU, K., NAKAGAWARA, J. & YAMAGUCHI, T. 2010. Residual vessel length on magnetic resonance angiography identifies poor responders to alteplase in acute middle cerebral artery occlusion patients: exploratory analysis of the Japan Alteplase Clinical Trial II. *Stroke,* 41, 2828-33.

HOPEWELL, S., MCDONALD, S., CLARKE, M. & EGGER, M. 2007. Grey literature in meta-analyses of randomized trials of health care interventions. *Cochrane Database Syst Rev*, Mr000010.

HOSSMANN, K. A. 1994. Glutamate-mediated injury in focal cerebral ischemia: the excitotoxin hypothesis revised. *Brain Pathol,* 4, 23-36.

ISMAIL, M., ARMOIRY, X., TAU, N., ZHU, F., SADEH-GONIK, U., PIOTIN, M., BLANC, R., MAZIGHI, M., BRACARD, S., ANXIONNAT, R., SCHMITT, E., MIONE, G., HUMBERTJEAN, L., LACOUR, J.-C., RICHARD, S., BARBIER, C., LAPERGUE, B. & GORY, B. 2019. Mothership versus drip and ship for thrombectomy in patients who had an acute stroke: a systematic review and meta-analysis. 11, 14-19.

JAUCH, E. C., SAVER, J. L., ADAMS, H. P., JR., BRUNO, A., CONNORS, J. J., DEMAERSCHALK, B. M., KHATRI, P., MCMULLAN, P. W., JR., QURESHI, A. I., ROSENFIELD, K., SCOTT, P. A., SUMMERS, D. R., WANG, D. Z.,

WINTERMARK, M. & YONAS, H. 2013. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke,* 44**,** 870-947.

JAYARAMAN, M. V., GROSSBERG, J. A., MEISEL, K. M., SHAIKHOUNI, A. & SILVER, B. 2013. The clinical and radiographic importance of distinguishing partial from near-complete reperfusion following intra-arterial stroke therapy. *AJNR Am J Neuroradiol,* 34**,** 135-9.

JIA, B., FENG, L., LIEBESKIND, D. S., HUO, X., GAO, F., MA, N., MO, D., LIAO, X., WANG, C., ZHAO, X., PAN, Y., LI, H., LIU, L., WANG, Y., WANG, Y. & MIAO, Z. R. 2018. Mechanical thrombectomy and rescue therapy for intracranial large artery occlusion with underlying atherosclerosis. *J Neurointerv Surg,* 10**,** 746-750.

JOHNSON, C. O., NGUYEN, M., ROTH, G. A., NICHOLS, E., ALAM, T., ABATE, D., ABD-ALLAH, F., ABDELALIM, A., ABRAHA, H. N. & ABU-RMEILEH, N. M. 2019. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology,* 18**,** 439-458.

JONES, C. E. A., CHARLES, J. & EDWARDS, R. 2019. *Identification, measurement, and valuation of resource use in economic evaluations of public health interventions. In Tudor Edwards R, McIntosh E, editors, Applied Health Economics for Public Health Practice and Research.* , Oxford University Press.

JOVIN, T. G., CHAMORRO, A., COBO, E., DE MIQUEL, M. A., MOLINA, C. A., ROVIRA, A., SAN ROMÁN, L., SERENA, J., ABILLEIRA, S., RIBÓ, M., MILLÁN, M., URRA, X., CARDONA, P., LÓPEZ-CANCIO, E., TOMASELLO, A., CASTAÑO, C., BLASCO, J., AJA, L., DORADO, L., QUESADA, H., RUBIERA, M., HERNANDEZ-PÉREZ, M., GOYAL, M., DEMCHUK, A. M., VON KUMMER, R., GALLOFRÉ, M. & DÁVALOS, A. 2015. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med,* 372**,** 2296-306.

JUNG, S. & MATTLE, H. P. 2019. Is it a vascular event and where is the lesion? Identifying and interpreting the symptoms and signs of cerebrovascular disease. *Warlow's Stroke: Practical Management***,** 37-128.

KABORE, N., MARNAT, G., ROUANET, F., BARREAU, X., VERPILLOT, E., MENEGON, P., MAACHI, I., BERGE, J., SIBON, I. & BENARD, A. 2019. Cost-effectiveness analysis of mechanical thrombectomy plus tissue-type plasminogen activator compared with tissue-type plasminogen activator alone for acute ischemic stroke in France. *Rev Neurol (Paris),* 175**,** 252-260.

KAMALIAN, S., MORAIS, L. T., POMERANTZ, S. R., ACEVES, M., SIT, S. P., BOSE, A., HIRSCH, J. A., LEV, M. H. & YOO, A. J. 2013. Clot length distribution and predictors in anterior circulation stroke: implications for intra-arterial therapy. *Stroke,* 44**,** 3553-6.

KANSAGRA, A. P., MEYERS, G. C., KRUZICH, M. S., CROSS, D. T., 3RD & MORAN, C. J. 2017. Wide Variability in Prethrombectomy Workflow Practices in the United States: A Multicenter Survey. *AJNR Am J Neuroradiol,* 38**,** 2238-2242.

KASS-HOUT, T., KASS-HOUT, O., SUN, C. H., KASS-HOUT, T., BELAGAJE, S. R., ANDERSON, A. M., FRANKEL, M. R., GUPTA, R. & NOGUEIRA, R. G. 2015. Periprocedural cost-effectiveness analysis of mechanical thrombectomy for acute ischemic stroke in the stent retriever era. *Interv Neurol,* 3**,** 107-13.

KATZ, B. S., MCMULLAN, J. T., SUCHAREW, H., ADEOYE, O. & BRODERICK, J. P. 2015. Design and validation of a prehospital scale to predict stroke severity: Cincinnati Prehospital Stroke Severity Scale. *Stroke,* 46**,** 1508-12.

KAWANO, H., BIVARD, A., LIN, L., MA, H., CHENG, X., AVIV, R., O'BRIEN, B., BUTCHER, K., LOU, M., ZHANG, J., JANNES, J., DONG, Q., LEVI, C. R. & PARSONS, M. W. 2017. Perfusion computed tomography in patients with stroke thrombolysis. *Brain,* 140**,** 684-691.

KHATRI, P., CONAWAY, M. R. & JOHNSTON, K. C. 2012. Ninety-day outcome rates of a prospective cohort of consecutive patients with mild ischemic stroke. *Stroke,* 43**,** 560-2.

KHATRI, P., YEATTS, S. D., MAZIGHI, M., BRODERICK, J. P., LIEBESKIND, D. S., DEMCHUK, A. M., AMARENCO, P., CARROZZELLA, J., SPILKER, J., FOSTER, L. D., GOYAL, M., HILL, M. D., PALESCH, Y. Y., JAUCH, E. C., HALEY, E. C., VAGAL, A. & TOMSICK, T. A. 2014. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. *Lancet Neurol,* 13**,** 567-74.

KHOURY, N. N., DARSAUT, T. E., GHOSTINE, J., DESCHAINTRE, Y., DANEAULT, N., DUROCHER, A., LANTHIER, S., POPPE, A. Y., ODIER, C., LEBRUN, L. H., GUILBERT, F., GENTRIC, J. C., BATISTA, A., WEILL, A., ROY, D., BRACARD, S. & RAYMOND, J. 2017. Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: A randomized care trial. *J Neuroradiol,* 44**,** 198-202.

KIDWELL, C. S., JAHAN, R., GORNBEIN, J., ALGER, J. R., NENOV, V., AJANI, Z., FENG, L., MEYER, B. C., OLSON, S., SCHWAMM, L. H., YOO, A. J., MARSHALL, R. S., MEYERS, P. M., YAVAGAL, D. R., WINTERMARK, M., GUZY, J., STARKMAN, S. & SAVER, J. L. 2013. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med,* 368**,** 914-23.

KIM, D. H., KIM, B., JUNG, C., NAM, H. S., LEE, J. S., KIM, J. W., LEE, W. J., SEO, W. K., HEO, J. H., BAIK, S. K., KIM, B. M. & RHA, J. H. 2018. Consensus Statements by Korean Society of Interventional Neuroradiology and Korean Stroke Society: Hyperacute Endovascular Treatment Workflow to Reduce Door-to-Reperfusion Time. *Korean J Radiol,* 19**,** 838-848.

KING, D., WITTENBERG, R., PATEL, A., QUAYYUM, Z., BERDUNOV, V. & KNAPP, M. 2020. The future incidence, prevalence and costs of stroke in the UK. *Age Ageing,* 49**,** 277-282.

KING'S COLLEGE LONDON SSNAP. 2018. *Sentinel Stroke National Audit Programme (SSNAP). Annual Portfolio for April 2017-March 2018 admissions and discharges: national results.* [Online]. Available: Sentinel Stroke National Audit Programme.https://www.strokeaudit.org/results/Clinical-audit/National-Results.aspx. [Accessed 15 December 2019 2019].

KLEINE, J. F., WUNDERLICH, S., ZIMMER, C. & KAESMACHER, J. 2017. Time to redefine success? TICI 3 versus TICI 2b recanalization in middle cerebral artery occlusion treated with thrombectomy. *J Neurointerv Surg,* 9**,** 117-121.

KUANG, H., QIU, W., NAJM, M., DOWLATSHAHI, D., MIKULIK, R., POPPE, A. Y., PUIG, J., CASTELLANOS, M., SOHN, S. I., AHN, S. H., CALLEJA, A., JIN, A., ASIL, T., ASDAGHI, N., FIELD, T. S., COUTTS, S., HILL, M. D., DEMCHUK, A. M., GOYAL, M. & MENON, B. K. 2020. Validation of an automated ASPECTS method on non-contrast computed tomography scans of acute ischemic stroke patients. *International Journal of Stroke,* 15**,** 528-534.

KUNTZE-SÖDERQVIST, A., KAIJSER, M., SÖDERMAN, M., HOLMIN, S., WAHLGREN, N. & ANDERSSON, T. 2014. Mechanical thrombectomy in acute ischemic stroke-experience from 6 years of practice. *Neuroradiology,* 56**,** 477-86.

KUNZ, W. G., HUNINK, M. G., DIMITRIADIS, K., HUBER, T., DORN, F., MEINEL, F. G., SABEL, B. O., OTHMAN, A. E., REISER, M. F., ERTL-WAGNER, B., SOMMER, W. H. & THIERFELDER, K. M. 2018. Cost-effectiveness of Endovascular Therapy for Acute Ischemic Stroke: A Systematic Review of the Impact of Patient Age. *Radiology,* 288**,** 518-526.

KUNZ, W. G., HUNINK, M. G., SOMMER, W. H., BEYER, S. E., MEINEL, F. G., DORN, F., WIRTH, S., REISER, M. F., ERTL-WAGNER, B. & THIERFELDER, K. M. 2016. Cost-Effectiveness of Endovascular Stroke Therapy: A Patient Subgroup Analysis From a US Healthcare Perspective. *Stroke,* 47**,** 2797-2804.

KWAN, J., BROWN, M., BENTLEY, P., BROWN, Z., D'ANNA, L., HALL, C., HALSE, O., JAMIL, S., JENKINS, H., KALLADKA, D., PATEL, M., RANE, N., SINGH, A., TAYLOR, E., VENTER, M. & BANERJEE, S. 2020. Impact of COVID-19 Pandemic on a Regional Stroke Thrombectomy Service in the United Kingdom. *Cerebrovasc Dis*, 1-7.

KWON, S., HARTZEMA, A. G., DUNCAN, P. W. & MIN-LAI, S. 2004. Disability measures in stroke: relationship among the Barthel Index, the Functional Independence Measure, and the Modified Rankin Scale. *Stroke,* 35**,** 918-23.

LAKHAN, S. E., KIRCHGESSNER, A. & HOFER, M. 2009. Inflammatory mechanisms in ischemic stroke: therapeutic approaches. *Journal of Translational Medicine,* 7**,** 97.

LANSBERG, M. G., ALBERS, G. W., BEAULIEU, C. & MARKS, M. P. 2000. Comparison of diffusion-weighted MRI and CT in acute stroke. *Neurology,* 54**,** 1557-61.

LAPERGUE, B., BLANC, R., GORY, B., LABREUCHE, J., DUHAMEL, A., MARNAT, G., SALEME, S., COSTALAT, V., BRACARD, S., DESAL, H., MAZIGHI, M., CONSOLI, A. & PIOTIN, M. 2017. Effect of Endovascular Contact Aspiration vs Stent Retriever on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion: The ASTER Randomized Clinical Trial. *Jama,* 318**,** 443-452.

LARRUE, V., VON KUMMER, R., DEL ZOPPO, G. & BLUHMKI, E. 1997. Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the European Cooperative Acute Stroke Study. *Stroke,* 28**,** 957-60.

LEES, K. R., BLUHMKI, E., VON KUMMER, R., BROTT, T. G., TONI, D., GROTTA, J. C., ALBERS, G. W., KASTE, M., MARLER, J. R., HAMILTON, S. A., TILLEY, B. C., DAVIS, S. M., DONNAN, G. A., HACKE, W., ALLEN, K., MAU, J., MEIER, D., DEL ZOPPO, G., DE SILVA, D. A., BUTCHER, K. S., PARSONS, M. W., BARBER, P. A., LEVI, C., BLADIN, C. & BYRNES, G. 2010. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet,* 375**,** 1695-703.

LEES, K. R., FORD, G. A., MUIR, K. W., AHMED, N., DYKER, A. G., ATULA, S., KALRA, L., WARBURTON, E. A., BARON, J. C., JENKINSON, D. F., WAHLGREN, N. G. & WALTERS, M. R. 2008. Thrombolytic therapy for acute stroke in the United Kingdom: experience from the safe implementation of thrombolysis in stroke (SITS) register. *Qjm,* 101**,** 863-9.

LEIRA, E. C., STILLEY, J. D., SCHNELL, T., AUDEBERT, H. J. & ADAMS, H. P., JR. 2016. Helicopter transportation in the era of thrombectomy: The next frontier for acute stroke treatment and research. *Eur Stroke J,* 1**,** 171-179.

LEIVA-SALINAS, C., JIANG, B. & WINTERMARK, M. 2018. Computed Tomography, Computed Tomography Angiography, and Perfusion Computed Tomography Evaluation of Acute Ischemic Stroke. *Neuroimaging Clin N Am,* 28**,** 565-572.

LEPPERT, M. H., CAMPBELL, J. D., SIMPSON, J. R. & BURKE, J. F. 2015. Cost-Effectiveness of Intra-Arterial Treatment as an Adjunct to Intravenous Tissue-Type Plasminogen Activator for Acute Ischemic Stroke. *Stroke,* 46**,** 1870-6.

LI, L., SCOTT, C. A. & ROTHWELL, P. M. 2020. Trends in Stroke Incidence in High-Income Countries in the 21st Century. *Stroke,* 51**,** 1372-1380.

LIMA, F. O., FURIE, K. L., SILVA, G. S., LEV, M. H., CAMARGO, E. C., SINGHAL, A. B., HARRIS, G. J., HALPERN, E. F., KOROSHETZ, W. J., SMITH, W. S. & NOGUEIRA, R. G. 2014. Prognosis of untreated strokes due to anterior circulation proximal intracranial arterial occlusions detected by use of computed tomography angiography. *JAMA Neurol,* 71**,** 151-7.

LIN, M. P. & LIEBESKIND, D. S. 2016. Imaging of Ischemic Stroke. *Continuum (Minneap Minn),* 22**,** 1399-1423.

LIU, Q., RANTA, A. A., ABERNETHY, G. & BARBER, P. A. 2017. Trends in New Zealand stroke thrombolysis treatment rates. *NZ Med J,* 130**,** 50-56.

LLANES, J. N., KIDWELL, C. S., STARKMAN, S., LEARY, M. C., ECKSTEIN, M. & SAVER, J. L. 2004. THE LOS ANGELES MOTOR SCALE (LAMS): A NEW MEASURE TO CHARACTERIZE STROKE SEVERITY IN THE FIELD. *Prehospital Emergency Care,* 8**,** 46-50.

LOBOTESIS, K., VELTKAMP, R., CARPENTER, I. H., CLAXTON, L. M., SAVER, J. L. & HODGSON, R. 2016. Cost-effectiveness of stent-retriever thrombectomy in combination with IV t-PA compared with IV t-PA alone for acute ischemic stroke in the UK. *J Med Econ,* 19**,** 785-94.

LUENGO-FERNANDEZ, R., GRAY, A. M. & ROTHWELL, P. M. 2012. A population-based study of hospital care costs during 5 years after transient ischemic attack and stroke. *Stroke,* 43**,** 3343-51.

LUENGO-FERNANDEZ, R., PAUL, N. L., GRAY, A. M., PENDLEBURY, S. T., BULL, L. M., WELCH, S. J., CUTHBERTSON, F. C. & ROTHWELL, P. M. 2013. Population-based study of disability and institutionalization after transient ischemic attack and stroke: 10-year results of the Oxford Vascular Study. *Stroke,* 44**,** 2854-61.

LUENGO-FERNANDEZ, R., VIOLATO, M., CANDIO, P. & LEAL, J. 2020. Economic burden of stroke across Europe: A population-based cost analysis. *Eur Stroke J,* 5**,** 17-25.

LYDEN, P., BROTT, T., TILLEY, B., WELCH, K. M., MASCHA, E. J., LEVINE, S., HALEY, E. C., GROTTA, J. & MARLER, J. 1994. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke,* 25**,** 2220-6.

MAHMUD, E., NAGHI, J., ANG, L., HARRISON, J., BEHNAMFAR, O., POURDJABBAR, A., REEVES, R. & PATEL, M. 2017. Demonstration of the Safety and Feasibility of Robotically Assisted Percutaneous Coronary Intervention in Complex Coronary Lesions: Results of the CORA-PCI Study (Complex Robotically Assisted Percutaneous Coronary Intervention). *JACC Cardiovasc Interv,* 10**,** 1320-1327.

MAHONEY, F. I. & BARTHEL, D. W. 1965. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. *Md State Med J,* 14**,** 61-5.

MAJID, A. 2014. Neuroprotection in stroke: past, present, and future. *ISRN Neurol,* 2014**,** 515716.

MANGLA, S., O'CONNELL, K., KUMARI, D. & SHAHRZAD, M. 2016. Novel model of direct and indirect cost-benefit analysis of mechanical embolectomy over IV tPA for large vessel occlusions: a real-world dollar analysis based on improvements in mRS. *J Neurointerv Surg,* 8**,** 1312-1316.

MARTINS, S. O., MONT'ALVERNE, F., REBELLO, L. C., ABUD, D. G., SILVA, G. S., LIMA, F. O., PARENTE, B. S. M., NAKIRI, G. S., FARIA, M. B., FRUDIT, M. E., DE CARVALHO, J. J. F., WAIHRICH, E., FIOROT, J. A., JR., CARDOSO, F. B., HIDALGO, R. C. T., ZÉTOLA, V. F., CARVALHO, F. M., DE SOUZA, A. C., DIAS, F. A., BANDEIRA, D., MIRANDA ALVES, M., WAGNER, M. B., CARBONERA, L. A., OLIVEIRA-FILHO, J., BEZERRA, D. C., LIEBESKIND, D. S., BRODERICK, J., MOLINA, C. A., FOGOLIN PASSOS, J. E., SAVER, J. L., PONTES-NETO, O. M. & NOGUEIRA, R. G. 2020. Thrombectomy for Stroke in the Public Health Care System of Brazil. *N Engl J Med,* 382**,** 2316-2326.

MAZIGHI, M., SERFATY, J. M., LABREUCHE, J., LAISSY, J. P., MESEGUER, E., LAVALLÉE, P. C., CABREJO, L., SLAOUI, T., GUIDOUX, C., LAPERGUE, B., KLEIN, I. F., OLIVOT, J. M., ABBOUD, H., SIMON, O., NICLOT, P., NIFLE, C., TOUBOUL, P. J., RAPHAELI, G., GOHIN, C., CLAEYS, E. S. & AMARENCO, P. 2009. Comparison of intravenous alteplase with a combined intravenous-endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): a prospective cohort study. *Lancet Neurol,* 8**,** 802-9.

MCCUSKER, M. W., ROBINSON, S., LOOBY, S., POWER, S., TI, J. P., GRECH, R., GALVIN, L., O'HARE, A., BRENNAN, P., O'KELLY, P., O'BRIEN, P., COLLINS,

R., DOLAN, E., WILLIAMS, D. J. & THORNTON, J. 2015. Endovascular treatment for acute ischaemic stroke with large vessel occlusion: the experience of a regional stroke service. *Clin Radiol,* 70**,** 1408-13.

MCMEEKIN, P., FLYNN, D., ALLEN, M., COUGHLAN, D., FORD, G. A., LUMLEY, H., BALAMI, J. S., JAMES, M. A., STEIN, K., BURGESS, D. & WHITE, P. 2019. Estimating the effectiveness and cost-effectiveness of establishing additional endovascular Thrombectomy stroke Centres in England: a discrete event simulation. *BMC Health Serv Res,* 19**,** 821.

MCMEEKIN, P., WHITE, P., JAMES, M. A., PRICE, C. I., FLYNN, D. & FORD, G. A. 2017. Estimating the number of UK stroke patients eligible for endovascular thrombectomy. *Eur Stroke J,* 2**,** 319-326.

MCTAGGART, R. A., ANSARI, S. A., GOYAL, M., ABRUZZO, T. A., ALBANI, B., ARTHUR, A. J., ALEXANDER, M. J., ALBUQUERQUE, F. C., BAXTER, B., BULSARA, K. R., CHEN, M., ALMANDOZ, J. E., FRASER, J. F., FREI, D., GANDHI, C. D., HECK, D. V., HETTS, S. W., HUSSAIN, M. S., KELLY, M., KLUCZNIK, R., LEE, S. K., LESLIE-MAWZI, T., MEYERS, P. M., PRESTIGIACOMO, C. J., PRIDE, G. L., PATSALIDES, A., STARKE, R. M., SUNENSHINE, P., RASMUSSEN, P. A. & JAYARAMAN, M. V. 2017. Initial hospital management of patients with emergent large vessel occlusion (ELVO): report of the standards and guidelines committee of the Society of NeuroInterventional Surgery. *J Neurointerv Surg,* 9**,** 316-323.

MCTAGGART, R. A., JOVIN, T. G., LANSBERG, M. G., MLYNASH, M., JAYARAMAN, M. V., CHOUDHRI, O. A., INOUE, M., MARKS, M. P. & ALBERS, G. W. 2015. Alberta stroke program early computed tomographic scoring performance in a series of patients undergoing computed tomography and MRI: reader agreement, modality agreement, and outcome prediction. *Stroke,* 46**,** 407-412.

MENON, B. K., AL-AJLAN, F. S., NAJM, M., PUIG, J., CASTELLANOS, M., DOWLATSHAHI, D., CALLEJA, A., SOHN, S. I., AHN, S. H., POPPE, A., MIKULIK, R., ASDAGHI, N., FIELD, T. S., JIN, A., ASIL, T., BOULANGER, J. M., SMITH, E. E., COUTTS, S. B., BARBER, P. A., BAL, S., SUBRAMANIAN, S., MISHRA, S., TRIVEDI, A., DEY, S., EESA, M., SAJOBI, T., GOYAL, M., HILL, M. D. & DEMCHUK, A. M. 2018. Association of Clinical, Imaging, and Thrombus Characteristics With Recanalization of Visible Intracranial Occlusion in Patients With Acute Ischemic Stroke. *Jama,* 320**,** 1017-1026.

MENON, B. K., D'ESTERRE, C. D., QAZI, E. M., ALMEKHLAFI, M., HAHN, L., DEMCHUK, A. M. & GOYAL, M. 2015. Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke. *Radiology,* 275**,** 510-20.

MERETOJA, A., STRBIAN, D., MUSTANOJA, S., TATLISUMAK, T., LINDSBERG, P. J. & KASTE, M. 2012. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology,* 79**,** 306-13.

MERETOJA, A. & TATLISUMAK, T. 2006. Thrombolytic therapy in acute ischemic stroke - Basic concepts. *Current Vascular Pharmacology,* 4**,** 31-44.

MERETOJA, A., WEIR, L., UGALDE, M., YASSI, N., YAN, B., HAND, P., TRUESDALE, M., DAVIS, S. M. & CAMPBELL, B. C. 2013. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. *Neurology,* 81**,** 1071-6.

MERGENTHALER, P., DIRNAGL, U. & MEISEL, A. 2004. Pathophysiology of stroke: lessons from animal models. *Metab Brain Dis,* 19**,** 151-67.

MEYER, B. C. & LYDEN, P. D. 2009. The modified National Institutes of Health Stroke Scale: its time has come. *Int J Stroke,* 4**,** 267-73.

MINNERUP, J., WERSCHING, H., TEUBER, A., WELLMANN, J., EYDING, J., WEBER, R., REIMANN, G., WEBER, W., KRAUSE, L. U., KURTH, T. & BERGER, K. 2016. Outcome After Thrombectomy and Intravenous Thrombolysis in Patients

With Acute Ischemic Stroke: A Prospective Observational Study. *Stroke,* 47**,** 1584-92.
MISHRA, S. M., DYKEMAN, J., SAJOBI, T. T., TRIVEDI, A., ALMEKHLAFI, M., SOHN, S. I., BAL, S., QAZI, E., CALLEJA, A., EESA, M., GOYAL, M., DEMCHUK, A. M. & MENON, B. K. 2014. Early reperfusion rates with IV tPA are determined by CTA clot characteristics. *AJNR Am J Neuroradiol,* 35**,** 2265-72.
MITEFF, F., LEVI, C. R., BATEMAN, G. A., SPRATT, N., MCELDUFF, P. & PARSONS, M. W. 2009. The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. *Brain,* 132**,** 2231-2238.
MITSIOS, N., GAFFNEY, J., KUMAR, P., KRUPINSKI, J. & SLEVIN, M. 2006. Pathophysiology of Acute Ischaemic Stroke: An Analysis of Common Signalling Mechanisms and Identification of New Molecular Targets. *Pathobiology : journal of immunopathology, molecular and cellular biology,* 73**,** 159-75.
MOCCO, J., ZAIDAT, O. O., VON KUMMER, R., YOO, A. J., GUPTA, R., LOPES, D., FREI, D., SHOWNKEEN, H., BUDZIK, R., AJANI, Z. A., GROSSMAN, A., ALTSCHUL, D., MCDOUGALL, C., BLAKE, L., FITZSIMMONS, B. F., YAVAGAL, D., TERRY, J., FARKAS, J., LEE, S. K., BAXTER, B., WIESMANN, M., KNAUTH, M., HECK, D., HUSSAIN, S., CHIU, D., ALEXANDER, M. J., MALISCH, T., KIRMANI, J., MISKOLCZI, L. & KHATRI, P. 2016. Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone. *Stroke,* 47**,** 2331-8.
MOHER, D., LIBERATI, A., TETZLAFF, J. & ALTMAN, D. G. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Bmj,* 339**,** b2535.
MOKIN, M., ANSARI, S. A., MCTAGGART, R. A., BULSARA, K. R., GOYAL, M., CHEN, M. & FRASER, J. F. 2019. Indications for thrombectomy in acute ischemic stroke from emergent large vessel occlusion (ELVO): report of the SNIS Standards and Guidelines Committee. *J Neurointerv Surg,* 11**,** 215-220.
MOKIN, M., KASS-HOUT, T., KASS-HOUT, O., DUMONT, T. M., KAN, P., SNYDER, K. V., HOPKINS, L. N., SIDDIQUI, A. H. & LEVY, E. I. 2012. Intravenous thrombolysis and endovascular therapy for acute ischemic stroke with internal carotid artery occlusion: a systematic review of clinical outcomes. *Stroke,* 43**,** 2362-8.
MORRIS, S., HUNTER, R., DAVIE, C., THOMPSON, A., WALKER, H., THOMSON, N. & MOUNTFORD, J. 2011. Cost-effectiveness analysis of the london stroke service. *London: University College*.
MORRIS, S., HUNTER, R. M., RAMSAY, A. I., BOADEN, R., MCKEVITT, C., PERRY, C., PURSANI, N., RUDD, A. G., SCHWAMM, L. H., TURNER, S. J., TYRRELL, P. J., WOLFE, C. D. & FULOP, N. J. 2014. Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: difference-in-differences analysis. *Bmj,* 349**,** g4757.
MOSKOWITZ, M. A., LO, E. H. & IADECOLA, C. 2010. The science of stroke: mechanisms in search of treatments. *Neuron,* 67**,** 181-98.
MOTYER, R., THORNTON, J., POWER, S., BRENNAN, P., O'HARE, A., LOOBY, S., WILLIAMS, D. J., MOYNIHAN, B. & MURPHY, S. 2018. Endovascular thrombectomy beyond 12 hours of stroke onset: a stroke network's experience of late intervention. *Journal of neurointerventional surgery,* 10**,** 1043-1046.
MSAC AUSTRALIA. 2016. *Mechanical thrombectomy For acute ischaemic stroke due to large vessel occlusion. Submission to the Medical Services Advisory Committee (MSAC) Application 1428. Medtronic June* [Online]. Available: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/B33F7E83847E3E48CA25801000123C16/$File/MSAC%201428_SBA%20Mechanical%20Thrombectomy%20for%20AIS%20-main%20body_REDACTED.pdf [Accessed 15 December 2018].

MUELLER-KRONAST, N. H., ZAIDAT, O. O., FROEHLER, M. T., JAHAN, R., AZIZ-SULTAN, M. A., KLUCZNIK, R. P., SAVER, J. L., HELLINGER, F. R., JR., YAVAGAL, D. R., YAO, T. L., LIEBESKIND, D. S., JADHAV, A. P., GUPTA, R., HASSAN, A. E., MARTIN, C. O., BOZORGCHAMI, H., KAUSHAL, R., NOGUEIRA, R. G., GANDHI, R. H., PETERSON, E. C., DASHTI, S. R., GIVEN, C. A., 2ND, MEHTA, B. P., DESHMUKH, V., STARKMAN, S., LINFANTE, I., MCPHERSON, S. H., KVAMME, P., GROBELNY, T. J., HUSSAIN, M. S., THACKER, I., VORA, N., CHEN, P. R., MONTEITH, S. J., ECKER, R. D., SCHIRMER, C. M., SAUVAGEAU, E., ABOU-CHEBL, A., DERDEYN, C. P., MAIDAN, L., BADRUDDIN, A., SIDDIQUI, A. H., DUMONT, T. M., ALHAJERI, A., TAQI, M. A., ASI, K., CARPENTER, J., BOULOS, A., JINDAL, G., PURI, A. S., CHITALE, R., DESHAIES, E. M., ROBINSON, D. H., KALLMES, D. F., BAXTER, B. W., JUMAA, M. A., SUNENSHINE, P., MAJJHOO, A., ENGLISH, J. D., SUZUKI, S., FESSLER, R. D., DELGADO ALMANDOZ, J. E., MARTIN, J. C. & HAUSSEN, D. C. 2017. Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke: Primary Results of the STRATIS Registry. *Stroke,* 48**,** 2760-2768.

MUIR, K. W., FORD, G. A., MESSOW, C. M., FORD, I., MURRAY, A., CLIFTON, A., BROWN, M. M., MADIGAN, J., LENTHALL, R., ROBERTSON, F., DIXIT, A., CLOUD, G. C., WARDLAW, J., FREEMAN, J. & WHITE, P. 2017. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry,* 88**,** 38-44.

NAGEL, S., SINHA, D., DAY, D., REITH, W., CHAPOT, R., PAPANAGIOTOU, P., WARBURTON, E. A., GUYLER, P., TYSOE, S. & FASSBENDER, K. 2017. e-ASPECTS software is non-inferior to neuroradiologists in applying the ASPECT score to computed tomography scans of acute ischemic stroke patients. *International Journal of Stroke,* 12**,** 615-622.

NAM, J., JING, H. & O'REILLY, D. 2015. Intra-arterial thrombolysis vs. standard treatment or intravenous thrombolysis in adults with acute ischemic stroke: a systematic review and meta-analysis. *Int J Stroke,* 10**,** 13-22.

NEUHAUS, A. A., COUCH, Y., HADLEY, G. & BUCHAN, A. M. 2017. Neuroprotection in stroke: the importance of collaboration and reproducibility. *Brain,* 140**,** 2079-2092.

NEWTON, J. N., BRIGGS, A. D., MURRAY, C. J., DICKER, D., FOREMAN, K. J., WANG, H., NAGHAVI, M., FOROUZANFAR, M. H., OHNO, S. L., BARBER, R. M., VOS, T., STANAWAY, J. D., SCHMIDT, J. C., HUGHES, A. J., FAY, D. F., ECOB, R., GRESSER, C., MCKEE, M., RUTTER, H., ABUBAKAR, I., ALI, R., ANDERSON, H. R., BANERJEE, A., BENNETT, D. A., BERNABÉ, E., BHUI, K. S., BIRYUKOV, S. M., BOURNE, R. R., BRAYNE, C. E., BRUCE, N. G., BRUGHA, T. S., BURCH, M., CAPEWELL, S., CASEY, D., CHOWDHURY, R., COATES, M. M., COOPER, C., CRITCHLEY, J. A., DARGAN, P. I., DHERANI, M. K., ELLIOTT, P., EZZATI, M., FENTON, K. A., FRASER, M. S., FÜRST, T., GREAVES, F., GREEN, M. A., GUNNELL, D. J., HANNIGAN, B. M., HAY, R. J., HAY, S. I., HEMINGWAY, H., LARSON, H. J., LOOKER, K. J., LUNEVICIUS, R., LYONS, R. A., MARCENES, W., MASON-JONES, A. J., MATTHEWS, F. E., MOLLER, H., MURDOCH, M. E., NEWTON, C. R., PEARCE, N., PIEL, F. B., POPE, D., RAHIMI, K., RODRIGUEZ, A., SCARBOROUGH, P., SCHUMACHER, A. E., SHIUE, I., SMEETH, L., TEDSTONE, A., VALABHJI, J., WILLIAMS, H. C., WOLFE, C. D., WOOLF, A. D. & DAVIS, A. C. 2015. Changes in health in England, with analysis by English regions and areas of deprivation, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet,* 386**,** 2257-74.

NG, F. C., LOW, E., ANDREW, E., SMITH, K., CAMPBELL, B. C. V., HAND, P. J., CROMPTON, D. E., WIJERATNE, T., DEWEY, H. M. & CHOI, P. M. 2017.

Deconstruction of Interhospital Transfer Workflow in Large Vessel Occlusion: Real-World Data in the Thrombectomy Era. *Stroke,* 48**,** 1976-1979.
NG, Y. S., STEIN, J., NING, M. & BLACK-SCHAFFER, R. M. 2007. Comparison of clinical characteristics and functional outcomes of ischemic stroke in different vascular territories. *Stroke,* 38**,** 2309-14.
NHS ENGLAND. 2018. *Clinical Commissioning Policy: Mechanical thrombectomy for acute ischaemic stroke (all ages). Published 2 March* [Online]. Available: https://www.england.nhs.uk/publication/clinical-commissioning-policy-mechanical-thrombectomy-for-acute-ischaemic-stroke-all-ages/ [Accessed 20 April 2018].
NHS IMPROVEMENT. 2018. *Reference costs 2017/18: highlights, analysis and introduction to the data. NHS Improvement, November* [Online]. Available: https://improvement.nhs.uk/documents/1972/1_-_Reference_costs_201718.pdf [Accessed 20 December 2018].
NHS NATIONAL SERVICES SCOTLAND. 2018. *Scottish stroke improvement programme.* [Online]. Available: https://www.strokeaudit.scot.nhs.uk/Publications/docs/2018-07-10- SSCA-Report.pdf. [Accessed 15 December 2018].
NICE. 2007. *Alteplase for treating acute ischaemic stroke. Technology appraisal guidance [TA122]Published date: 27 June 2007. National Institute for Health and Care Excellence* [Online]. Available: https://www.nice.org.uk/guidance/TA122 [Accessed 10 December 2019].
NICE. 2012. *Alteplase for treating acute ischaemic stroke. London (UK): National Institute for Health and Care Excellence (NICE).* [Online]. Available: https://www.guideline.gov/summaries/summary/38443/alteplase-for-treating-acute-ischaemic-strokereview- of-technology-appraisal-guidance-122. [Accessed 10 December 2019].
NICE. 2015. *Developing NICE guidelines: the manual- Appendix H Appraisal checklists, evidence tables, GRADE and economic profiles. First published July* [Online]. Available: https://www.nice.org.uk/process/pmg20/resources/appendix-h-appraisal-checklists-evidence-tables-grade-and-economic-profiles-pdf-8779777885 [Accessed 04 March 2019].
NICE. 2016. *National Institute for Health and Care Excellence. Mechanical clot retrieval for treating acute ischaemic stroke* [Online]. Available: https://www.nice.org.uk/guidance/ipg548 [Accessed 24 June 2019].
NICE. 2018a. *National Institute For Health and Care Excellence (NICE) Guide to the processes of technology appraisal* [Online]. Available: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/technology-appraisal-processes-guide-apr-2018.pdf [Accessed 15 January 2019].
NICE. 2018b. *National Institute for Health and Care Excellence (NICE). Mechanical Thrombectomy devices for acute ischaemic stroke* [Online]. Available: https://www.nice.org.uk/advice/mib153 [Accessed July 2018].
NICE MIBS. 2018. *The National Institute for Health and Care Excellence. Mechanical thrombectomy devices for acute ischaemic stroke MedTech innovation briefing (MIB) Published: 30 July 2018 nice.org.uk/guidance/mib153.* [Online]. Available: https://www.nice.org.uk/advice/mib153/resources/mechanical-thrombectomy-devices-for-acute-ischaemic-stroke-pdf-2285963514951109 [Accessed].
NICEIMPACT. 2019. *National Institute for Health and Care Excellence. NICEimpact stroke. Published May 2019, London: National Institute for Health and Care Excellence* [Online]. Available: https://www.nice.org.uk/media/default/about/what-we-do/into-practice/measuring-uptake/nice-impact-stroke.pdf [Accessed 10 July 2020 2020].

NICHOLS-LARSEN, D. S., CLARK, P. C., ZERINGUE, A., GREENSPAN, A. & BLANTON, S. 2005. Factors influencing stroke survivors' quality of life during subacute recovery. *Stroke,* 36**,** 1480-4.

NIKOUBASHMAN, O., JUNGBLUTH, M., SCHÜRMANN, K., MÜLLER, M., FALKENBURGER, B., TAUBER, S. C., WIESMANN, M., SCHULZ, J. B. & REICH, A. 2016. Neurothrombectomy in acute ischaemic stroke: a prospective single-centre study and comparison with randomized controlled trials. *Eur J Neurol,* 23**,** 807-16.

NINDS 1995. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.

Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med,* 333**,** 1581-7.

NINDS T-PA STROKE STUDY GROUP 1997. Intracerebral Hemorrhage After Intravenous t-PA Therapy for Ischemic Stroke. *Stroke,* 28**,** 2109-2118.

NOGUEIRA, R. G., JADHAV, A. P., HAUSSEN, D. C., BONAFE, A., BUDZIK, R. F., BHUVA, P., YAVAGAL, D. R., RIBO, M., COGNARD, C., HANEL, R. A., SILA, C. A., HASSAN, A. E., MILLAN, M., LEVY, E. I., MITCHELL, P., CHEN, M., ENGLISH, J. D., SHAH, Q. A., SILVER, F. L., PEREIRA, V. M., MEHTA, B. P., BAXTER, B. W., ABRAHAM, M. G., CARDONA, P., VEZNEDAROGLU, E., HELLINGER, F. R., FENG, L., KIRMANI, J. F., LOPES, D. K., JANKOWITZ, B. T., FRANKEL, M. R., COSTALAT, V., VORA, N. A., YOO, A. J., MALIK, A. M., FURLAN, A. J., RUBIERA, M., AGHAEBRAHIM, A., OLIVOT, J. M., TEKLE, W. G., SHIELDS, R., GRAVES, T., LEWIS, R. J., SMITH, W. S., LIEBESKIND, D. S., SAVER, J. L. & JOVIN, T. G. 2018. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *N Engl J Med,* 378**,** 11-21.

NOGUEIRA, R. G., LUTSEP, H. L., GUPTA, R., JOVIN, T. G., ALBERS, G. W., WALKER, G. A., LIEBESKIND, D. S. & SMITH, W. S. 2012. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *The Lancet,* 380**,** 1231-1240.

O'COLLINS, V. E., MACLEOD, M. R., DONNAN, G. A., HORKY, L. L., VAN DER WORP, B. H. & HOWELLS, D. W. 2006. 1,026 experimental treatments in acute stroke. *Ann Neurol,* 59**,** 467-77.

OBRENOVITCH, T. P., URENJAK, J., RICHARDS, D. A., UEDA, Y., CURZON, G. & SYMON, L. 1993. Extracellular neuroactive amino acids in the rat striatum during ischaemia: comparison between penumbral conditions and ischaemia with sustained anoxic depolarisation. *J Neurochem,* 61**,** 178-86.

OLIVE-GADEA, M., MARTINS, N., BONED, S., CARVAJAL, J., MORENO, M. J., MUCHADA, M., MOLINA, C. A., TOMASELLO, A., RIBO, M. & RUBIERA, M. 2019. Baseline ASPECTS and e-ASPECTS Correlation with Infarct Volume and Functional Outcome in Patients Undergoing Mechanical Thrombectomy. *J Neuroimaging,* 29**,** 198-202.

ONTARIO HEALTH TECHNOLOGY ASSESSMENT 2016. Mechanical Thrombectomy in Patients With Acute Ischemic Stroke: A Health Technology Assessment. *Ontario Health Technol Assessment Ser,* 16**,** 1-79.

OSANAI, T., PASUPULETI, V., DESHPANDE, A., THOTA, P., ROMAN, Y., HERNANDEZ, A. V. & UCHINO, K. 2015. Acute endovascular reperfusion therapy in ischemic stroke: a systematic review and meta-analysis of randomized controlled trials. *PLoS One,* 10**,** e0122806.

OSSA, N. P. D. L., CARRERA, D., GORCHS, M., QUEROL, M., MILLÁN, M., GOMIS, M., DORADO, L., LÓPEZ-CANCIO, E., HERNÁNDEZ-PÉREZ, M., CHICHARRO, V., ESCALADA, X., JIMÉNEZ, X. & DÁVALOS, A. 2014. Design and Validation of a Prehospital Stroke Scale to Predict Large Arterial Occlusion. *Stroke,* 45**,** 87-91.

PAN, Y., CAI, X., HUO, X., ZHAO, X., LIU, L., WANG, Y., MIAO, Z. & WANG, Y. 2018. Cost-effectiveness of mechanical thrombectomy within 6 hours of acute ischaemic stroke in China. *BMJ Open,* 8**,** e018951.

PARTHASARATHY, R., SOHN, S. I., JEERAKATHIL, T., KATE, M. P., MISHRA, S. M., NAMBIAR, V. K., AHMAD, A., MENON, B. K. & SHUAIB, A. 2015. A Combined Arterial and Venous Grading Scale to Predict Outcome in Anterior Circulation Ischemic Stroke. *J Neuroimaging,* 25**,** 969-77.

PASC. 2016. *Mechanical thrombectomy for acute ischaemic stroke due to large vessel occlusion. Medtronic Australasia Protocol advisory Subcommittee (PASC) June* [Online]. Available: https://docsbay.net/for-acute-ischaemic-stroke-due-to-large-vessel-occlusion [Accessed 15 March 2019].

PATEL, A., BERDUNOV, V., KING, D., QUAYYUM, Z., WITTENBERG, R. & KNAPP, M. 2017. Current, future and avoidable costs of stroke in the UK. *Executive summary Part 2: Societal costs of stroke in the next 20 years and potential returns from increased spending on research*.

PATEL, A., BERDUNOV, V., QUAYYUM, Z., KING, D., KNAPP, M. & WITTENBERG, R. 2020. Estimated societal costs of stroke in the UK based on a discrete event simulation. *Age Ageing,* 49**,** 270-276.

PATEL, T. M., SHAH, S. C. & PANCHOLY, S. B. 2019. Long Distance Tele-Robotic-Assisted Percutaneous Coronary Intervention: A Report of First-in-Human Experience. *EClinicalMedicine,* 14**,** 53-58.

PEARS 2. *Promoting Effective And Rapid Stroke care (PEARS)* [Online]. Available: https://www.fundingawards.nihr.ac.uk/award/RP-PG-1211-20012 [Accessed].

PENUMBRA PIVOTAL STROKE TRIAL INVESTIGATORS 2009. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke,* 40**,** 2761-8.

PHAN, T. G., DONNAN, G. A., KOGA, M., MITCHELL, L. A., MOLAN, M., FITT, G., CHONG, W., HOLT, M. & REUTENS, D. C. 2006. The ASPECTS template is weighted in favor of the striatocapsular region. *NeuroImage,* 31**,** 477-481.

PIZZO, E., DUMBA, M. & LOBOTESIS, K. 2019. Cost-utility analysis of mechanical thrombectomy between 6 and 24 hours in acute ischemic stroke. *Int J Stroke***,** 1747493019830587.

POWERS, W. J., DERDEYN, C. P., BILLER, J., COFFEY, C. S., HOH, B. L., JAUCH, E. C., JOHNSTON, K. C., JOHNSTON, S. C., KHALESSI, A. A., KIDWELL, C. S., MESCHIA, J. F., OVBIAGELE, B. & YAVAGAL, D. R. 2015. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke,* 46**,** 3020-35.

POWERS, W. J., RABINSTEIN, A. A., ACKERSON, T., ADEOYE, O. M., BAMBAKIDIS, N. C., BECKER, K., BILLER, J., BROWN, M., DEMAERSCHALK, B. M., HOH, B., JAUCH, E. C., KIDWELL, C. S., LESLIE-MAZWI, T. M., OVBIAGELE, B., SCOTT, P. A., SHETH, K. N., SOUTHERLAND, A. M., SUMMERS, D. V. & TIRSCHWELL, D. L. 2018. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke,* 49**,** e46-e110.

POWERS, W. J., RABINSTEIN, A. A., ACKERSON, T., ADEOYE, O. M., BAMBAKIDIS, N. C., BECKER, K., BILLER, J., BROWN, M., DEMAERSCHALK, B. M., HOH, B., JAUCH, E. C., KIDWELL, C. S., LESLIE-MAZWI, T. M., OVBIAGELE, B., SCOTT, P. A., SHETH, K. N., SOUTHERLAND, A. M., SUMMERS, D. V. & TIRSCHWELL, D. L. 2019. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke,* 50**,** e344-e418.

PUETZ, V., SYLAJA, P. N., COUTTS, S. B., HILL, M. D., DZIALOWSKI, I., MUELLER, P., BECKER, U., URBAN, G., O'REILLY, C., BARBER, P. A., SHARMA, P., GOYAL, M., GAHN, G., VON KUMMER, R. & DEMCHUK, A. M. 2008. Extent of hypoattenuation on CT angiography source images predicts functional outcome in patients with basilar artery occlusion. *Stroke,* 39**,** 2485-90.

QUINN, T. J., DAWSON, J., WALTERS, M. R. & LEES, K. R. 2009. Functional outcome measures in contemporary stroke trials. *Int J Stroke,* 4**,** 200-5.

R CORE TEAM. 2016. *R Core Team (2016). R: A language and environment for statistical computing.R Foundation for Statistical Computing, Vienna, Austria* [Online]. Available: https://www.R-project.org/ [Accessed].

RAI, A. T. & EVANS, K. 2015. Hospital-based financial analysis of endovascular therapy and intravenous thrombolysis for large vessel acute ischemic strokes: the 'bottom line'. *Journal of Neurointerventional Surgery,* 7**,** 150-6.

RAI, A. T., SELDON, A. E., BOO, S., LINK, P. S., DOMICO, J. R., TARABISHY, A. R., LUCKE-WOLD, N. & CARPENTER, J. S. 2017. A population-based incidence of acute large vessel occlusions and thrombectomy eligible patients indicates significant potential for growth of endovascular stroke therapy in the USA. *J Neurointerv Surg,* 9**,** 722-726.

RAJSIC, S., GOTHE, H., BORBA, H. H., SROCZYNSKI, G., VUJICIC, J., TOELL, T. & SIEBERT, U. 2019. Economic burden of stroke: a systematic review on post-stroke care. *Eur J Health Econ,* 20**,** 107-134.

RAMSEY, S. D., WILLKE, R. J., GLICK, H., REED, S. D., AUGUSTOVSKI, F., JONSSON, B., BRIGGS, A. & SULLIVAN, S. D. 2015. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. *Value Health,* 18**,** 161-72.

RANGARAJU, S., STREIB, C., AGHAEBRAHIM, A., JADHAV, A., FRANKEL, M. & JOVIN, T. G. 2015. Relationship Between Lesion Topology and Clinical Outcome in Anterior Circulation Large Vessel Occlusions. *Stroke,* 46**,** 1787-92.

RANKIN, J. 1957. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J,* 2**,** 200-15.

RAVINDRAN, A. V., KILLINGSWORTH, M. C. & BHASKAR, S. 2021. Cerebral collaterals in acute ischaemia: Implications for acute ischaemic stroke patients receiving reperfusion therapy. *European Journal of Neuroscience,* 53**,** 1238-1261.

RCP. 2016. *Royal College of Physicians (National Clinical Guideline for Stroke, 5th Edition* [Online]. Available: https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines [Accessed 20 March 2017].

REBELLO, L. C., HAUSSEN, D. C., GROSSBERG, J. A., BELAGAJE, S., LIMA, A., ANDERSON, A., FRANKEL, M. R. & NOGUEIRA, R. G. 2016. Early Endovascular Treatment in Intravenous Tissue Plasminogen Activator-Ineligible Patients. *Stroke,* 47**,** 1131-4.

RHA, J. H. & SAVER, J. L. 2007. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke,* 38**,** 967-73.

RIEDEL, C. H., ZIMMERMANN, P., JENSEN-KONDERING, U., STINGELE, R., DEUSCHL, G. & JANSEN, O. 2011. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke,* 42**,** 1775-7.

RIVERO-ARIAS, O., OUELLET, M., GRAY, A., WOLSTENHOLME, J., ROTHWELL, P. M. & LUENGO-FERNANDEZ, R. 2010. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. *Med Decis Making,* 30**,** 341-54.

ROTHWELL, P. M., COULL, A. J., GILES, M. F., HOWARD, S. C., SILVER, L. E., BULL, L. M., GUTNIKOV, S. A., EDWARDS, P., MANT, D., SACKLEY, C. M., FARMER, A., SANDERCOCK, P. A., DENNIS, M. S., WARLOW, C. P., BAMFORD, J. M. & ANSLOW, P. 2004. Change in stroke incidence, mortality, case-fatality, severity,

and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet,* 363**,** 1925-33.

ROTHWELL, P. M., COULL, A. J., SILVER, L. E., FAIRHEAD, J. F., GILES, M. F., LOVELOCK, C. E., REDGRAVE, J. N., BULL, L. M., WELCH, S. J., CUTHBERTSON, F. C., BINNEY, L. E., GUTNIKOV, S. A., ANSLOW, P., BANNING, A. P., MANT, D. & MEHTA, Z. 2005. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet,* 366**,** 1773-83.

RUBIERA, M., ALVAREZ-SABÍN, J., RIBO, M., MONTANER, J., SANTAMARINA, E., ARENILLAS, J. F., HUERTAS, R., DELGADO, P., PURROY, F. & MOLINA, C. A. 2005. Predictors of Early Arterial Reocclusion After Tissue Plasminogen Activator-Induced Recanalization in Acute Ischemic Stroke. *Stroke,* 36**,** 1452-1456.

RUGGERI, M., BASILE, M., ZINI, A., MANGIAFICO, S., AGOSTONI, E. C., LOBOTESIS, K., SAVER, J., CORETTI, S., DRAGO, C. & CICCHETTI, A. 2018. Cost-effectiveness analysis of mechanical thrombectomy with stent retriever in the treatment of acute ischemic stroke in Italy. *J Med Econ,* 21**,** 902-911.

RYU, W. H. A., YANG, M. M. H., MURAM, S., JACOBS, W. B., CASHA, S. & RIVA-CAMBRIN, J. 2018. Systematic review of health economic studies in cranial neurosurgery. *Neurosurg Focus,* 44**,** E2.

SAARINEN, J. T., SILLANPÄÄ, N., RUSANEN, H., HAKOMÄKI, J., HUHTALA, H., LÄHTEELÄ, A., DASTIDAR, P., SOIMAKALLIO, S. & ELOVAARA, I. 2012. The mid-M1 segment of the middle cerebral artery is a cutoff clot location for good outcome in intravenous thrombolysis. *Eur J Neurol,* 19**,** 1121-7.

SACKS, D., BAXTER, B., CAMPBELL, B. C. V., CARPENTER, J. S., COGNARD, C., DIPPEL, D., EESA, M., FISCHER, U., HAUSEGGER, K., HIRSCH, J. A., SHAZAM HUSSAIN, M., JANSEN, O., JAYARAMAN, M. V., KHALESSI, A. A., KLUCK, B. W., LAVINE, S., MEYERS, P. M., RAMEE, S., RÜFENACHT, D. A., SCHIRMER, C. M. & VORWERK, D. 2018. Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke. 13**,** 612-632.

SAFE. 2015. *The Burden of Stroke in Europe. Report King's College London for the Stroke Alliance For Europe (Safe)* [Online]. Available: https://strokeeurope.eu/ [Accessed 18 January 2020].

SAFER CARE VICTORIA. 2018. *Safer Care Victoria/Stroke Clinical Network. Endovascular clot retrieval for acute stroke. State-wide Service Protocol for Victoria. October* [Online]. Available: https://www.bettersafercare.vic.gov.au/sites/default/files/2018-11/PROTOCOL_ECR%20for%20acute%20stroke_October%202018.pdf [Accessed 15 March 2019].

SAKA, O., SERRA, V., SAMYSHKIN, Y., MCGUIRE, A. & WOLFE, C. C. 2009. Cost-effectiveness of stroke unit care followed by early supported discharge. *Stroke,* 40**,** 24-9.

SALEH, A. A., RATAJESKI, M. A. & BERTOLET, M. 2014. Grey Literature Searching for Health Sciences Systematic Reviews: A Prospective Study of Time Spent and Resources Utilized. *Evid Based Libr Inf Pract,* 9**,** 28-50.

SANDERCOCK, P., BERGE, E., DENNIS, M., FORBES, J., HAND, P., KWAN, J., LEWIS, S., LINDLEY, R., NEILSON, A., THOMAS, B. & WARDLAW, J. 2002. A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. *Health Technol Assess,* 6**,** 1-112.

SANTOS, T., CARVALHO, A., CUNHA, A. A., RODRIGUES, M., GREGÓRIO, T., PAREDES, L., COSTA, H., RORIZ, J. M., PINHO, J. & VELOSO, M. 2019. NCCT and CTA-based imaging protocol for endovascular treatment selection in late

presenting or wake-up strokes. *Journal of neurointerventional surgery,* 11**,** 200-203.
SAQQUR, M., UCHINO, K., DEMCHUK, A. M., MOLINA, C. A., GARAMI, Z., CALLEJA, S., AKHTAR, N., OROUK, F. O., SALAM, A., SHUAIB, A. & ALEXANDROV, A. V. 2007. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke,* 38**,** 948-54.
SAVER, J. L. 2006. Time is brain--quantified. *Stroke,* 37**,** 263-6.
SAVER, J. L. 2017. Penumbral salvage and thrombolysis outcome: a drop of brain, a week of life. *Brain,* 140**,** 519-522.
SAVER, J. L., GOYAL, M., BONAFE, A., DIENER, H. C., LEVY, E. I., PEREIRA, V. M., ALBERS, G. W., COGNARD, C., COHEN, D. J., HACKE, W., JANSEN, O., JOVIN, T. G., MATTLE, H. P., NOGUEIRA, R. G., SIDDIQUI, A. H., YAVAGAL, D. R., BAXTER, B. W., DEVLIN, T. G., LOPES, D. K., REDDY, V. K., DU MESNIL DE ROCHEMONT, R., SINGER, O. C. & JAHAN, R. 2015. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med,* 372**,** 2285-95.
SAVER, J. L., GOYAL, M., VAN DER LUGT, A., MENON, B. K., MAJOIE, C. B., DIPPEL, D. W., CAMPBELL, B. C., NOGUEIRA, R. G., DEMCHUK, A. M., TOMASELLO, A., CARDONA, P., DEVLIN, T. G., FREI, D. F., DU MESNIL DE ROCHEMONT, R., BERKHEMER, O. A., JOVIN, T. G., SIDDIQUI, A. H., VAN ZWAM, W. H., DAVIS, S. M., CASTAÑO, C., SAPKOTA, B. L., FRANSEN, P. S., MOLINA, C., VAN OOSTENBRUGGE, R. J., CHAMORRO, Á., LINGSMA, H., SILVER, F. L., DONNAN, G. A., SHUAIB, A., BROWN, S., STOUCH, B., MITCHELL, P. J., DAVALOS, A., ROOS, Y. B. & HILL, M. D. 2016. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. *Jama,* 316**,** 1279-88.
SAVER, J. L., JAHAN, R., LEVY, E. I., JOVIN, T. G., BAXTER, B., NOGUEIRA, R. G., CLARK, W., BUDZIK, R. & ZAIDAT, O. O. 2012. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *The Lancet,* 380**,** 1241-1249.
SCANDINAVIAN STROKE STUDY GROUP 1985. Multicenter trial of hemodilution in ischemic stroke--background and study protocol. Scandinavian Stroke Study Group. *Stroke,* 16**,** 885-90.
SCHELLINGER, P. D., FIEBACH, J. B. & HACKE, W. 2003. Imaging-based decision making in thrombolytic therapy for ischemic stroke: present status. *Stroke,* 34**,** 575-83.
SCHERF, S., LIMBURG, M., WIMMERS, R., MIDDELKOOP, I. & LINGSMA, H. 2016. Increase in national intravenous thrombolysis rates for ischaemic stroke between 2005 and 2012: is bigger better? *BMC Neurol,* 16**,** 53.
SCHRÖDER, J. & THOMALLA, G. 2016. A Critical Review of Alberta Stroke Program Early CT Score for Evaluation of Acute Stroke Imaging. *Front Neurol,* 7**,** 245.
SEKER, F., MÖHLENBRUCH, M. A., NAGEL, S., ULFERT, C., SCHÖNENBERGER, S., PFAFF, J., RINGLEB, P. A., STEINER, T., BENDSZUS, M. & HERWEH, C. 2018. Clinical results of a new concept of neurothrombectomy coverage at a remote hospital—"drive the doctor". 13**,** 696-699.
SERLES, W., GATTRINGER, T., MUTZENBACH, S., SEYFANG, L., TRENKLER, J., KILLER-OBERPFALZER, M., DEUTSCHMANN, H., NIEDERKORN, K., WOLF, F., GRUBER, A., HAUSEGGER, K., WEBER, J., THURNHER, S., GIZEWSKI, E., WILLEIT, J., KARAIC, R., FERTL, E., NAŠEL, C., BRAININ, M., ERIAN, J., OBERNDORFER, S., KARNEL, F., GRISOLD, W., AUFF, E., FAZEKAS, F., HARING, H. P. & LANG, W. 2016. Endovascular stroke therapy in Austria: a nationwide 1-year experience. *Eur J Neurol,* 23**,** 906-11.
SEVICK, L. K., GHALI, S., HILL, M. D., DANTHUREBANDARA, V., LORENZETTI, D. L., NOSEWORTHY, T., SPACKMAN, E. & CLEMENT, F. 2017. Systematic

Review of the Cost and Cost-Effectiveness of Rapid Endovascular Therapy for Acute Ischemic Stroke. *Stroke,* 48**,** 2519-2526.

SHI, Z. S., LIEBESKIND, D. S., XIANG, B., GE, S. G., FENG, L., ALBERS, G. W., BUDZIK, R., DEVLIN, T., GUPTA, R., JANSEN, O., JOVIN, T. G., KILLER-OBERPFALZER, M., LUTSEP, H. L., MACHO, J., NOGUEIRA, R. G., RYMER, M., SMITH, W. S., WAHLGREN, N. & DUCKWILER, G. R. 2014. Predictors of functional dependence despite successful revascularization in large-vessel occlusion strokes. *Stroke,* 45**,** 1977-84.

SHIREMAN, T. I., WANG, K., SAVER, J. L., GOYAL, M., BONAFÉ, A., DIENER, H. C., LEVY, E. I., PEREIRA, V. M., ALBERS, G. W., COGNARD, C., HACKE, W., JANSEN, O., JOVIN, T. G., MATTLE, H. P., NOGUEIRA, R. G., SIDDIQUI, A. H., YAVAGAL, D. R., DEVLIN, T. G., LOPES, D. K., REDDY, V. K., DU MESNIL DE ROCHEMONT, R., JAHAN, R., VILAIN, K. A., HOUSE, J., LEE, J. M. & COHEN, D. J. 2017. Cost-Effectiveness of Solitaire Stent Retriever Thrombectomy for Acute Ischemic Stroke: Results From the SWIFT-PRIME Trial (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke). *Stroke,* 48**,** 379-387.

SILVER, B., DEMAERSCHALK, B., MERINO, J. G., WONG, E., TAMAYO, A., DEVASENAPATHY, A., O'CALLAGHAN, C., KERTESZ, A., YOUNG, G. B., FOX, A. J., SPENCE, J. D. & HACHINSKI, V. 2001. Improved outcomes in stroke thrombolysis with pre-specified imaging criteria. *Can J Neurol Sci,* 28**,** 113-9.

SIMPSON, K. N., SIMPSON, A. N., MAULDIN, P. D., HILL, M. D., YEATTS, S. D., SPILKER, J. A., FOSTER, L. D., KHATRI, P., MARTIN, R., JAUCH, E. C., KLEINDORFER, D., PALESCH, Y. Y., BRODERICK, J. P. & INVESTIGATORS, I. I. 2014. Drivers of costs associated with reperfusion therapy in acute stroke: the Interventional Management of Stroke III Trial. *Stroke,* 45**,** 1791-8.

SIMPSON, K. N., SIMPSON, A. N., MAULDIN, P. D., PALESCH, Y. Y., YEATTS, S. D., KLEINDORFER, D., TOMSICK, T. A., FOSTER, L. D., DEMCHUK, A. M., KHATRI, P., HILL, M. D., JAUCH, E. C., JOVIN, T. G., YAN, B., VON KUMMER, R., MOLINA, C. A., GOYAL, M., SCHONEWILLE, W. J., MAZIGHI, M., ENGELTER, S. T., ANDERSON, C., SPILKER, J., CARROZZELLA, J., RYCKBORST, K. J., JANIS, L. S. & BRODERICK, J. P. 2017. Observed Cost and Variations in Short Term Cost-Effectiveness of Therapy for Ischemic Stroke in Interventional Management of Stroke (IMS) III. *J Am Heart Assoc,* 6.

SINGH, B., PARSAIK, A. K., PROKOP, L. J. & MITTAL, M. K. 2013. Endovascular therapy for acute ischemic stroke: a systematic review and meta-analysis. *Mayo Clin Proc,* 88**,** 1056-65.

SITS-ISTR. *Safe Implementation of Treatments in Stroke (SITS) international stroke thrombolysis registry (SITS-ISTR)* [Online]. Available: https://sitsinternational.org/news/sits-scientifcreport- (accessed 6 April 2016). [Accessed].

SITS-TBY. *Safe Implementation of Treatments in Stroke (SITS) thrombectomy registry (SITS TBY).* [Online]. Available: https:/sitsinternational.org/news/sits-thrombectomy-registry (accessed 6 April 2016). [Accessed].

SMITH, C. J. S., H. HERWADKAR, A. SIRIPURAPU, R CARROLL, C.WILLIAMS, T. LAITT, R. 2018. *Emergency intra-arterial intervention in acute ischaemic stroke. Salford Royal NHS, University Teaching Foundation Trust. April*

[Online]. Available: https://gmisdn.org.uk/wp-content/uploads/2020/04/TC2309-Issue-No-4.1-Emergency-intra-arterial-intervention-in-acute-ischaemic-stroke.pdf [Accessed 16 March 2019].

SMITH, E. E., FONAROW, G. C., REEVES, M. J., COX, M., OLSON, D. M., HERNANDEZ, A. F. & SCHWAMM, L. H. 2011. Outcomes in mild or rapidly improving stroke not treated with intravenous recombinant tissue-type plasminogen activator: findings from Get With The Guidelines-Stroke. *Stroke,* 42**,** 3110-5.

SMITH, W. S., LEV, M. H., ENGLISH, J. D., CAMARGO, E. C., CHOU, M., JOHNSTON, S. C., GONZALEZ, G., SCHAEFER, P. W., DILLON, W. P., KOROSHETZ, W. J. & FURIE, K. L. 2009. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. *Stroke,* 40**,** 3834-40.

SMITH, W. S., SUNG, G., SAVER, J., BUDZIK, R., DUCKWILER, G., LIEBESKIND, D. S., LUTSEP, H. L., RYMER, M. M., HIGASHIDA, R. T., STARKMAN, S., GOBIN, Y. P., FREI, D., GROBELNY, T., HELLINGER, F., HUDDLE, D., KIDWELL, C., KOROSHETZ, W., MARKS, M., NESBIT, G. & SILVERMAN, I. E. 2008. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke,* 39**,** 1205-12.

SMITH, W. S., SUNG, G., STARKMAN, S., SAVER, J. L., KIDWELL, C. S., GOBIN, Y. P., LUTSEP, H. L., NESBIT, G. M., GROBELNY, T., RYMER, M. M., SILVERMAN, I. E., HIGASHIDA, R. T., BUDZIK, R. F. & MARKS, M. P. 2005. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke,* 36**,** 1432-8.

SOUZA, L. C., YOO, A. J., CHAUDHRY, Z. A., PAYABVASH, S., KEMMLING, A., SCHAEFER, P. W., HIRSCH, J. A., FURIE, K. L., GONZÁLEZ, R. G., NOGUEIRA, R. G. & LEV, M. H. 2012. Malignant CTA collateral profile is highly specific for large admission DWI infarct core and poor outcome in acute stroke. *AJNR Am J Neuroradiol,* 33**,** 1331-6.

SSNAP. 2016. *Royal College of Physicians (2016). Sentinel Stroke National Audit Programme (SSNAP) Acute Organisational Audit.* [Online]. Available: https://www.strokeaudit.org/Documents/National/AcuteOrg/2016/2016-AOANationalReport.aspx [Accessed 15 December 2020].

SSNAP. 2017a. *National Stroke National Audit Programme (SSNAP) Thrombectomy Report for April 2016 - March 2017.* [Online]. Available: https://www.hqip.org.uk/public/cms/253/625/19/905/National%20SSNAP%20Thrombectomy%20Report%2016.17.pdf?realName=3N5pxG.pdf&v=0. Acessed on 11 October 2017 [Accessed].

SSNAP. 2017b. *Sentinel Stroke National Audit Programme (SSNAP): Thrombectomy Report for April 2016 – March 2017. Published 11 August* [Online]. Available: https://www.hqip.org.uk/resource/sentinel-stroke-national-audit-programme-ssnap-thrombectomy-report-for-april-2016-march-2017/#.YFdJEpP7RH1 [Accessed 15 September 2017].

SSNAP. 2021. *Sentinel Stroke National Audit Programme (SSNAP). National Results-Clinical (October - December 2020)* [Online]. Available: https://www.strokeaudit.org/results/Clinical-audit/National-Results.aspx [Accessed 22 March 2021].

SSNAP REPORT. 2021. *The Seventh SSNAP Annual Report 2019-20. Stroke care received for patients admitted to hospital between April 2019 to March 2020. Published: 14 Jan* [Online]. Available: https://www.hqip.org.uk/resource/sentinel-stroke-national-audit-programme-annual-report-2019-20/#.YEyaH5P7R5w [Accessed 15 February 2021].

STEEN CARLSSON, K., ANDSBERG, G., PETERSSON, J. & NORRVING, B. 2017. Long-term cost-effectiveness of thrombectomy for acute ischaemic stroke in real life: An analysis based on data from the Swedish Stroke Register (Riksstroke). *Int J Stroke,* 12**,** 802-814.

STROKE ASSOCIATION. 2018. *State of the Nation Stroke Statistics February 2018. Stroke.org.uk* [Online]. Available: https://www.stroke.org.uk/sites/default/files/state_of_the_nation_2018.pdf [Accessed 17 December 2019].

STROKE FOUNDATION. 2020. *The economic impact of stroke in Australia, 2020 Stroke Foundation November* [Online]. Available: https://www2.deloitte.com/content/dam/Deloitte/au/Documents/Economics/deloi

tte-au-dae-economic-impact-stroke-report-061120.pdf [Accessed 15 January 2021].
SULTER, G., STEEN, C. & DE KEYSER, J. 1999. Use of the Barthel index and modified Rankin scale in acute stroke trials. *Stroke,* 30**,** 1538-41.
SUN, X., ORLEWSKA, E., LI, Y.-P., CHENG, G. & YANG, H. 2006. Methods for economic evaluation of marketed medicines Ⅱ: conducting primary economic evaluation. *Chin J Evid Based Med,* 6**,** 218-223.
SUNDARAM, V. K., GOLDSTEIN, J., WHEELWRIGHT, D., AGGARWAL, A., PAWHA, P. S., DOSHI, A., FIFI, J. T., LEACY, R., MOCCO, J., PUIG, J. & NAEL, K. 2019. Automated ASPECTS in Acute Ischemic Stroke: A Comparative Analysis with CT Perfusion. *AJNR Am J Neuroradiol,* 40**,** 2033-2038.
SUTHERLAND, B. A., MINNERUP, J., BALAMI, J. S., ARBA, F., BUCHAN, A. M. & KLEINSCHNITZ, C. 2012. Neuroprotection for ischaemic stroke: translation from the bench to the bedside. *Int J Stroke,* 7**,** 407-18.
TAN, I. Y., DEMCHUK, A. M., HOPYAN, J., ZHANG, L., GLADSTONE, D., WONG, K., MARTIN, M., SYMONS, S. P., FOX, A. J. & AVIV, R. I. 2009. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am J Neuroradiol,* 30**,** 525-31.
TAWIL, S. E., CHERIPELLI, B., HUANG, X., MORETON, F., KALLADKA, D., MACDOUGAL, N. J., MCVERRY, F. & MUIR, K. W. 2016. How many stroke patients might be eligible for mechanical thrombectomy? 1**,** 264-271.
TELJEUR, C., HARRINGTON, P., GLYNN, R. W. & RYAN, M. 2018. Acute ischaemic stroke: a systematic review of the cost-effectiveness of emergency endovascular therapy using mechanical thrombectomy. *Ir J Med Sci*.
TELJEUR, C., HARRINGTON, P., GLYNN, R. W. & RYAN, M. 2019. Acute ischaemic stroke: a systematic review of the cost-effectiveness of emergency endovascular therapy using mechanical thrombectomy. *Ir J Med Sci,* 188**,** 751-759.
THAMES VALLEY CLINICAL SENATE. 2020. *Thrombectomy Service – FINAL report from the Stakeholder Forum NHS England and NHS Improvement* [Online]. Available: https://secsenate.nhs.uk/wp-content/uploads/2020/06/FINAL-Thames-Valley-Clinical-Senate-Thrombectomy-Report.pdf [Accessed 10 January 2021].
THE ROYAL COLLEGE OF RADIOLOGISTS. 2020. *Mechanical thrombectomy for ischaemic stroke. Update September 2020. Training of interventional radiologists* [Online]. Available: https://www.rcr.ac.uk/clinical-radiology/being-consultant/mechanical-thrombectomy-ischaemic-stroke [Accessed 15 December 2020].
THOMALLA, G., BOUTITIE, F., MA, H., KOGA, M., RINGLEB, P., SCHWAMM, L. H., WU, O., BENDSZUS, M., BLADIN, C. F., CAMPBELL, B. C. V., CHENG, B., CHURILOV, L., EBINGER, M., ENDRES, M., FIEBACH, J. B., FUKUDA-DOI, M., INOUE, M., KLEINIG, T. J., LATOUR, L. L., LEMMENS, R., LEVI, C. R., LEYS, D., MIWA, K., MOLINA, C. A., MUIR, K. W., NIGHOGHOSSIAN, N., PARSONS, M. W., PEDRAZA, S., SCHELLINGER, P. D., SCHWAB, S., SIMONSEN, C. Z., SONG, S. S., THIJS, V., TONI, D., HSU, C. Y., WAHLGREN, N., YAMAMOTO, H., YASSI, N., YOSHIMURA, S., WARACH, S., HACKE, W., TOYODA, K., DONNAN, G. A., DAVIS, S. M., GERLOFF, C., ACOSTA, B. R., AEGIDIUS, K., ALBIKER, C., ALEGIANI, A., ALMENDROTE, M., ALONSO, A., ALTHAUS, K., AMARENCO, P., AMIRI, H., ANDERS, B., ANICULAESEI, A., APPLETON, J., ARENILLAS, J., BACK, C., BÄHR, C., BARDUTZKY, J., BARONNET-CHAUVET, F., BATHE-PETERS, R., BAYER-KARPINSKA, A., BECERRA, J. L., BECK, C., BELCHÍ GUILLAMON, O., BENOIT, A., BERHOUNE, N., BINDILA, D., BIRCHENALL, J., BLANC-LASSERRE, K., BLANCO GONZALES, M., BOBINGER, T., BODECHTEL, U., BODIGUEL, E., BOJARYN, U., BONNET, L., BOUAMRA, B., BOURGEOIS, P., BOUTITIE, F., BREUER, L., BREYNAERT, L.,

BROUGHTON, D., BROUNS, R., BRUGIRARD, S., BRUNEEL, B., BUGGLE, F., CAKMAK, S., CALLEJA, A., CALVET, D., CARRERA, D., CHEN, H.-C., CHENG, B., CHERIPELLI, B., CHO, T.-H., CHOE, C.-U., CHOY, L., CHRISTENSEN, H., CIATIPIS, M., et al. 2020. Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data. *The Lancet,* 396**,** 1574-1584.

THORVALDSEN, P., ASPLUND, K., KUULASMAA, K., RAJAKANGAS, A. M. & SCHROLL, M. 1995. Stroke incidence, case fatality, and mortality in the WHO MONICA project. World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. *Stroke,* 26**,** 361-7.

THURMAN, J. S., B. ECKARD, N. NILSSON, C. HIORT, S. 2015. Cost-effectiveness analysis of thrombectomy for treatment of acute severe ischemic stroke. Stockholm: Swedish Dental and Pharmaceutical Benefits Agency, 2015. Contract No.: 01009/2015.

TORRES-MOZQUEDA, F., HE, J., YEH, I. B., SCHWAMM, L. H., LEV, M. H., SCHAEFER, P. W. & GONZÁLEZ, R. G. 2008. An acute ischemic stroke classification instrument that includes CT or MR angiography: the Boston Acute Stroke Imaging Scale. *AJNR Am J Neuroradiol,* 29**,** 1111-7.

TOWNSEND, N., WILSON, L., BHATNAGAR, P., WICKRAMASINGHE, K., RAYNER, M. & NICHOLS, M. 2016. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J,* 37**,** 3232-3245.

TREASURY, H. 2019. GDP deflators at market prices, and money GDP: June 2016 (Quarterly National Accounts). *HM Treasury*.

TREURNIET, K. M., LECOUFFE, N. E., KAPPELHOF, M., EMMER, B. J., VAN ES, A., BOITEN, J., LYCKLAMA, G. J., KEIZER, K., YO, L. S. F., LINGSMA, H. F., VAN ZWAM, W. H., DE RIDDER, I., VAN OOSTENBRUGGE, R. J., VAN DER LUGT, A., DIPPEL, D. W. J., COUTINHO, J. M., ROOS, Y. & MAJOIE, C. 2021. MR CLEAN-NO IV: intravenous treatment followed by endovascular treatment versus direct endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion-study protocol for a randomized clinical trial. *Trials,* 22**,** 141.

TRIPPOLI, S., CACCESE, E., MARINAI, C. & MESSORI, A. 2018. Value-based procurement of medical devices: Application to devices for mechanical thrombectomy in ischemic stroke. *Clin Neurol Neurosurg,* 166**,** 61-65.

TURC, G., BHOGAL, P., FISCHER, U., KHATRI, P., LOBOTESIS, K., MAZIGHI, M., SCHELLINGER, P. D., TONI, D., DE VRIES, J., WHITE, P. & FIEHLER, J. 2019. European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke. *J Neurointerv Surg*.

TURK, A. S., TURNER, R., SPIOTTA, A., VARGAS, J., HOLMSTEDT, C., OZARK, S., CHALELA, J., TURAN, T., ADAMS, R., JAUCH, E. C., BATTENHOUSE, H., WHITSITT, B., WAIN, M. & CHAUDRY, M. I. 2014. Comparison of endovascular treatment approaches for acute ischemic stroke: cost effectiveness, technical success, and clinical outcomes (Provisional abstract). *Journal of NeuroInterventional Surgery* [Online]. Available: http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-22014029251/frame.html.

TURK, A. S., TURNER, R., SPIOTTA, A., VARGAS, J., HOLMSTEDT, C., OZARK, S., CHALELA, J., TURAN, T., ADAMS, R., JAUCH, E. C., BATTENHOUSE, H., WHITSITT, B., WAIN, M. & CHAUDRY, M. I. 2015. Comparison of endovascular treatment approaches for acute ischemic stroke: cost effectiveness, technical success, and clinical outcomes. *J Neurointerv Surg,* 7**,** 666-70.

UNIVERSITY OF YORK. 2008. *Systematic Reviews Centre for Reviews and Dissemination's (CRD) guidance for undertaking reviews in health care(University of York).* [Online]. Centre for Reviews and Dissemination, University of York, 2008 Published by CRD. Available:

https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf [Accessed 07 July 2019].
URANSILP, N., DHARMASAROJA, P. A., WATCHARAKORN, A. & MUENGTAWEEPONGSA, S. 2019. Implementation of multiphase computed tomography angiography in management of patients with acute ischemic stroke in clinical practice. *Journal of Clinical Neuroscience,* 62**,** 100-104.
URRA, X., ABILLEIRA, S., DORADO, L., RIBÓ, M., CARDONA, P., MILLÁN, M., CHAMORRO, A., MOLINA, C., COBO, E., DÁVALOS, A., JOVIN, T. G. & GALLOFRÉ, M. 2015. Mechanical Thrombectomy in and Outside the REVASCAT Trial: Insights From a Concurrent Population-Based Stroke Registry. *Stroke,* 46**,** 3437-42.
VAGAL, A., WINTERMARK, M., NAEL, K., BIVARD, A., PARSONS, M., GROSSMAN, A. W. & KHATRI, P. 2019. Automated CT perfusion imaging for acute ischemic stroke: Pearls and pitfalls for real-world use. *Neurology,* 93**,** 888-898.
VALKO, M., LEIBFRITZ, D., MONCOL, J., CRONIN, M. T., MAZUR, M. & TELSER, J. 2007. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol,* 39**,** 44-84.
VAN SWIETEN, J. C., KOUDSTAAL, P. J., VISSER, M. C., SCHOUTEN, H. J. & VAN GIJN, J. 1988. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke,* 19**,** 604-7.
VEGA-VALDES, P., MURIAS-QUINTANA, E., MORALES-SANTOS, E., CIGARRAN-SEXTO, H., LARROSA-CAMPO, D., BENAVENTE-FERNANDEZ, L., GONZALEZ-DELGADO, M., CALLEJA-PUERTA, S. & GARCIA-ARIAS, F. 2018. [Analysis of the direct costs associated with mechanical thrombectomy and intravenous fibrinolysis in the Hospital Universitario Central de Asturias]. *Rev Neurol,* 66**,** 7-14.
VICTORIA STATE GOVERNMENT. 2016. *Department of Health & Human Services, Victoria State Government. Endovascular clot retrieval for acute stroke – statewide service protocol. Policies and Guidelines. February 10* [Online]. Available: https://www2.health.vic.gov.au/about/publications/policiesandguidelines/endovascular-clot-retrieval-for-acute-stroke-statewide-service-protocol [Accessed 15 March 2019].
VIDAL, G. A. & MILBURN, J. M. 2016. The Penumbra 5MAX ACE catheter is safe, efficient, and cost saving as a primary mechanical thrombectomy device for large vessel occlusions in acute ischemic stroke. *Ochsner Journal,* 16**,** 486-491.
VON KUMMER, R., HOLLE, R., GIZYSKA, U., HOFMANN, E., JANSEN, O., PETERSEN, D., SCHUMACHER, M. & SARTOR, K. 1996. Interobserver agreement in assessing early CT signs of middle cerebral artery infarction. *AJNR Am J Neuroradiol,* 17**,** 1743-8.
WAFA, H. A., WOLFE, C. D. A., EMMETT, E., ROTH, G. A., JOHNSON, C. O. & WANG, Y. 2020. Burden of Stroke in Europe. *Stroke,* 51**,** 2418-2427.
WAHLGREN, N., AHMED, N., DÁVALOS, A., FORD, G. A., GROND, M., HACKE, W., HENNERICI, M. G., KASTE, M., KUELKENS, S., LARRUE, V., LEES, K. R., ROINE, R. O., SOINNE, L., TONI, D. & VANHOOREN, G. 2007. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet,* 369**,** 275-82.
WAHLGREN, N., AHMED, N., ERIKSSON, N., AICHNER, F., BLUHMKI, E., DÁVALOS, A., ERILÄ, T., FORD, G. A., GROND, M., HACKE, W., HENNERICI, M. G., KASTE, M., KÖHRMANN, M., LARRUE, V., LEES, K. R., MACHNIG, T., ROINE, R. O., TONI, D. & VANHOOREN, G. 2008. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). *Stroke,* 39**,** 3316-22.

WAHLGREN, N., MOREIRA, T., MICHEL, P., STEINER, T., JANSEN, O., COGNARD, C., MATTLE, H. P., VAN ZWAM, W., HOLMIN, S., TATLISUMAK, T., PETERSSON, J., CASO, V., HACKE, W., MAZIGHI, M., ARNOLD, M., FISCHER, U., SZIKORA, I., PIEROT, L., FIEHLER, J., GRALLA, J., FAZEKAS, F. & LEES, K. R. 2016. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. *International Journal of Stroke,* 11**,** 134-147.

WANG, D. & WANG, Y. 2019. Tissue window, not the time window, will guide acute stroke treatment. *Stroke and Vascular Neurology,* 4**,** 1-2.

WANG, H., NAGHAVI, M., ALLEN, C., BARBER, R., CARTER, A., CASEY, D., CHARLSON, F., CHEN, A., COATES, M. & COGGESHALL, M. 2016. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980â 2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet,* 388**,** 1459-1544.

WANG, H., THEVATHASAN, A., DOWLING, R., BUSH, S., MITCHELL, P. & YAN, B. 2017. Streamlining Workflow for Endovascular Mechanical Thrombectomy: Lessons Learned from a Comprehensive Stroke Center. *J Stroke Cerebrovasc Dis,* 26**,** 1655-1662.

WANG, Y., RUDD, A. G. & WOLFE, C. D. 2013. Age and ethnic disparities in incidence of stroke over time: the South London Stroke Register. *Stroke,* 44**,** 3298-304.

WARDLAW, J. M., MURRAY, V., BERGE, E., DEL ZOPPO, G., SANDERCOCK, P., LINDLEY, R. L. & COHEN, G. 2012. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet,* 379**,** 2364-72.

WARLOW, C., VAN GIJN, J., DENNIS, M., WARDLAW, J., BAMFORD, J., HANKEY, G., SANDERCOCK, P., RINKEL, G., LANGHORNE, P. & SUDLOW, C. 2008. Is it a vascular event and where is the lesion? Identifying and interpreting the symptoms and signs of cerebrovascular disease. *Stroke: Practical Management***,** 35-130.

WATKINS, J., MAXWELL, J., PURVIS, T., REYNEKE, M., KILKENNY, M., CADILHAC, D., ASLETT, T. & JAMES, P. 2019. National Stroke Audit: Acute Services Report 2019. *Stroke Foundation-Level,* 7**,** 461.

WEBER, R., NORDMEYER, H., HADISURYA, J., HEDDIER, M., STAUDER, M., STRACKE, P., BERGER, K. & CHAPOT, R. 2017. Comparison of outcome and interventional complication rate in patients with acute stroke treated with mechanical thrombectomy with and without bridging thrombolysis. *J Neurointerv Surg,* 9**,** 229-233.

WEI, D., OXLEY, T. J., NISTAL, D. A., MASCITELLI, J. R., WILSON, N., STEIN, L., LIANG, J., TURKHEIMER, L. M., MOREY, J. R., SCHWEGEL, C., AWAD, A. J., SHOIRAH, H., KELLNER, C. P., DE LEACY, R. A., MAYER, S. A., TUHRIM, S., PARAMASIVAM, S., MOCCO, J. & FIFI, J. T. 2017. Mobile Interventional Stroke Teams Lead to Faster Treatment Times for Thrombectomy in Large Vessel Occlusion. *Stroke,* 48**,** 3295-3300.

WEISZ, G., METZGER, D. C., CAPUTO, R. P., DELGADO, J. A., MARSHALL, J. J., VETROVEC, G. W., REISMAN, M., WAKSMAN, R., GRANADA, J. F., NOVACK, V., MOSES, J. W. & CARROZZA, J. P. 2013. Safety and feasibility of robotic percutaneous coronary intervention: PRECISE (Percutaneous Robotically-Enhanced Coronary Intervention) Study. *J Am Coll Cardiol,* 61**,** 1596-600.

WERNER, M. F., LÓPEZ-RUEDA, A., ZARCO, F. X., BLASCO, J., SAN ROMÁN, L., AMARO, S., CARRERO, E., VALERO, R., OLEAGA, L., MACHO, J. M. & BARGALLÓ, N. 2019. Value of Posterior circulation ASPECTS and Pons-Midbrain Index on non-contrast CT and CT Angiography Source Images in patients with basilar artery occlusion recanalized after mechanical thrombectomy. *Radiologia,* 61**,** 143-152.

WHITE, P., BHALLA A, DINSMORE J, JAMES M, MCCONACHIE N, ROFFE C & G., Y. 2015. *Standards for providing safe acute ischaemic stroke thrombectomy services* [Online]. Available: https://basp.ac.uk/wp content/uploads/2016/12/Final_ThrombectomyStandardsSeptember-2015-2-1-1. [Accessed 2016].

WHITE, P. M., BHALLA, A., DINSMORE, J., JAMES, M., MCCONACHIE, N., ROFFE, C. & YOUNG, G. 2017. Standards for providing safe acute ischaemic stroke thrombectomy services (September 2015). *Clin Radiol,* 72**,** 175.e1-175.e9.

WHITELEY, W. N., EMBERSON, J., LEES, K. R., BLACKWELL, L., ALBERS, G., BLUHMKI, E., BROTT, T., COHEN, G., DAVIS, S., DONNAN, G., GROTTA, J., HOWARD, G., KASTE, M., KOGA, M., VON KUMMER, R., LANSBERG, M. G., LINDLEY, R. I., LYDEN, P., OLIVOT, J. M., PARSONS, M., TONI, D., TOYODA, K., WAHLGREN, N., WARDLAW, J., DEL ZOPPO, G. J., SANDERCOCK, P., HACKE, W. & BAIGENT, C. 2016. Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis. *Lancet Neurol,* 15**,** 925-933.

WIJNGAARDEN, J. D. H. V., DIRKS, M., HUIJSMAN, R., NIESSEN, L. W., FABBRICOTTI, I. N. & DIPPEL, D. W. J. 2009. Hospital Rates of Thrombolysis for Acute Ischemic Stroke. *Stroke,* 40**,** 3390-3392.

WILKINS, E., WILSON, L., WICKRAMASINGHE, K., BHATNAGAR, P., LEAL, J., LUENGO-FERNANDEZ, R., BURNS, R., RAYNER, M. & TOWNSEND, N. 2017. *European cardiovascular disease statistics 2017* [Online]. Available: http://www.ehnheart.org/images/CVD-statistics-report-August-2017.pdf [Accessed 10 January 2020].

WILSON, J. T., HAREENDRAN, A., HENDRY, A., POTTER, J., BONE, I. & MUIR, K. W. 2005. Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview. *Stroke,* 36**,** 777-81.

WINTERMARK, M., FLANDERS, A. E., VELTHUIS, B., MEULI, R., VAN LEEUWEN, M., GOLDSHER, D., PINEDA, C., SERENA, J., VAN DER SCHAAF, I., WAAIJER, A., ANDERSON, J., NESBIT, G., GABRIELY, I., MEDINA, V., QUILES, A., POHLMAN, S., QUIST, M., SCHNYDER, P., BOGOUSSLAVSKY, J., DILLON, W. P. & PEDRAZA, S. 2006. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke,* 37**,** 979-85.

WINTERMARK, M., MAEDER, P., THIRAN, J.-P., SCHNYDER, P. & MEULI, R. 2001. Quantitative assessment of regional cerebral blood flows by perfusion CT studies at low injection rates: a critical review of the underlying theoretical models. *European radiology,* 11**,** 1220-1230.

WOLPERT, S. M., BRUCKMANN, H., GREENLEE, R., WECHSLER, L., PESSIN, M. S. & DEL ZOPPO, G. J. 1993. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. *AJNR Am J Neuroradiol,* 14**,** 3-13.

WORLD STROKE ORGANIZATION. 2019. *Global Stroke Fact Sheet. World Stroke Organization (WSO)* [Online]. Available: WSO https://www.world-stroke.org/ images/WSO_Global_Stroke_Fact_Sheet_final.pdf [Accessed 10 March 2020].

WU, T. Y., COLEMAN, E., WRIGHT, S. L., MASON, D. F., REIMERS, J., DUNCAN, R., GRIFFITHS, M., HURRELL, M., DIXON, D., WEAVER, J., MERETOJA, A. & FINK, J. N. 2018. Helsinki Stroke Model Is Transferrable With "Real-World" Resources and Reduced Stroke Thrombolysis Delay to 34 min in Christchurch. *Front Neurol,* 9**,** 290.

WUFUER, A., WUBULI, A., MIJITI, P., ZHOU, J., TUERXUN, S., CAI, J., MA, J. & ZHANG, X. 2018. Impact of collateral circulation status on favorable outcomes in thrombolysis treatment: A systematic review and meta-analysis. *Experimental and therapeutic medicine,* 15**,** 707-718.

XIANG, X. & CAO, F. 2019. Time window and “tissue window”: two approaches to assist decision-making in strokes. *Journal of Neurology,* 266**,** 283-288.

XIE, X., LAMBRINOS, A., CHAN, B., DHALLA, I. A., KRINGS, T., CASAUBON, L. K., LUM, C., SIKICH, N., BHARATHA, A., PEREIRA, V. M., STOTTS, G., SAPOSNIK, G., O'CALLAGHAN, C., KELLOWAY, L. & HILL, M. D. 2016. Mechanical thrombectomy in patients with acute ischemic stroke: a cost-utility analysis. *CMAJ Open,* 4**,** E316-25.

XU, X. M., VESTESSON, E., PALEY, L., DESIKAN, A., WONDERLING, D., HOFFMAN, A., WOLFE, C. D., RUDD, A. G. & BRAY, B. D. 2018. The economic burden of stroke care in England, Wales and Northern Ireland: Using a national stroke register to estimate and report patient-level health economic outcomes in stroke. *Eur Stroke J,* 3**,** 82-91.

YAMAL, J. M., RAJAN, S. S., PARKER, S. A., JACOB, A. P., GONZALEZ, M. O., GONZALES, N. R., BOWRY, R., BARRETO, A. D., WU, T. C., LAIRSON, D. R., PERSSE, D., TILLEY, B. C., CHIU, D., SUAREZ, J. I., JONES, W. J., ALEXANDROV, A. & GROTTA, J. C. 2018. Benefits of stroke treatment delivered using a mobile stroke unit trial. *Int J Stroke,* 13**,** 321-327.

YANG, P., TREURNIET, K. M., ZHANG, L., ZHANG, Y., LI, Z., XING, P., ZHANG, Y., ZHANG, P., WANG, H., HONG, B., DIPPEL, D. W., ROOS, Y. B., MAJOIE, C. B., DENG, B. & LIU, J. 2020. Direct Intra-arterial thrombectomy in order to Revascularize AIS patients with large vessel occlusion Efficiently in Chinese Tertiary hospitals: A Multicenter randomized clinical Trial (DIRECT-MT)-Protocol. *Int J Stroke,* 15**,** 689-698.

YOO, A. J., BARAK, E. R., COPEN, W. A., KAMALIAN, S., GHARAI, L. R., PERVEZ, M. A., SCHWAMM, L. H., GONZÁLEZ, R. G. & SCHAEFER, P. W. 2010. Combining acute diffusion-weighted imaging and mean transmit time lesion volumes with National Institutes of Health Stroke Scale Score improves the prediction of acute stroke outcome. *Stroke,* 41**,** 1728-35.

YU, A. Y., ZERNA, C., ASSIS, Z., HOLODINSKY, J. K., RANDHAWA, P. A., NAJM, M., GOYAL, M., MENON, B. K., DEMCHUK, A. M., COUTTS, S. B. & HILL, M. D. 2016. Multiphase CT angiography increases detection of anterior circulation intracranial occlusion. *Neurology,* 87**,** 609-16.

ZAIDAT, O. O., CASTONGUAY, A. C., GUPTA, R., SUN, C. H., MARTIN, C., HOLLOWAY, W. E., MUELLER-KRONAST, N., ENGLISH, J. D., LINFANTE, I., DABUS, G., MALISCH, T. W., MARDEN, F. A., BOZORGCHAMI, H., XAVIER, A., RAI, A. T., FROEHLER, M. T., BADRUDDIN, A., NGUYEN, T. N., TAQI, M. A., ABRAHAM, M. G., JANARDHAN, V., SHALTONI, H., NOVAKOVIC, R., YOO, A. J., ABOU-CHEBL, A., CHEN, P. R., BRITZ, G. W., KAUSHAL, R., NANDA, A., ISSA, M. A. & NOGUEIRA, R. G. 2014. North American Solitaire Stent Retriever Acute Stroke registry: post-marketing revascularization and clinical outcome results. *J Neurointerv Surg,* 6**,** 584-8.

ZAIDAT, O. O., CASTONGUAY, A. C., GUPTA, R., SUN, C. J., MARTIN, C., HOLLOWAY, W. E., MUELLER-KRONAST, N., ENGLISH, J. D., LINFANTE, I., DABUS, G., MALISCH, T. W., MARDEN, F. A., BOZORGCHAMI, H., XAVIER, A., RAI, A. T., FROEHLER, M. T., BADRUDDIN, A., NGUYEN, T. N., TAQI, M. A., ABRAHAM, M. G., JANARDHAN, V., SHALTONI, H., NOVAKOVIC, R., YOO, A. J., ABOU-CHEBL, A., CHEN, P. R., BRITZ, G. W., KAUSHAL, R., NANDA, A., ISSA, M. A. & NOGUEIRA, R. G. 2018. North American Solitaire Stent Retriever Acute Stroke registry: post-marketing revascularization and clinical outcome results. *J Neurointerv Surg,* 10**,** i45-i49.

ZAIDAT, O. O., YOO, A. J., KHATRI, P., TOMSICK, T. A., VON KUMMER, R., SAVER, J. L., MARKS, M. P., PRABHAKARAN, S., KALLMES, D. F., FITZSIMMONS, B. F., MOCCO, J., WARDLAW, J. M., BARNWELL, S. L., JOVIN, T. G., LINFANTE, I., SIDDIQUI, A. H., ALEXANDER, M. J., HIRSCH, J. A., WINTERMARK, M., ALBERS, G., WOO, H. H., HECK, D. V., LEV, M., AVIV, R., HACKE, W.,

WARACH, S., BRODERICK, J., DERDEYN, C. P., FURLAN, A., NOGUEIRA, R. G., YAVAGAL, D. R., GOYAL, M., DEMCHUK, A. M., BENDSZUS, M. & LIEBESKIND, D. S. 2013. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke,* 44**,** 2650-63.

ZAIDI, S. F., SHAWVER, J., ESPINOSA MORALES, A., SALAHUDDIN, H., TIETJEN, G., LINDSTROM, D., PARQUETTE, B., ADAMS, A., KORSNACK, A. & JUMAA, M. A. 2017. Stroke care: initial data from a county-based bypass protocol for patients with acute stroke. *J Neurointerv Surg,* 9**,** 631-635.

ZERNA, C., ASSIS, Z., D'ESTERRE, C. D., MENON, B. K. & GOYAL, M. 2016. Imaging, Intervention, and Workflow in Acute Ischemic Stroke: The Calgary Approach. *AJNR Am J Neuroradiol,* 37**,** 978-84.

Appendices

Oxford University Hospitals NHS
NHS Foundation Trust

UNIVERSITY OF OXFORD

CTRG Clinical Trials and Research Governance

Joint Research Office
Block 60, Churchill Hospital
Oxford, OX3 7LE

9 Sept 2016

Dr Joyce Balami
Joyce.balami@kellog.ox.ac.uk

Dear Dr Balami,

Title: The Clinical Effectiveness of Thrombectomy for the Treatment of Acute Ischaemic Stroke: Delivering an Efficient and Cost-Effective Thrombectomy service within the NHS

Thank you for submitting your study for review by the Joint Research Office study classification group.

I can confirm our opinion that the study falls outside of the definition of research as set out by the Health Research Authority (HRA) and would not be considered research in the NHS. As such, this study is not subject to the Department of Health's *Research Governance Framework for Health and Social Care* (2005). This opinion can be reviewed by reference to the HRA's algorithm, available at http://www.hra-decisiontools.org.uk/research/ and attendant leaflet, *Defining Research.*

Because the study constitutes service evaluation being undertaken the NHS, it is necessary to register it with Clinical Audit and to meet their requirements before commencing.

Should you require further information, please do not hesitate to contact me.

Sincerely,

Dr Karen Melham
Senior Clinical Research Support Manager
Clinical Trials and Research Governance

Participant information

Title of study: The Clinical Effectiveness of Endovascular Thrombectomy for the Treatment of Acute Ischaemic Stroke: Delivering an Efficient and Cost-Effective Thrombectomy Service within the NHS

We would like to invite you to participate in this research project. Before you decide whether you want to participate, it is important to understand why the research is being done and what your participation will involve. Please take some time to read the following information carefully and discuss it with others if you wish. Ask any further questions if there is anything that is not clear or if you would like more information. Contact details can be found at the end of this document.

What is the study all about?
Evidence from several clinical randomised trials (RCTs) has shown the benefit of clot retrieval using mechanical thrombectomy (MT) procedure, alongside Intravenous thrombolysis (IVT) for the treatment of acute large vessel occlusive stroke. Based on the level I evidence from these trials; NICE has recommended MT for the treatment of patients with acute ischaemic stroke (AIS). Economic evaluation using data from the RCTs, found MT to be cost-effective. There is but limited information on the cost estimates and cost-effectiveness of delivering MT in routine clinical practice in the NHS.

What is the purpose of the Study?
The purpose of this study is to generate the cost estimates for MT and IVT for AIS patient treatment. In particular, it aims to estimate NHS treatment costs for the new treatment. Information will be collected on full resource use and costs of thrombectomy and conventional care on the stroke pathway as currently provided in the NHS. The output from this stage will provide a more detailed understanding of the costs associated with AIS patients progressing through the treatment pathway, the various resources that might be used and their costs. Additionally, the information from this stage will provide an estimate of the cost of performing the MT procedure compared to standard IVT therapy and will provide an overall cost for an MT service in routine clinical practice.
By using the information from this interview alongside other registry data this project hopes to provide the cost estimates for mechanical thrombectomy on the NHS.

Who is organising and funding the research?
The research is being undertaken by Dr. Joyce Balami, who is a DPhil (doctoral) student in the Department of Continuing Education at the University of Oxford. This project is being supervised by Professor Alastair Gray; a Professor of Health Economics at the University of Oxford with extensive experience of using methods to estimate the likely cost-effectiveness of new and existing health care interventions, Professor Alastair Buchan and Professor Gary Ford; both Professors of Stroke with extensive experience in stroke research. The research is funded by Kellogg College and has been approved by the University of Oxford Central University Research Ethics Committee (CUREC).

Why have I been asked to participate?
This project aims to interview key NHS staff from few thrombectomy centres with clinical and financial knowledge of delivering EVT. This hospital is one of the chosen Neuroscience thrombectomy centres, and you have been contacted because of your role in providing thrombectomy services.

Do I have to take part?

It is up to you to decide whether or not to take part in this study and you may ask the researcher questions or ask for more information before deciding whether or not to participate. However, we believe that based on your current role you can contribute to this study by proving information on the costs of delivering the new intervention.

What are the possible benefits of taking part?
The information from this interview will help provide an improved estimate of the cost of performing the MT procedure compared to standard IVT therapy and will provide an overall cost for MT provision in routine clinical practice.

What are the possible disadvantages and risks of taking part?
Participation in this study might involve you taking time out of your busy schedule for the interview. There is the possibility that this will interfere with your busy schedule. There are no identifiable risks during the interview. You will at no point be obliged to provide any information that makes you uncomfortable.

How will my interview be used?
The information from this interview will provide a more detailed understanding of the costs associated with acute ischaemic stroke patients progressing through the treatment pathway, the various resources that might be used and their costs.

What happens to the interviews collected during the study?
The information collected on the individual itemised costing of the stroke pathway for MT and IVT will be stored digitally and managed by the researcher for the duration of the project.

What happens at the end of the project?
If you agree to participate in this project, the information collected will be used to estimate the cost and cost-effectiveness of EVT. The research will be written up as a thesis. All participants can request a summary of the research findings should they wish to by contacting the researcher. On successful submission of the thesis, it will be deposited both in print and online at the University of Oxford, to facilitate its use in future research. The online digital copy of the thesis will be stored in the Oxford University Research Archive (ORA) and will be published with open access, meaning that it will be available to all Internet users. The information will also be presented at conferences and published in peer-review journals for publication

What should I do if I have any concerns or complaints?
If you have a concern about any aspect of this project, please speak to the researcher Dr Joyce Balami (Contact details below) who will do her best to answer you query. The researcher should acknowledge your concern within ten working days and give you an indication of how she intends to deal with it. If you remain unhappy or wish to make a formal complaint, please contact the chair of the Research Ethics Committee at the University of Oxford (Chair, Continuing Education Inter- Departmental Research Ethics Committee [D-REC]; Email: researchethics@conted.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD). The chair will seek to resolve the matter in a reasonably expeditious manner.

Contact details of researcher:
Dr Joyce Balami
Email: Joyce.balami @kellogg.ox.ac.uk
Contact number: 07501414416

DEPARTMENT FOR CONTINUING EDUCATION

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20/04/2018

Jacquie Kemp
Lead Commissioner
The Neuroscience Clinical Reference Group (CRG)
NHS England
jacquiekemp@nhs.net

Dear Ms Jacquie Kemp

Re: Published Tariff for Mechanical Thrombectomy

I understand that you are the leader of the team who has recently published the tariff for mechanical thrombectomy. I am a consultant stroke physician at the Norfolk and Norwich University Hospitals NHS Foundation Trust and DPhil student at the University of Oxford under the supervision of Professors Gary Ford, Alastair Buchan and Alastair Gray. My research involves estimating the resource use and the costs associated with different clinical pathways/teams for delivering mechanical thrombectomy in the UK.

It would be valuable to my research studies to understand the factors taken into account to derive the current tariff for thrombectomy. Professor Tony Rudd suggested that you were the best person to contact to discuss this. Would it be possible to meet you or alternatively discuss this by telephone?

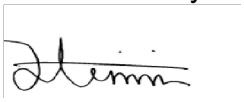
I am calculating the costs of delivering thrombectomy in six UK stroke services and would be happy to share these data with you once my work is complete.

I will acknowledge your contribution to my research and in any publication.

Thank you for considering my request.

I look forward to hearing from you.

Yours sincerely



Dr Joyce Balami

Chapter 2 Appendix

Appendix 2.A - The National Institutes of Health stroke scale (NIHSS)

The National Institutes of Health stroke scale (NIHSS) is a commonly used scale for measuring stroke severity, employing a 42-point scale that quantifies neurologic deficits assessed across 11 categories

Subject	Score
Loss of Consciousness	0 alert 1 drowsy 2 stuporous 3 coma
Loss of Consciousness questions	0 both correct 1 one correct 2 incorrect
Loss of Consciousness commands	0 both correct 1 one correct 2 incorrect
Best gaze	0 normal 1 partial gaze palsy 2 forced deviation
Best visual	0 visual loss 1 partial hemianopia 2 complete hemianopia 3 bilateral hemianopia
Facial palsy	0 normal 1 minor 2 partial 3 complete
Motor left arm	0 no drift 1 drift 2 can’t resist gravity 3 no effort against gravity 3 no movement
Motor right arm	0 no drift 1 drift 2 can’t resist gravity 3 no effort against gravity 4 no movement
Motor left leg	0 no drift 1 drift 2 can’t resist gravity 3 no effort against gravity 4 no movement
Motor right leg	0 no drift 1 drift 2 can’t resist gravity 3 no effort against gravity 4 no movement

Subject	Score
Limb ataxia	0 absent 1 present in upper or lower 2 present in both 3 amputation
Sensory	0 normal 1 mild to moderate 2 severe to total
Best language	0 absent 1 present in upper or lower 2 severe 3 mute
Dysarthria	0 normal articulation 1 mild to moderate dysarthria 2 near unintelligible
Extinction and inattention	0 normal 2 partial 3 profound
Total	

Appendix 2.B - The modified Thrombolysis in Cerebral Infarction (TICI)

The modified Thrombolysis in Cerebral Infarction (TICI) scale

Grade	Description
0	No perfusion
1	Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion
2a	Perfusion of less than half of the vascular distribution of the occluded artery
2b	Perfusion of half or greater of the vascular distribution of the occluded artery
3	Full perfusion with filling of all distal branches

Appendix 2.C - The Modified Rankin score (mRS)

The Modified Rankin score (mRS) is a commonly used scale for measuring pre-stroke functional status and functional disability after stroke (Sulter G 1999, van Swieten 1988). It is a 6-point scale where 0 indicates the absence of disability and 5 indicates severe disability.

The modified Rankin scale (mRS)*

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

Chapter 3 Appendix

Appendix 3.A - Search Strategy

Literature Search Strategies: Key Term Search

Search terms relevant to the disease state, including stroke (isch(a)emia, brain, cerebral, cerebrovascular accident, stroke, large artery occlusion) were combined using the Boolean operator AND, with terms reflecting the treatment, Endovascular mechanical thrombectomy (thrombectomy, mechanical thrombectomy, mechanical thrombus removal, endovascular therapy, endovascular intervention, clot retrieval, clot disruption, clot aspiration, stent-assisted) and

Search terms:

1, Brain ischaemia/ischemia, acute ischaemic/ischemic stroke, Cerebral infarction, cerebrovascular accident, CVA

2, Mechanical thrombolysis, endovascular therapy, endovascular treatment, endovascular embolectomy, endovascular thrombectomy, intra-arterial intervention, intraarterial intervention, intra-arterial treatment, intraarterial treatment, intra-arterial therapy, intraarterial therapy, intra-arterial thrombolysis, intraarterial thrombolysis, neurothrombectomy, neuro-thrombectomy

The developed search terms were first used in MEDLINE and then adjusted accordingly for other databases.

Database: Embase 1974 to present
Search Strategy:
1 exp *cerebrovascular accident/ (81577)
2 exp cerebrovascular accident/ (210436)
3 stroke*.ti,ab. (392431)
4 *brain ischemia/ (75563)
5 brain ischemia/ (141850)
6 brain isch?emia.ti,ab. (7171)
7 cerebrovascular accident*.ti,ab. (10290)
8 large artery occlusion*.ti,ab. (492)
9 *cerebrovascular disease/ (22300)
10 cerebrovascular disease/ (55195)
11 *brain infarction/ (19693)
12 brain infarction/ (52620)

13 *thromboembolism/ (17696)
14 thromboembolism/ (65277)
15 ((brain* or cerebr* or cerebell* or cortical or vertebrobasilar or hemispher* or intracran* or intracerebral of infratentorial or supraentorial of mca or anterior circulation or posterior circulation) adj5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypox* or obstruction or vasculopathy)).tw. (165554)
16 cva*.ti,ab. (9268)
17 1 or 3 or 4 or 6 or 7 or 8 or 9 or 11 or 13 or 15 or 16 (553106)
18 2 or 3 or 5 or 6 or 7 or 8 or 10 or 12 or 14 or 15 or 16 (676325)
19 mechanical thrombolysis*.ti,ab. (295)
20 *mechanical thrombectomy/ (3155)
21 mechanical thrombectomy/ (6868)
22 mechanical thrombectom*.ti,ab. (5432)
23 neuro-thrombectom*.ti,ab. (3)
24 thrombectom*.ti,ab. (17390)
25 thrombolys*.ti,ab. (39847)
26 intraarterial.ti,ab. (7804)
27 intra-arterial.ti,ab. (18228)
28 (endovascular adj3 (therap* or treat* or embolectom* or thrombectom* or intervention* or procedur*)).ti,ab. (40370)
29 (intra-arterial adj3 (therap* or treat* or embolectom* or thrombectom* or intervention* or procedur*)).ti,ab. (3791)
30 (intraarterial adj3 (therap* or treat* or embolectom* or thrombectom* or intervention* or procedur*)).ti,ab. (1426)
31 (clot* adj3 (retriev* or disrupt* or remov* or aspirat* or stent assisted)).ti,ab. (2700)
32 (embol* or thrombos* or clot*).ti,ab. (442119)
33 (mechanic* adj3 remov*).ti,ab. (2522)
34 32 and 33 (193)
35 19 or 20 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 31 or 34 (109683)
36 19 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 31 or 34 (110604)
37 (intravenous* adj3 thrombolys*).ti,ab. (5919)
38 *tissue plasminogen activator/ (10472)
39 tissue plasminogen activator/ (29110)
40 *intravenous drug administration/ (5242)
41 intravenous drug administration/ (357444)
42 iv.ti,ab. (580718)
43 intravenous*.ti,ab. (445072)
44 40 or 42 or 43 (966997)
45 41 or 42 or 43 (1183485)
46 38 and 44 (2058)
47 39 and 45 (6315)
48 (intravenous tissue adj3 plasminogen activator*).ti,ab. (1640)
49 iv tpa.ti,ab. (2233)
50 ivtpa.ti,ab. (156)
51 ivrtpa.ti,ab. (18)
52 iv rtpa.ti,ab. (458)
53 tpa.ti,ab. (29569)
54 alteplase.ti,ab. (3718)
55 53 or 54 (32860)
56 44 and 55 (6147)
57 45 and 55 (6387)
58 *fibrinolytic agent/ (9558)
59 fibrinolytic agent/ (24953)
60 fibrinoly*.ti,ab. (38829)
61 thrombolyt*.ti,ab. (25423)

62 antithrombotic*.ti,ab. (26587)
63 anti thrombotic*.ti,ab. (3413)
64 standard treatment*.ti,ab. (46620)
65 standard therap*.ti,ab. (28371)
66 standard care.ti,ab. (14587)
67 supportive treatment*.ti,ab. (4893)
68 supportive therap*.ti,ab. (6852)
69 supportive care.ti,ab. (28303)
70 (recombinant adj3 plasminogen activator*).ti,ab. (5464)
71 44 and 70 (2448)
72 45 and 70 (2760)
73 58 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 (218256)
74 44 and 73 (24174)
75 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 (227320)
76 45 and 75 (29727)
77 37 or 46 or 48 or 49 or 50 or 51 or 52 or 56 or 71 or 74 (33732)
78 37 or 47 or 48 or 49 or 50 or 51 or 52 or 57 or 72 or 76 (40006)
79 17 and 35 and 77 (9395)
80 18 and 36 and 78 (9820)

Appendix 3.B - CASP Randomised Controlled Trials Checklist

Quality of RCTs using the CASP Randomised Controlled Trials Checklist

Trial, Author, Year	Clearly focused issues	Randomi-sation	Blinding	Similar at start	Groups treated equally	All patients accounted for at end	Size of treatment effect	Precision of treatment effect	Applied to local context	All clinically important outcomes	Benefits worth harms and costs
ESCAPE Goyal, 2015	yes	yes	yes	yes	yes	yes	Significant	See table 2	yes	yes	Yes
EXTEND 1A Campbell, 2015	yes	yes	yes	yes	yes	yes	Significant	See table 2	yes	yes	Yes
IMS III Broderick, 2013	yes	yes	yes	yes	yes	yes	Not significant	See table 2	yes	yes	Unclear
MR CLEAN Berkhemer,2015	yes	yes	yes	yes	yes	yes	Significant	See table 2	yes	yes	Yes
MR RESCUE Kidwell, 2013	yes	yes	yes	Treatment groups had fewer with congestive heart failure	yes	yes	Not significant	See table 2	yes	yes	Unclear

REVASCAT **Jovin, 2015)**	yes	yes	yes	yes	yes	yes	Significant	See table 2	yes	yes	Yes
SWIFT PRIME **Saver, 2015**	yes	yes	yes	yes	yes	yes	Significant	See table 2	yes	yes	Yes
SYNTHESIS **Ciccone, 2013**	yes	yes	yes	Treatment group had fewer with atrial fibrillation	Treatment group was not given t-PA while waiting	yes	Not significant	See table 2	yes	yes	Unclear

Appendix 3.C - Symmetrical Funnel plot.

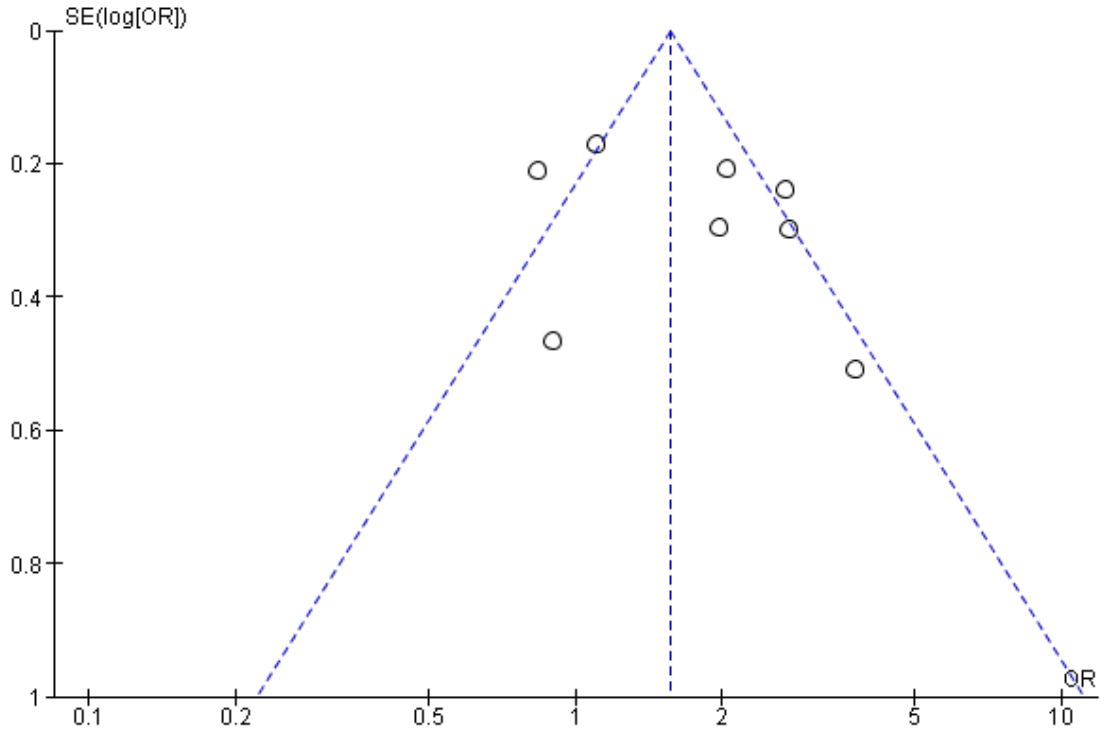


Figure 1: Funnel plot of included studies for the primary outcome (mRS 0-2) showing symmetry of studies suggestive of lack of publication bias.

Appendix 3.D - Complications of Mechanical Thrombectomy from the Randomised Controlled Trials (RCTs)

	MR CLEAN (500) **233**/267	ESCAPE (315) **165** /150	EXTEND-1A (70) **35**/35	SWIFT PRIME (196) **98**/98	REVASCAT (206) **103**/103	IMS III (656) **434**/222	MR RESCUE (118) **64**/54	SYNTHESIS (362) **181**/181
No of reported events	26/233 (11.2%)	18/165 (10.9%)	4/35 (11.4%)	5/98 (5.1%)	30/103 (29%)	70/434 (16.1%)	10/64 (15.6%)	NR
Access-site complications								
Groin haematoma / Haematoma at puncture site	NR	3 (1.8%)	1(2.9%)	NR	11 (10.7%)	NNS*	NR	NR
Groin pseudo aneurysm	NR	NR	NR	NR	1 (1%)		NR	NR
Haemorrhagic complications							NR	NR
sICH	18 (7.7%) (IV-6.4)	(3.6%)[EC] IV- 2.7)	0 (0%)[NC] (IV-6)	0 (0%) (IV 3.1)	2(1.9%)[SM] 5 (4.9%)[EC]	27 (6.7%) IV-13(5.9)	3 (4.7%)	10 (5.5%)
SAH	2 (0.9%)	1 (0.6%)	NR	4 (4. %)	5 (4.9%)	48/417 (11.5%)	NR	NR
IVH	NR	NR	NR	1 (1%)	NR	27/417 (6.5%)	NR	NR
Device-related complications	26 (11.2%)	18 (10.9%)	4 (11.4%)	5 (5%)	30 (29%)	NR70/434 (16.1%)	NR	NR
Device failure (Stent detachment/ fracture/ displacement/	NR	NR	NR	NR	NR	NR	1 (1.6%)	NR
Arterial perforation	2 (0.9%	1 (0.6%)	1 (2.9%)	1 (1%)	5 (4.9%)	NNS*	7 (10.9%)	NR
Arterial dissection	4 (1.7%)	1 (0.6%)	NR	NR	4 (3.9%)	NNS*	1 (1.6%)	NR
Vasospasm	NR	NR	NR	4 (4%)	4 (3.9%)	NR	33 (23%)	NR
Distal arterial embolisation/ new ischaemic event in a new vascular territory	20 (8.6%)	8 (4.9%)	2 (5.7%)	NR	5 (4.9%)	NNS*	1 (1.6%)	1 (0.6%)
Mortality								
Early Mortality (7 days)	27 (11.6%)	NR	NR	NR	10 (9.7%)	52 (12)	14 (6·9%)	NR
Late mortality (90days)	21%	10.4%	8.6%	9 (9.2%)	19 (18.4%)	83 (191%)	26 (13%)	NR
Mortality	18.9% (30 days)	10.4%	3 (9%)	9 (9%)	NR	NR	12%	12%
Other complications	22 (9.4%)	14 (8.5%)	NR	NR	NR	NR	NR	3 (9%)
Any serious adverse event	110 (47.2%)	NR	NR	35(36%)	NR	NR	NR	11 (34%)

NR= None reported. *NNS= Number not specified. Haemorrhagic Classification (EC= ECASS; SM= SITS-MOST; NC= NINDS criteria. aICH (asymptomatic intracerebral haemorrhage), sICH (symptomatic intracerebral haemorrhage).

Appendix 3.E - New trials from updated search

Trial, Author, Year	Trial period	Location of trial	Number of centres	Total number of patients	Type of devices	Time window to treatment
THERAPY Mocco 2016	2012–2015	USA, Germany	36	**105** (62/43)	Penumbra, Solitaire or Trevo	≤6 hours
THRACE Bracard, 2016	2010-2015	France	26	**402** (200/202)	Merci, Penumbra, Catch, Solitaire	0-5 hours
PISTE Muir 2016	2013-2015	UK	10	**65** (33/32)	Stent retriever or aspiration	≤6 hours
EASI Khoury 2017	2013 - 2014	Canada	1	**77** (40/37)	All approves devices	≤6 hours
DEFUSE 3 Albers 2018	2016-2017	USA	38	**182** (92/90)	Stent retriever, Direct aspiration	6-16 hours
DAWN Nogueira 2018	2014–2017	USA, Europe, Canada, Australia	26	**206** (107/99)	Trevo stent retriever	6-24 hours
RESILIENT Martins 2020	2017-2019	Brazil	12	**221** (111/110)	Solitaire FR (Flow Restoration) stent retriever or Penumbra aspiration system	0-8 hours

Appendix Chapter 5

Appendix 5.A - Search Strategy

Treatment Pathways: Key Term Search

The search terms relevant to the disease state, stroke (isch(a)emia, brain, cerebral, cerebrovascular accident, stroke, large artery occlusion) were combined using the Boolean operator AND, with terms reflecting the treatment, Endovascular mechanical thrombectomy (thrombectomy, mechanical thrombectomy, mechanical thrombus removal, endovascular therapy, endovascular intervention, clot retrieval, , clot disruption, clot aspiration, stent-assisted) and treatment pathways(Stroke Treatment pathways, Treatment pathways, management pathway, thrombectomy pathway, thrombolysis pathway,

Search terms:

1, Brain ischaemia/ischemia, acute ischaemic/ischemic stroke, Cerebral infarction, cerebrovascular accident, CVA

2, Mechanical thrombolysis, endovascular therapy, endovascular treatment, endovascular embolectomy, endovascular thrombectomy,intra-arterial intervention, intraarterial intervention, intra-arterial treatment, intraarterial treatment, intra-arterial therapy, intraarterial therapy, intra-arterial thrombolysis, intraarterial thrombolysis, neurothrombectomy, neuro-thrombectomy

3, Stroke Treatment pathways, management pathway, thrombectomy pathway, thrombolysis pathway

The developed search terms were first used in MEDLINE and then adjusted accordingly for other databases.

Database: Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present
Search Strategy:
---

1 exp stroke/ (133502)
2 stroke*.ti,ab. (245224)
3 brain ischemia/ (51836)
4 brain isch?emia.ti,ab. (5410)
5 cerebrovascular accident*.ti,ab. (6726)

6 large artery occlusion*.ti,ab. (252)
7 cerebrovascular disorders/ (46331)
8 exp brain infarction/ (37863)
9 exp "intracranial embolism and thrombosis"/ (21149)
10 ((brain* or cerebr* or cerebell* or cortical or vertebrobasilar or hemispher* or intracran* or intracerebral of infratentorial or supraentorial of mca or anterior circulation or posterior circulation) adj5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypox* or obstruction or vasculopathy)).tw. (117437)
11 cva*.ti,ab. (4313)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (391894)
13 mechanical thrombolys*.ti,ab. (186)
14 mechanical thrombectom*.ti,ab. (2794)
15 exp Thrombectomy/ (7446)
16 neurothrombectom*.ti,ab. (52)
17 neuro-thrombectom*.ti,ab. (2)
18 thrombectom*.ti,ab. (9842)
19 thrombolys*.ti,ab. (25002)
20 intraarterial.ti,ab. (5695)
21 intra-arterial.ti,ab. (15176)
22 (endovascular adj3 (therap* or treat* or embolectom* or thrombectom* or intervention* or procedur*)).ti,ab. (25460)
23 (intra-arterial adj3 (therap* or treat* or embolectom* or thrombectom* or intervention* or procedur*)).ti,ab. (2595)
24 (intraarterial adj3 (therap* or treat* or embolectom* or thrombectom* or intervention* or procedur*)).ti,ab. (920)
25 (clot* adj3 (retriev* or disrupt* or remov* or aspirat* or stent assisted)).ti,ab. (1621)
26 (embol* or thrombos* or clot*).ti,ab. (310135)
27 (mechanic* adj3 remov*).ti,ab. (2022)
28 26 and 27 (119)
29 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 28 (75748)
30 (intravenous* adj3 thrombolys*).ti,ab. (3173)
31 exp Tissue Plasminogen Activator/ (18625)
32 exp Administration, Intravenous/ (142697)
33 iv.ti,ab. (400413)
34 intravenous*.ti,ab. (338832)
35 32 or 33 or 34 (754507)
36 31 and 35 (4635)
37 (intravenous tissue adj3 plasminogen activator*).ti,ab. (1130)
38 iv tpa.ti,ab. (482)
39 ivtpa.ti,ab. (16)
40 ivrtpa.ti,ab. (4)
41 iv rtpa.ti,ab. (127)
42 alteplase.ti,ab. (1984)
43 33 or 34 (699238)
44 tpa.ti,ab. (22575)
45 43 and 44 (1810)
46 (recumbent adj3 plasminogen activator*).ti,ab. (0)
47 (recumbant adj3 plasminogen activator*).ti,ab. (0)
48 exp fibrinolytic agents/ (170744)
49 fibrinoly*.ti,ab. (32937)
50 thrombolyt*.ti,ab. (18220)
51 antithrombotic*.ti,ab. (17942)
52 anti thrombotic*.ti,ab. (1952)
53 standard treatment*.ti,ab. (27456)

54 standard therap*.ti,ab. (16169)
55 standard care.ti,ab. (9249)
56 supportive treatment*.ti,ab. (3066)
57 supportive therap*.ti,ab. (4513)
58 supportive care.ti,ab. (15182) stopped
59 30 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 (283655)
60 12 and 29 and 59 (8172)
61 exp guideline/ (34077)
62 Critical Pathways/ (6709)
63 Guideline*.ti,ab. (348188)
64 Guidance.ti,ab. (112212)
65 ((clinical or critical) adj3 (pathway* or path*)).ti,ab. (96218)
66 Protocol*.ti,ab. (438428)
67 61 or 62 or 63 or 64 or 65 or 66 (975178)
68 60 and 67 (980)

Appendix 5.B - Background of Included studies

Trials	Guidelines	Regional protocols	Hospital protocols	Hospital workflow following (case)	Business Case
ESCAPE Goyal, 2015	European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischemic Stroke February 2019	Safer care Victoria/ stroke clinical Network Royal Melbourne Hospital Monash Medical Centre October 2018	Mayo Hospital Goldstein 2018	Calgary Stroke Program Zerna 2016	Medtronic Australasia Protocol advisory Subcommittee (PASC) 2016
EXTEND 1A Campbell, 2015	Society of NeuroInterventional Surgery (SNIS) Mokin December 2018	The Victorian Stroke Clinical Network (VSCN) Service protocol Victoria Melbourne	Salford Royal NHS Foundation Trust Smith 2018		
MR CLEAN Berkhemer, 2015	Multisociety Consensus Quality Improvement Revised Consensus Statement Sacks November 2018	Christiana Care Health Systems Clinical Pathway 2016	Royal Melbourne Hospital Wang 2017		
REVASCAT Jovin, 2015	Korean Society of Interventional Neuroradiology and Korean Stroke Society Kim May 2018	Alberta Health Service Calgary Stroke Program 2016	Metropolitan hub-and-spoke service model Melbourne Ng 2017		
SWIFT PRIME Saver, 2015	Canadian stroke Association Guidelines Boulanger May 2018		Rhode Island Hospital McTaggart 2017		
THRACE Baccard 2016	AHA/ASA Guidelines Powers January 2018		University of Toledo Medical Center and Promedica Toledo Hospital Northwest Ohio, Lucas County Zaidi 2016		
THERAPY Mocco, 2016	Italian Neurological Society and Italian Stroke Organization Agostoni 2018				
PISTE Muir 2017	Society of Neuro-Interventional Surgery (SIN) McTaggart 2017				
EASI Khoury 2017	European Stroke Organisation - Karolinsa (ESO, ESMINT, ESNR and EAN) Wahlgren 2016				
DAWN Nogueira **2018**	Intercollegiate Stroke Working Party. White 2017/15				
DEFUSE 3 Marks 2018					
RESILIENT Nogueira 2019					

Appendix 5.C - Summary of included studies: main characteristics

Trial, Author, Year	Publication	Location	Components of Pathway covered	Inclusion criteria	Imaging	Components of pathway not covered
Clinical Trials						
ESCAPE Goyal, 2015	Trial	North America, Europe, South Korea	Acute Hospital care • Imaging • Consent • MT	Age – no limit NIHSS >5 Time < 12 hours from symptom onset ASPECTS 6	NCCT, CTA Collateral assessment on Multiphase CTA	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up
EXTEND 1A Campbell, 2015	Trial	Australia & New Zealand	Acute Hospital care	Age – ≥ 18 NIHSS No restriction Time: ≥ 6 hours from symptom onset	NCCT, CTA, CTP Mismatch	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up
MR CLEAN Berkhemer, 2015	Trial	Netherlands	Acute Hospital care	Age > 18 NIHSS score: ≥2 Time: 6 hours from symptom onset	NCCT /CTA ASPECTS	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up
REVASCAT Jovin, 2015	Trial	Spain	Acute Hospital care	Age – 18-85 NIHSS ≥6 hr Time: 8 hours from symptom onset ASPECTS 6	CTA or MRA	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up
SWIFT PRIME Saver, 2015	Trial	North America, Europe	Acute Hospital care	Age –18-80 years NIHSS > 8 and < 30 (8 -29) Time: ≥ 6 hours from symptom onset ASPECTS 6	NCCT, CTA, CTP or MRI/MRA/PWI	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up
THRACE Baccard 2016	Trial	Europe	Acute Hospital care	Age –18-80 years NIHSS ≥10 and 25 Time: ≥ 5 hours from symptom onset	CT+ CTA	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up
THERAPY Mocco, 2016	Trial	North America, Europe	Acute Hospital care	Age – 18-85 NIHSS > 7 Time ≥ 8 hours from symptom onset	CT ASPECTS	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up
PISTE **Muir 2017**	Trial	UK	Acute Hospital care	Age – ≥ 18 NIHSS > No restriction Time <5.5 hours from symptom onset	CT ASPECTS	Prehospital triage Transportation Hospital discharge Rehabilitation Follow-up
EASI Khoury 2017	Trial	Canada	Acute Hospital care	Age ≥ 18 NIHSS > 7 Time ≤6 hours from symptom onset	CT, CTA	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up
EAST	Trial	China	Acute Hospital care	Age ≥ 18 NIHSS >7 Time: ≥ 6 hours from symptom onset	CT, CTA, CTP/MR	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up
DAWN Nogueira **2018**	Trial	USA	Acute Hospital Care	Age ≥ 18 NIHSS ≥ 10 Time: 6 -24 hrs hours from symptom onset	CTP/MRP	Prehospital triage Transportation Hospital discharge Rehabilitation Follow-up
DEFUSE 3 **Marks 2018**	Trial	USA	Acute Hospital Care	Age ≥ 18 NIHSS ≥ 6 Time: 6 16 hours from symptom onset	CTP/MRP	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up
RESILIENT Nogueira 2019	Trial	Brazil		Age ≥ 18 NIHSS ≥ 8 Time: 8 hours from symptom onset	ASPECTS score of <6 on NCCT, or <5 on DWI MRI	Prehospital triage Transportation Hospital discharge Rehabilitation, Follow-up

Trial, Author, Year	Publication type	Location	Components of Pathway covered	Inclusion Criteria	Imaging	Components of pathway not covered
International and National Stroke guidelines/ consensus statements						
European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT Turc February 2019	Guidelines on Mechanical Thrombectomy	Europe	Patient selection Imaging Prehospital organisation model	Age – ≥18 NIHSS ≥5 Time: 6-24 hours from symptom onset Pre-stroke mRS 0-1 ASPECTS ≥ 6 Infarct Volume		Prehospital notification Transportation Arrival at ED Acute Hospital Care Post MT care Hospital discharge Rehabilitation Follow-up
Society of NeuroInterventional Surgery (SNIS) Mokin December 2018	Standard and Guidelines for thrombectomy	USA, Canada	Selection criteria • Imaging • Location of large vessel occlusion ➢ ICA and M1/M2	Age – ≥18 NIHSS ≥6 Time: 6-24 hours from symptom onset Pre-stroke mRS 0-1 ASPECTS ≥ 6	CTA, CTP, MRI DWI-PWI	Prehospital notification Transportation Arrival at ED Acute Hospital Care Post MT care Hospital discharge Rehabilitation Follow-up
Multisociety Consensus Quality Improvement Revised Consensus Statement Sacks November 2018	Consensus statement For Endovascular Therapy	USA Canada Europe, Australia	Patient selection Imaging Process of care Time process • Door to imaging • Imaging to puncture • Imaging -to – thrombus time • Puncture time to reperfusion Assessment of recanalisation/reperfusion • mTICI should be primary scale for assessment of angio reperfusion Post-MT imaging Complication/risk of thrombectomy • Symptomatic ICH • SAH • Embolisation of New Territory • Review of deaths within 72 hours Clinical outcomes • Document NIHSS score 20-36hrs post MT • Follow-up mRS score at 90 days Quality improvement • On-going quality improvement • Peer Review team			Prehospital notification Transportation Arrival at ED Type of anaesthesia Post MT care Hospital discharge Rehabilitation Follow-up
Korean Society of Interventional Neuroradiology and Korean Stroke Society Kim May 2018	Consensus Statement (Workflow recommendation for CSC)	Republic of Korea	Prehospital notification/Care Arrival at Emergency Department Acute Hospital Care • Imaging • IVT if indicated • Notification neurointervetion team • Preparation of angio suite ➢ Prepacked MT kit • Obtaining informed consent • Type of anaesthesia • Post MT Care • Transfer to ICU or Stroke Unit Continuous quality improvement • Time metrics • Feedback • Education		CT, CTA	Discharge Rehabilitation Follow-up

Trial, Author, Year	Publication type	Location	Components of Pathway covered	Inclusion Criteria	Imaging	Components of pathway not covered
International and National Stroke guidelines/ consensus statements						
Canadian stroke Association Guidelines Boulanger May 2018	Best practice recommendations for Acute Stroke Management	Canada	Prehospital notification/Care Transportation Arrival at Emergency Department Acute Hospital Care • Imaging • IVT • MT Type of sedation	Age ≥18 NIHSS Time:6 -24 hours from symptom onset Pre-stroke mRS 0-2 ASPECTS ≥ 6	CT, CTA	Post-op care Discharge Rehabilitation Follow-up
AHA/ASA Guidelines Powers January 2018	Guidelines	USA	Prehospital notification/Care Transfer protocol for Primary centres Arrival at Emergency Department Hospital Care • Imaging • IVT • MT	Age – ≥18 NIHSS ≥6 Time :6 -24 hours from symptom onset Pre-stroke mRS 0-2 ASPECTS ≥ 6	NCCT, CTA, CTP, DW-MRI or MRI Perfusion	Post-op care Follow-up
Italian Neurological Society and Italian Stroke Organization Agostoni 2018	Acute Ischaemic Stroke Management (PSC and CSC)	Italy	Prehospital pathway • Pre-hospital notification/care • Transportation In-hospital pathway	NIHSS ≥7	CT, CTA, CTP, DWI/PWI MRI	
Society of Neuro-Interventional Surgery (SIN) McTaggart 2017	Standards and guidelines (Workflow recommendations for both PC and CSC)	USA Canada	Prehospital notification/care Transportation • Direct transfer to CSC depending on prehospital scoring Acute Hospital Care • Imaging • IVT If indicated • Activation of neuro-intervention team • Informed consent • Preparation/arrival at angio suite ➢ Prepacked MT kit • Type of anaesthesia • Process times (onset through to recanalisation		NCCT, CTA, CTP/MRI	Post MT Care Discharge Rehabilitation Follow-up
European Stroke Organisation - Karolinsa (ESO, ESMINT, ESNR and EAN) Wahlgren 2016	Consensus statement	Europe	Patient selection	Age – ≥18 NIHSS ≥6 Time :6 hours from symptom onset Pre-stroke mRS xx ASPECTS score		Acute Hospital care Post MT Care Discharge Rehabilitation Follow-up
Intercollegiate Stroke Working Party. **White 2017/15**	Standards for providing safe MT Services (Primary Hospital and MT Centre	United Kingdom	Pre-hospital notification/Care Transportation Inter-Hospital Transfer Hospital Care Process of Care • Patient selection • Door to imaging • Type of Anaesthesia ➢ Pre-assessment ➢ Anaesthetic management ➢ Airway management Outcome measures • Revascularisation • Rankin at 90 days • SICH • Death within 72 hours Post-op care Audit	Age – ≥18 NIHSS ≥6 Time :6 hours from symptom onset (12-24 for POCS) Pre-stroke mRS 0-2	NCCT, CTA, MRI/MRA	Hospital discharge Rehabilitation Follow-up

Title, Author, Year	Publication type	Location	Stroke Pathway covered	Inclusion criteria	Imaging	Components of pathway not covered
Regional Clinical Pathways/Protocols, Workflows in Clinical Settings						
Safer care Victoria/ stroke clinical Network Royal Melbourne Hospital Monash Medical Centre October 2018	Statewide service protocol for Victoria (for assessment and referral to MT Centre)	Australia	Pre-Hospital notification/ Care Transportation to primary hospital Inter-hospital transfer to MT centre Hospital Care Post-procedure care Repatriation Discharge	Age – ≥18 NIHSS Time :6 -24 hours from symptom onset Pre-stroke mRS 0-2	CT, CTA, CTP	Rehabilitation Follow-up
Medtronic Australasia Protocol advisory Subcommittee (PASC) 2016	Protocol (local and transferred patients MS)	Australia	Pre-Hospital notification/Care Ambulance transportation Arrival at ED Hospital Care Repatriation/Discharge	Age – no limit NIHSS xx Time 6 hours from symptom onset -	CT+ CTA	Rehabilitation Follow-up
The Victorian Stroke Clinical Network (VSCN) Service protocol Victoria Melbourne 2016	Endovascular clot retrieval for acute stroke State-wide service protocol for Victoria Referral to CSC		Pre-hospital notification/ care Arrival at PSC Hospital • Imaging • IVT • Referral to CSC Transportation to CSC • Repeat imaging if indicated • MT Post-op care 24h hour post-op repeat imaging Repatriation Hospital-Discharge	Age – XX NIHSS > XX Time: 6 hours from symptom onset Pre-stroke mRS 0-2		Rehabilitation Follow-up
Mayo Hospital Goldstein 2018	Hospital clinical pathway (ED arrivals and hospital transfers	USA	Arrival at PSC • Imaging • Referral to CSC • Transfer to CSC Arrival at ED Hospital care • Imaging • IVT Pre-intervention pathway • Order interventional procedure • Procedure suite preparation • MT Post MT care • ICU stay- • hospital stay- Hospital discharge	NIHSS ≥ 6 Time :12 hours from symptom onset ASPECTS ≥ 6	CT/CTA/CTP	Pre-hospital notification Type of anaesthesia Rehabilitation Follow-up
Salford Royal NHS Foundation Trust Smith 2018	Hospital clinical pathway (local protocol)	United Kingdom	Arrival at hospital Hospital care • Imaging • IVT • Transfer to angiography suite • MT Post MT care • ICU	Age – ≥18 NIHSS > 6 Time :6 hours from symptom onset Pre-stroke mRS 0-2 ASPECTS ≥ 7	CT/CTA ± MR DWI	Pre-hospital notification Hospital discharge Rehabilitation Follow-up

Title, Author, Year	Publication type	Location	Stroke Pathway covered	Inclusion criteria	Imaging/	Components of pathway not covered
Regional Clinical Pathways/Protocols, Workflows in Clinical Settings						
Royal Melbourne Hospital Wang 2017	Workflow for MT (work-flow at MT Centre for both transferred and local patients)	Australia	Pre-hospital Notification Arrival at ED Hospital Care • Imaging • Initiation of IVT in CT room • Notification of interventional team and anaesthetist • Transfer to angiography suite • Anaesthesia	--	CT, CTA, CTP	Post-op care Hospital discharge Rehabilitation Follow-up
Metropolitan hub-and-spoke service model Melbourne Ng 2017	Hospital Clinical Pathway Inter-hospital transfer workflow	Australia	Prehospital Notification • Transport Arrival at PSC • Imaging • Retrieval Request to Ambulance arrival • Transport to CSC Arrival at CSC • Door-to-arterial -puncture • Arterial puncture to reperfusion Overall treatment workflow			Post-op care Rehabilitation Hospital discharge
Rhode Island Hospital McTaggart 2017	Hospital clinical pathway for transfer of patients to CSC from PSC- DS)	USA	Pre-hospital Triage (LAMS ≥) • Arrival at PSC • Imaging • Transfer of images to CSC • Transfer to CSC Ambulance transportation Arrival at CSC Hospital Care • Imaging if indicated • Activation of Neurointerventional team • Transfer to Angiography suite • MT	Age ≥18 NIHSS ≥ 6 Time :6 hours from symptom onset Pre-stroke mRS 0-1 ASPECTS ≥ 6	CT, CTA	Post MT Care Discharge Rehabilitation Follow-up
Christiana Care Health Systems Clinical Pathway 2016	Hospital clinical pathway	USA	Pre-hospital notification/ care Ambulance transportation Arrival at ED Hospital Care • Imaging • Initiation of IVT • Provision of MT • post-op care • on-going investigations Hospital-Discharge Post Discharge Care Follow-up	Age ≥18 NIHSS ≥ 6 Time :6 hours from symptom onset Pre-stroke mRS 0-1 ASPECTS ≥ 6	CT, CTA/MRA	Type of anaesthesia Rehabilitation
Alberta Health Service Calgary Stroke Program 2016	Care Pathway (Primary and comprehensive stroke centre)	Canada	Pre-hospital notification/Communication Transportation Arrival at ED Hospital Care Hospital-Discharge Post Discharge Care	LAMBS score ≥ 4	CT, Multiphase CTA	Type of anaesthesia Rehabilitation Follow-up

Title, Author, Year	Publication type	Location	Stroke Pathway covered	Inclusion criteria	Imaging/	Components of pathway not covered
Regional Clinical Pathways/Protocols, Workflows in Clinical Settings						
Calgary Stroke Program Zerna 2016	Hospital workflow in AIS Following a case to finish at a CSC	Canada	Pre-hospital scene • EMS arrival at patient's home • Prehospital notification Arrival at hospital • Imaging • Initiation of IVT in CT • Consent • Transfer to angiography suite • Prepacked stroke kit • Sedation • MT • Transfer to Neurology critical care In-hospital follow-up (24 hour post-up) Post-up Imaging Hospital discharge Home Follow-up at 90 days			Pathway for PSC Rehabilitation
University of Toledo Medical centre and Premedical Toledo Hospital Northwest Ohio, Lucas County Zaidi 2016	Hospital clinical pathway (Transfer to Primary or comprehensive stroke centre)	USA	Pre-hospital notification • Notification to Stroke team, ER, Vascular and interventional neurologist, Radiology Dept, ICU Ambulance transportation Arrival at ED Hospital Care • Imaging • IVT • MT Discharge Post Discharge Care Rehabilitation		CTA, CTA	Follow-up

Appendix Chapter 6

Appendix 6.A - Staff time, unit cost and sources of information for all centres

Category of staff	Unit cost (£)	References	Unit (hours)	References	Total cost (£)
Consultant Anaesthetist	157	PSSRU	3.00	Current practice and Expert opinion	471
Anaesthetist assistant	58	PSSRU	3.00	Current practice and Expert opinion	174
Radiographer	58	PSSRU	2.00	Current practice and Expert opinion	116
Consultant INR	140	PSSRU	3.00	Lobotesis 2016	420
Registrar	60	PSSRU	3.00	Lobotesis 2016	180
Nurse (band 7)	58	PSSRU	3.00	Lobotesis 2016	174
Scrub Nurse Band 5	49	PSSRU	3.00	Lobotesis 2016	147
Scrub Nurse Band 7	58	PSSRU	3.00	Lobotesis 2016	174
General Anaesthesia	3.79/minx60	PSSRU	1.00	Current practice and Expert opinion	227.4
Conscious sedation	2.79/minx60	PSSRU	1.00	Current practice and Expert opinion	167.4
Local Anaesthesia	27.06	PSSRU	1.00	Current practice and Expert opinion	27.06
Stroke Consultant	140	PSSRU	3.00	Current practice and Expert opinion	420
Stroke SpR	60	PSSRU	3.00	Current practice and Expert opinion	180
Stroke Nurse	58	PSSRU	3.00	Lobotesis 2016	174
Recovery Area	1.51/min x60 min	PSSRU	1.00	Current practice and Expert opinion	90.2
Recovery Nurse Band 5	49	PSSRU	1.00	Current practice and Expert opinion	58
Anaesthetist assistant	58	PSSRU	1.00	Current practice and Expert opinion	58

Appendix 6.B - Resources used along the treatment pathways at Centre A

Resources- (Centre A)	Mechanical thrombectomy	Intravenous thrombolysis
Pre-hospital Notification	Paramedics are usually called out via 999 emergency call to the location of symptom onset	**All local patients**
Transport Mode: • Ambulance • Others Staff: Two Paramedics	Land ambulances transported all patients both the local and referred patients from other hospitals to **Centre A.** **Centre A.**	All patients were local, none transported from other hospitals for IVT.
Arrival at Emergency Department (ED) Venue: • Resuscitation bay or majors bay Staff: • Stroke Nurse (Band 6) • Stroke Consultant	ED was the first point of entry for all patients joining the treatment pathways, except for inpatient stroke cases. The resources used were the same for all patients admitted to ED. The Stroke Team was pre-alerted about any potential thrombolysis patient by the ambulance team before arrival at ED. Patients transferred from other hospitals were first discussed with the Centre Stroke Consultant and CT/CTA images linked via a picture archiving and communication system (PACS) to Centre A. The referred patient came via ED to be registered before taken to the Radiology Department. The Stroke Team received the patient in ED, who was then taken to Radiology.	The Stroke Team was pre-alerted about any potential thrombolysis patients by the Ambulance Team before arrival at ED. Intravenous thrombolysis was provided 24 hours.
Diagnostic imaging (Radiology) Imaging: • CT head scan • CT angiogram (CTA) • CT perfusion (CTP) Staff: • Radiographer (Band 7) • Radiology SpR • Radiology Consultant	All patients had a CT and CTA and those with unknown time of onset got an additional CT perfusion scan. Images were reported initially by the Radiology SpR and later by the Consultant Radiologist for patients having IVT only. The Consultant Radiologist reviewed all scans for patients undergoing MT before the procedure.	All patients had a CT and CTA and those with unknown time of onset had an additional CTP scan. Images were reported initially by the Radiology SpR and later by the Consultant Radiologist for patients having IVT only. Not all scans were reported by a Consultant Radiologist before commencement of intravenous thrombolysis.
Treatment Phase **Intravenous thrombolysis** Drug: • Alteplase Equipment: • IV tubing • IV pump • others Staff: • Stroke Nurse (Band 6) • Stroke Consultant •		Intravenous thrombolysis was provided to all eligible patients before MT and patients referred from other hospitals were thrombolysed if eligible before being transferred to Centre A for MT. The Stroke Consultant authorised all thrombolysis either within or out of hours and the Stroke Nurse administered IVT in ED.

Resources- (Centre A)	Mechanical thrombectomy	Intravenous thrombolysis
Mechanical Thrombectomy Venue: • Interventional Radiology Suite (with biplane angio) Staff Anaesthetic team: • Consultant Anaesthetist • Operational Dependent Practitioner or Assistant (ODP/ODA) Band 6 Interventional team: • Interventional Radiologist (1) Radiographer: • Radiographer band 6 (2) Scrub Nurse: • Scrub Nurses (2) band 5 and 6 Stroke Team: • Stroke Consultant Pre-op: Anaesthesia • GA • LA • CS **Thrombectomy Devices/**** Stent retriever Aspiration Catheter **Thrombectomy ancillary** Micro-catheters Guide wires Others **Carotid Stenting** **Miscellaneous material** Drapes, syringes Others	All thrombectomy procedures were performed in the Interventional Radiology suite (IRS), using existing infrastructure. The intervention was provided 24/7. Within working hours (9 am to 8pm) the Interventional Team consisted of more staff (two radiographers and two scrub nurses while out of hours (between 8 pm and 9 am) the Interventional Team consisted of one scrub nurse and one radiographer. Thrombectomy was performed under GA for 65% of patients, LA in 26% and CS in 9% of patients. Different devices were used depending on the location of the occlusion and presence or absence of carotid occlusion Additional costs for patients with carotid stenosis.	

Resources- (Centre A)	Mechanical thrombectomy	Intravenous thrombolysis
Post-thrombectomy Venue: • Recovery Area Staff: • Nurse (Band 5) • Anaesthetist • Stroke Consultant	Post -thrombectomy, patients were transferred to the Recovery Area outside the IRS where they were monitored for about one hour. Once awakened, especially those who had MT under GA, they were moved to the Stroke Unit. Patients who were unstable are transferred to ICU/HDU. While in recovery they were monitored by the Recovery Nurse, reviewed by the Consultant Anaesthetist and Stroke Consultant before they are being transferred to the Stroke Unit.	
ICU/HDU • ICU/HDU bed Staff: • ICU Consultant • ICU Nurse • ICU SpR	Post-thrombectomy: All unstable patients were transferred directly to ICU/HDU. The rest were moved to the Recovery Area.	
Transfer to the Stroke Unit Venue: • Hyperacute Stroke ward Staff: • Stroke team Investigations: • Repeat CT • MRI	All patients went to the Stroke Unit either from Recovery Area or ICU/HDU. All patients had a 24-hour CT head scan, while a small proportion had an MRI head scan. Additional routine blood tests were performed at need.	Patients treated with Intravenous thrombolysis alone were transferred from ED directly to the Stroke Unit. All patients had a 24-hour CT scan. For some patients, additional routine bloods tests were performed.
Discharge Transport Repatriation • Ambulance Home with or without ESD • Non-emergency transport Transfer to a community hospital • Non-emergency transport Transfer to a care home • Non- emergency transport	Patients referred from other hospitals were repatriated to their primary hospital using land ambulance. Other discharges made were via non-urgent transfer with other forms of transportation, such as hospital taxis, private family cars.	Other discharges made via non-urgent transfer with other forms of transportation, such as hospital taxis, private family cars.

Appendix 6.C - Unit costs for resource use in each phase in the treatment pathway at Centre A

Item(s) - Centre A	Unit Cost (£)	unit	References
Pre-hospital Notification **999 telephone call** **Referral from non-MT centre** consultant-to-consultant referral	7 per call 6 per call	1 1	Regional Service NHS Foundation Trust Centre A switch board
Transport^	204.77	1	West Midlands Ambulance Service NHS Foundation Trust
ED attendance^ Time in ED (Centre A) Time in ED (referring Hospitals) Staff Stroke Consultant Stroke Nurse	 322 299 140 per hour 58 per hour	1 1 1 1 	 NHS reference Costs 2018/2019- code VB01Z NHS reference Costs 2018/2019- code VB02Z Personal Social Services Unit (PSSRU) Personal Social Services Unit (PSSRU)
Imaging ^			
Non-Contrast CT Brain	71.60	1	NHS reference Costs 2018/2019- code RD20A.
CT angiogram (CTA)	85	1	NHS reference Costs 2018/2019- code RD21A.
CT Perfusion (CTP) Staff Radiographer (Band 7) Radiology SpR /Fellow review	133 1 1	1	NHS reference Costs 2016/2017-code RN20Z (Based on Myocardial Perfusion scan). PSSRU PSSRU
Transfer of images from referring hospital PACS	 0.6	 1	 Expert opinion (estimate from radiographer)
Treatment			
Intravenous thrombolysis Alteplase Tariff for IVT	 578 1,671	 1 1	 British National Formulary (BNF) NHS reference Costs- 2018/19 AA23E
Mechanical thrombectomy			
Venue (IRS)	£6.75/min	2	Centre A Trust Finance Department/Expert opinion
Anaesthesia General anaesthesia (GA) Conscious sedation (CS) Local anaesthesia (LA)	 3.79/min 2.79/min 27.06	 1 1 1	 Centre A NHS Trust Finance Department, Expert Opinion

Item(s) - Centre A	Unit Cost (£)		References
Thrombectomy Devices/**			
Stent retriever	3200	1	
Solitaire platinum	2500	1	
Solitaire -2 027in 6mmX20mm	2300	1	
Trevo XP ProVue			
Aspiration Catheter	595	1	
Catheter Distal Access Sofia	250	1	
Traxcess EX 14			Centre A NHS Trust Finance Department
Thrombectomy ancillary		1	
Microcatheters	395	1	
Headway micro delivery catheter	395	1	
Microcatheter straight shapeable	295		
Catheter micro delivery REBAR			
Guide wires		1	
Guidewire Docking TRAXCESS 014in 115 cm	150	1	
Guidewire Micro TRAXCESS 14 014in X200 cm		1	
Guidewire Support Hydrophilic TRAXCESS 14EX STR 014in 200cm			
Others		1	
SHEATH crosscut valve RHV Neuro MAX-088	250	1	
Balloon PTA Dilation Submarine RAPIDO	95	1	
Angio-seal Vascular closure	90		
Carotid Stenting		1	
Stent Carotid CASPER RX 5F 8mm 143cn	800	1	
Stent Carotid CASPER RX 7mmX30mm 154cm	700		
		1	
Miscellaneous material	200		
Drapes, syringes, others			
Staff			Personal Social Services Unit (PSSRU)
Consultant Anaesthetist	167/hr	3*	Lobestosis
Anaesthetist assistant	58/hr	3	
Radiographer	58/hr	2	
Consultant INR	140/hr	3	
Scrub nurse (Band 7)	58/hr	2	
Scrub nurse (Band 6)	58/hr	2	
Stroke Consultant	140/hr	3	

Item(s) - Centre A	Unit Cost (£)		References
Anaesthesia GA CS LA	 3.79/min 2.79/min 27.06	 1 1 1	Centre A: NHS Trust Finance Department
ICU/HDU	1420/day	1	Centre A: NHS Trust Finance Department
Stroke Unit^	480 (first 48hr) 300/day post 48 hrs	1 1	Centre A NHS Trust Finance Department
24-hour post treatment scan^ CT head MRI	 71:60 114	 1 1	 NHS reference costs 2018/2019 NHS reference costs 2018/2019
Discharge			
Transport: Repatriation without paramedic escort Repatriation with paramedic escort	 115 140	 1 1	 Centre A: NHS Trust Finance Department

Appendix 6.D Resources used along the treatment pathways at other MT centres

Appendix 6.D (1) - Resources used along the treatment pathways at Centre B

Resources- (Centre B)	MT	IVT
Pre-hospital Notification	Paramedics are usually called out via 999 emergency call to the location of symptom onset	Local patients
Transport • Ambulance • Others Staff: Two Paramedics: Band 5 and 3 • Escort for transferred patients (Junior Doctor or Band 6 Nurse)	Land ambulances transported all patients both the local and referred patients from other hospitals to Centre B. The referred patients were escorted by either a junior Doctor or Nurse.	All patients were local, none transported from other hospitals for IVT.
Arrival at ED Venue: • Resuscitation bay or majors bay Staff: • Stroke Nurse (Band 6) • Stroke SHO (FY2/CT1-2) • Stroke SpR • Stroke Consultant/Neurology	ED was the first point of entry for all patients joining the treatment pathways, except for inpatient stroke cases. The resources used were the same for all patients admitted to ED. The Stroke Team was pre-alerted about any potential thrombolysis patient by the ambulance team before arrival at ED. Patients transferred from other hospitals were first discussed with Centre B Stroke Consultant and CT images linked via a picture archiving and communication system (PACS) to Centre B. The referred patients bypassed ED and taken directly to the Radiology Department. The Stroke Team received the patient with the escort in Radiology Thrombectomy was only provided between 8 am and 8 pm with ad-hoc service out of hours and at weekends.	The Stroke Team was pre-alerted about any potential thrombolysis patients by the Ambulance Team before arrival at ED. Intravenous thrombolysis was provided 24 hours.
Diagnostic imaging (Radiology) • CT head scan • CT angiogram (CTA) • CT perfusion (CTP) Staff: • Radiographer • Radiology SpR • Radiology Consultant	All patients had a CT and CTA and those with unknown time of onset got an additional CT perfusion scan. Images were reported initially by the Radiology SpR and later by the Consultant Radiologist for patients having IVT only. The Consultant Radiologist reviewed all scans for patients undergoing MT before the procedure.	All patients had a CT and CTA and those with unknown time of onset had an additional CTP scan. Images were reported initially by the Radiology SpR and later by the Consultant Radiologist for patients having IVT only. Not all scans were reported by a Consultant Radiologist before commencement of intravenous thrombolysis.
Treatment Phase **Intravenous thrombolysis** Drug: • Alteplase Equipment: • IV tubing • IV pump Staff: • Stroke Nurse (Band 6) • Stroke Consultant/Neurologist • Stroke SpR • Core trainee doctor (CMT)		Intravenous thrombolysis was provided to all eligible patients before MT and patients referred from other hospitals were thrombolysed if eligible before being transferred to Centre B for MT. The Stroke Consultant authorised all thrombolysis either within or out of hours and the Stroke Nurse administered IVT in ED.

Resources -(Centre B)	MT	IVT
Mechanical Thrombectomy Venue: • Interventional Radiology suite (with biplane angio) Staff Anaesthetic team: • Consultant Anaesthetist • Anaesthetic Nurse Practitioner (ANP)/Scrub Nurse (SN)Band 6 Interventional team: • Interventional Radiologist (1) Radiographer: • Radiographer band 6 (1) Scrub Nurse: • Anaesthetic Nurse Practitioner (ANP)/Scrub Nurse (SN)Band 6 • Scrub Nurses band 6 Stroke Team: • Stroke Consultant/Neurologist • Stroke SpR/SHO • Stroke Nurse Pre-op: • GA • LA • CS **Thrombectomy Devices/**** Stent retriever Aspiration Catheter **Thrombectomy ancillary** Micro-catheters Guide wires Others **Carotid Stenting** **Miscellaneous material** Drapes, syringes Others	All thrombectomy procedures were performed in the Interventional Radiology Suite (IRS), using existing infrastructure. A Practitioner (ANP)/Scrub Nurse was used instead of Practitioner or Assistant (ODP/ODA) and an Anaesthetist was usually not present during MT. The intervention was provided between 8 am to 5 pm. Out of hours (between 8 pm and 9 am) the Interventional team consisted of one scrub nurse and one radiographer. Thrombectomy was performed under GA for 16% of patients, LA in 80% and CS in 4% of patients. Stent-retrievers were the primary device used depending on the location of occlusion and presence or absence of carotid occlusion.	

Resources (Centre B)	MT	IVT
Post-thrombectomy Venue: • Direct to HASU Staff: • Nurse (Band 5 and 6) • Anaesthetist • Stroke Consultant/Neurologist	Post-thrombectomy, patients were transferred from the IRS to the Stroke Unit except for cases performed under GA or if unstable. Patients who were unstable were transferred to ICU/HDU.	
ICU/HDU Venue: • ICU/HDU bed Staff: • ICU Consultant • ICU Nurse • ICU SpR	Post-thrombectomy: All unstable patients were transferred directly to ICU/HDU.	
Transfer to the Stroke Unit • Hyperacute Stroke ward Staff: • Stroke team Investigations: • Repeat CT • MRI • Blood test Others	All patients went to the Stroke Unit, most of them directly from the IRS. All patients had a 24-hour CT head scan. Some additional routine bloods tests were performed.	Patients treated with Intravenous thrombolysis alone were transferred from ED directly to the Stroke Unit. All patients had a 24-hour CT scan. For some patients, additional routine bloods tests were performed.
Discharge Transport Repatriation • Ambulance Home with or without ESD • Non-emergency transport Transfer to a Care Home Non- emergency transport	Patients referred from other hospitals were repatriated to their primary hospital using land ambulance. Other discharges made via non-urgent transfer with other forms of transportation, such as hospital taxis, private family cars.	Other discharges made via non-urgent transfer with other forms of transportation, such as hospital taxis, private family cars.
Follow-up Venue: • Outpatient Clinic Staff • Stroke Consultant • Clerical staff • Nurse	Patients who underwent MT were followed-up at six weeks post-MT.	All thrombolysed patients were followed up.

The additional resource use at Centre B included Medical escort either a Nurse or Junior Doctors for the transferred patients and the additional CTP performed on around 60% of patients.

Appendix 6.D (2) - Resources used along the treatment pathways at MT Centre C

Resources (Centre C)	MT	IVT
Transport Mode: • Ambulance • Helicopter • Others Staff: • Two Paramedics	Land ambulances transported most patients both the local and referred patients from other hospitals to Centre C. Helicopter transported only two patients.	All patients were local, none transported from other hospitals for IVT.
Arrival at Emergency Department (ED) Venue: • Resuscitation bay or majors bay Staff: • Stroke Nurse (Band 6) • Stroke SHO (FY2/CT1-2) • Stroke SpR • Stroke Consultant	ED was the first point of entry for all local patients joining the treatment pathways, except for inpatient stroke cases. The resources used were the same for all patients admitted to ED. The Stroke Team was pre-alerted about any potential thrombolysis patient by the Ambulance Team before arrival at ED. Patients transferred from other hospitals were first discussed with Centre C Stroke Consultant and CT/CTA images linked via the Central Radiological Image Sharing (CRIS) platform not Picture Archiving and Communication System (PACS) to Centre C. The referred patients bypassed ED and taken directly to the Radiology Department. The Stroke Team received the patient with the escort in Radiology.	The Stroke Team was pre-alerted about any potential thrombolysis patients by the Ambulance Team before arrival at ED. Intravenous thrombolysis was provided 24 hours.
Diagnostic imaging (Radiology) • CT head scan • CT angiogram (CTA) • CT perfusion (CTP) Staff: • Radiographer • Radiology SpR • Radiology Consultant	All patients had a CT and CTA and those with unknown time of onset got an additional CT perfusion scan. Images were reported initially by the Radiology SpR and later by the Consultant Radiologist for patients having IVT only. The Consultant Radiologist reviewed all scans for patients undergoing MT before the procedure. Greater than 80% of referred patient do not get a repeat scan.	All patients had a CT and CTA and those with unknown time of onset had an additional CTP scan. Images were reported initially by the Radiology SpR and later by the Consultant Radiologist for patients having IVT only. Not all scans were reported by a Consultant Radiologist before commencement of intravenous thrombolysis.
Treatment Phase **Intravenous thrombolysis** • Alteplase Equipment: • IV tubing • IV pump Staff: • Stroke Nurse (Band 6) • Stroke SpR • Stroke Consultant Other Medications: • GTN • Labetalol		Intravenous thrombolysis was provided to all eligible patients before MT and patients referred from other hospitals were thrombolysed if eligible before being transferred to Centre C for MT. The Stroke Consultant authorised all thrombolysis either within or out of hours and the Stroke Nurse administered IVT in ED.

Resources (Centre C)	MT	IVT
Mechanical Thrombectomy Venue: • Neuro-interventional Radiology suite (with biplane angio) Staff Anaesthetic team: • Consultant Anaesthetist • Operational Dependent Practitioner or Assistant (ODP/ODA) Band 6 • Anaesthetic SpR Interventional team: • Interventional Radiologist (1) • Radiology SpR Radiographer: • Radiographers (2) One Band 6 and one Band 7 or two Band 6 Scrub Nurse: • Scrub Nurses (2) Band 5 and 6 Stroke Team: • Stroke Consultant • Stroke Nurse • Stroke SpR Pre-op: • GA • LA • CS **Thrombectomy Devices*** Stent retriever Aspiration Catheter **Thrombectomy ancillary** Micro-catheters Guide wires Others **Carotid Stenting**	All thrombectomy procedures were performed in the Neuro-interventional Radiology suite (NIRS), using existing infrastructure. The intervention was provided between 8 am to 5 pm. Out of hours (between 8 pm and 9 am) the Interventional team consisted of one scrub nurse and one radiographer. Thrombectomy was performed under GA for 31% of patients, LA in 32% and CS in 37%of patients. Thromboaspirators were the primary device used depending on the location of occlusion and presence or absence of carotid occlusion.	

Miscellaneous material Drapes, syringes Others		
Resources (Centre C)	**MT**	**IVT**
Post-thrombectomy Venue: Recovery Area Staff: • Nurse (Band 5) • Anaesthetist • Stroke Consultant	Post -thrombectomy, patients were moved to the CT room for a repeat scan before being transferred to the SU. Patient who had MT under GA are moved to Recovery Area outside the IRS where they were monitored by the OPD. Once awakened, they were moved to the SU. Patients who were unstable were transferred to ICU/HDU.	
Post-thrombectomy Scan • CT head scan Staff: • Radiographer • Radiology Consultant • Stroke Consultant		
Post-thrombectomy Scan • CT head scan Staff: • Radiographer • Radiology Consultant • Stroke Consultant		
ICU/HDU • Staff: ICU Consultant • ICU Nurse • ICU SpR	Post-thrombectomy: All unstable patients were transferred directly to ICU/HDU. The rest were moved to the Recovery Area.	
Transfer to the Stroke Unit Staff: • Stroke team Investigations: • Repeat CT • MRI	All patients went to the Stroke Unit, most of them directly from the NIRS. All patients had a 24-hour CT head scan. Some additional routine bloods tests were performed.	Patients treated with Intravenous thrombolysis alone were transferred from ED directly to the Stroke Unit. All patients had a 24-hour CT scan. For some patients, additional routine bloods tests were performed
Discharge Transport Repatriation • Ambulance Home with or without ESD • Non-emergency transport Transfer to a community hospital • Non-emergency transport Transfer to a care home Non- emergency transport	Patients referred from other hospitals were repatriated to their primary hospital using land ambulance. Other discharges made via non-urgent transfer with other forms of transportation, such as hospital taxis, private family cars.	Other discharges made via non-urgent transfer with other forms of transportation, such as hospital taxis, private family cars.

Follow-up Venue: Outpatient Clinic Staff: Stroke Consultant Clerical staff, Nurse	All local patients who underwent MT were followed-up at six weeks post-MT.	All thrombolysed patients were followed-up.

Appendix 6.D (3) - Resources used along the treatment pathways at MT Centre D

Resources (Centre D)	MT	IVT
Transport Mode: • Ambulance • Others Staff: • Two Paramedics: Band 5 and 3	Land ambulance transported all patients both the local and referred patients from other hospitals to the Centre D. Patients referred to the Centre D are not escorted by either a junior Doctor or Nurse.	All patients were local, none transported from other hospitals for IVT.
Arrival at hospital Venue: • Stroke Unit • ED Staff: • Stroke Nurse (Band 6) • Stroke Consultant • Stroke SpR	The Stroke Unit was the first point of entry for all patients joining the treatment pathways, between 9 am and 9 pm, unlike the ED in other hospitals. The exceptions were patients already in ED and inpatient stroke cases. The resources used were the same for all patients admitted to ED. The Stroke Team were pre-alerted about any potential thrombolysis or thrombectomy patient by the Ambulance Team before arrival at the Stroke Unit. Patients transferred from other hospitals were first discussed with the **Centre D** –Stroke Consultant and CT Images linked via a picture archiving and communication system (PACS) to **Centre D.**	The Stroke Team were pre-alerted about any potential thrombolysis patients by the Ambulance Team before arrival at the Stroke Unit
Diagnostic imaging (Radiology) • CT head scan • CT angiogram (CTA) • CT perfusion (CTP) Staff: • Radiographer • Radiology SpR • Radiology Consultant	All patients had a CT and CTA and those with unknown time of onset had an additional CT perfusion scan. Images were reported initially by the Radiology SpR and later by the Consultant Radiologist for patients treated with IVT only. The consultant Radiologist reviewed all scans for patients undergoing MT before the procedure.	All patients had a CT and CTA and those with unknown time of onset had an additional CTP scan. Images were reported initially by the Radiology SpR and later by the Consultant Radiologist for patients having IVT only. Not all scans were reported by a Consultant Radiologist before commencement of intravenous thrombolysis.
Treatment Phase **Intravenous thrombolysis** Drug: • Alteplase Equipment: • IV tubing • IV pump Staff: • Stroke Nurse (Band 6) • Stroke Consultant Other Medications: • GTN • Labetalol		Intravenous thrombolysis was provided to all eligible patients before MT and patients referred from other hospitals were thrombolysed if eligible before being transferred to Centre D for MT. The Stroke Consultant authorised all thrombolysis either within or out of hours and the Stroke Nurse administered IVT on the Stroke Unit.

Resources (Centre D)	MT	IVT
Mechanical Thrombectomy Venue: • Interventional Radiology Suite (with biplane angio) Staff Anaesthetic team: • Consultant Anaesthetist • Anaesthetic Nurse Practitioner (ANP)/Scrub Nurse (SN) Band 6 • Interventional team: • Interventional Radiologist (1) Radiographer: • Radiographer band 6 (1) Scrub Nurse: • A Scrub Nurses (2) Band 5 and 6 • Stroke Consultant • Stroke SpR/SHO Pre-op: • GA • LA • CS **Thrombectomy Devices/**** Stent retriever Aspiration Catheter **Thrombectomy ancillary** Micro-catheters Guide wires Others **Carotid Stenting** **Miscellaneous material** Drapes, syringes Others	All thrombectomy procedures were performed in the Theatre, not in the Interventional Radiology Suite, like in other centres. The intervention was performed using existing infrastructure. The intervention was provided 24/7. Note that, out of hours (between 8 pm and 9 am) the Interventional Team consisted of one Scrub Nurse and one Radiographer. Thrombectomy was performed under GA for 39% of patients, LA in 41% and CS in 20-% of patients. Different devices were used depending on the location of the occlusion and presence or absence of carotid occlusion.	

Resources(Centre D)	MT	IVT
Post-thrombectomy Venue: • Recovery Area Staff: • Nurse (Band 5) • Anaesthetist • Stroke Consultant	Post -thrombectomy, patients were transferred to the Recovery Area outside the Theatre where they were monitored for about one hour. Once awakened, especially those who had MT under GA, they were moved to the Stroke Unit. Patients who were unstable were transferred to ICU/HDU While in Recovery, they were monitored by the Recovery Nurse, reviewed by the Consultant Anaesthetist and the Stroke Consultant before transfer to the Stroke Unit.	
ICU/HDU Venue: • ICU/HDU bed Staff: • ICU Consultant • ICU Nurse • ICU SpR	Post-thrombectomy: All unstable patients were transferred directly to ICU/HDU. The rest were moved to the Recovery Area.	
Transfer to the Stroke Unit • Stroke team Investigations: • Repeat CT • MRI • Blood test Others	All patients were returned to the Stroke Unit either from the Recovery Area or ICU/HDU. All patients had either a 24-hour CT head scan or an MRI head scan. Additional routine bloods tests may have been performed.	Patients treated with Intravenous thrombolysis alone are usually on the Stroke Unit. All patients had a 24-hour CT scan. For some patients, additional routine bloods tests were performed.
Discharge Transport Repatriation • Ambulance Home with or without ESD • Non-emergency transport Transfer to a community hospital • Non-emergency transport Transfer to a care home Non- emergency transport	Patients referred from other hospitals were repatriated to their primary hospital using land ambulance. Other discharges made via non-urgent transfer with other forms of transportation, such as hospital taxis, private family cars.	Other discharges made via non-urgent transfer with other forms of transportation, such as hospital taxis, private family cars.
Follow-up Venue: Outpatient Clinic Staff • Stroke Consultant • Clerical staff • Nurse	All local patients who underwent MT were followed-up at six weeks post-MT.	All thrombolysed patients were followed-up.

Appendix 6.D (4) - Resources used along the treatment pathways at MT Centre E1/E2

Resources- (Centre E1/E2)	MT	IVT
Transport Mode: • Ambulance • Others Staff: • Two Paramedics Second Transport to QS for MT • Ambulance • Medical escort (Junior doctor)	Land ambulances transported all patients: the local and the direct transfers before repatriation to Centre E1 for imaging and thrombolysis. These patients and the referred patients from other hospitals who would have had their thrombolysis are transported directly to Centre E2. There is a medical escort for all secondary transfers from **Centre E1** to **Centre E2** for MT.	All patients were local or direct transfers to Centre E1 for IVT. No secondary transfer from other hospitals for IVT.
Arrival at Emergency Department (ED) Venue: • Resuscitation bay or majors bay Investigations: • Blood tests • ECG • Others Staff: • Stroke Nurse (Band 6) • Stroke SHO (FY2/CT1-2) • Stroke SpR • Stroke Consultant	ED was the first point of entry for all local patients and all direct transfers before repatriation joining the treatment pathways, except for inpatient stroke cases. The resources used were the same for all patients admitted to ED. The Stroke Team was pre-alerted about any potential thrombolysis patient by the Ambulance Team before arrival at ED. Patients transferred from other hospitals were first discussed with Centre E1 Stroke Consultant and CT/CTA images linked via Picture Archiving and Communication System (PACS). Thrombectomy was provided initially between 9 am and 5pm and now up to 11 pm	The Stroke Team was pre-alerted about any potential thrombolysis patients by the ambulance team before arrival at ED. Intravenous thrombolysis was provided 24 hours.
Diagnostic imaging (Radiology) • CT head scan • CT angiogram (CTA) Staff: • Radiographer • Radiology SpR • Radiology Consultant	All patients had a CT and CTA. Images were reported initially by the Radiology SpR and later by the Consultant Radiologist for patients having IVT only. The Consultant Radiologist reviewed all scans for patients undergoing MT before the procedure.	All patients had a CT and CTA. Images were reported initially by the Radiology SpR and later by the Consultant Radiologist for patients having IVT only. Not all scans were reported by a Consultant Radiologist before commencement of intravenous thrombolysis.
Treatment Phase **Intravenous thrombolysis** • Alteplase Equipment: • IV tubing • IV pump Staff: • Stroke Nurse (Band 6) • Stroke Consultant Other Medications:		Intravenous thrombolysis was provided to all eligible patients before MT. The Stroke Consultant authorised all thrombolysis either within or out of hours and the Stroke Nurse administered IVT in ED.

• GTN • Labetalol		
Resources (Centre E)	MT	**IVT**
Mechanical Thrombectomy Venue: Interventional Radiology suite (with biplane angio) Staff Anaesthetic team: • Consultant Anaesthetist • Operational Dependent Practitioner or Assistant (ODP/ODA) Band 6 • Anaesthetic SpR Interventional team: • Interventional Radiologist (1) • Radiology SpR Radiographer: • Radiographers (2) One Band 6 and one Band 7 or two Band 6 Scrub Nurse: • Scrub Nurses (3) Band 5 and 6x2 Stroke Team: • Stroke Consultant • Stroke Nurse • Stroke SpR Pre-op: GA, LA, CS **Thrombectomy Devices/**** Stent retriever Aspiration Catheter **Thrombectomy ancillary** Micro-catheters Guide wires Others **Carotid Stenting** **Miscellaneous material** Drapes, syringes Others	All thrombectomy procedures were performed at **Centre E2** suite (IRS), using existing infrastructure. Thrombectomy was performed under GA for 69% of patients, LA in 29% and CS in 2% of patients. Thromboaspirators were the primary device used depending on the location of occlusion and presence or absence of carotid occlusion.	

Resources Centre E	MT	IVT
Post-thrombectomy Venue: • ICU/HDU. **Staff:** • **INR** • **Anaesthetist** **Stroke Consultant**	Post-thrombectomy: All patients were transferred directly to ICU/HDU.	
Transfer to the Stroke Unit Venue: • Hyperacute Stroke Unit (HASU) • Acute stroke unit (ASU) Staff: • Stroke team **Post-thrombectomy Scan** • CT head scan Staff: • Radiographer 72 -hour scan: • MRI	All local patients are transported to HASU at Centre E1 directly from HDU/ICU All transferred patients went to ASU at Centre E2 , before repatriation. All patients had a 24-hour CT head scan and some an MRI at 72 hours Some additional routine bloods tests were performed.	Patients treated with Intravenous thrombolysis alone were transferred from ED directly to the Stroke Unit. All patients had a 24-hour CT scan. For some patients, additional routine bloods tests were performed
Discharge Transport Repatriation • Ambulance Home with or without ESD • Non-emergency transport Transfer to a community hospital • Non-emergency transport Transfer to a care home Non- emergency transport	Patients referred from other hospitals were repatriated to their primary hospital using land ambulance. Other discharges made via non-urgent transfer with other forms of transportation, such as hospital taxis, private family cars.	Other discharges made via non-urgent transfer with other forms of transportation, such as hospital taxis, private family cars.
Follow-up Venue: • Outpatient Clinic Staff • Stroke Consultant • Clerical staff • Nurse	All patients both local and direct transfer before repatriation were who underwent MT were followed-up.	All thrombolysed patients were followed-up.

6.5 Unit costs of Resources used along the treatment pathways

Patients travelling through each phase of the pathways naturally would accumulate different costs for each item of resource used. The resources used were costed using the NHS Reference Costs (Department of Health 2016/17); British National Formulary (BNF website); Personal Social Services Research Unit (PSSRU) (Unit Costs of Health and Social Care 2017); Hospitals NHS Trust Finance Departments; local sources and published literature.

Most unit costs such as transportation, imaging, devices and consumables are specific for each hospital, while some, such as staffing costs and thrombolysis were applied across all centres.

The unit costs for the resources used for both IVT and MT along the pathways at other centres are shown in Appendix 6.E (1-4)

Appendix 6E (1) - Hospital specific unit costs for resource use in each phase in the treatment pathway at Centre B

Item (s)- (Centre B)	Unit Cost (£)	References	Additional costs (£)
Transport^ Medical Escort (Jnr Doctor or Stroke Nurse)	210 58	NHS Reference Costs 2016/2017 Personal Social Services Research Unit (PSSRU)	
The total ambulance costs were based on ambulances' transfer from home and transfer from referring hospitals both of which fall under the category of 'Red type 2' meaning response within eight minutes. This was the cost of the regional Ambulance Service NHS Trust. The transport cost is similar for both IVT and MT treated patients, but patients referred for MT were transported first to their primary stroke centre before the transfer to Centre B. Patients transferred to Centre B were escorted either by a nurse or junior doctor (no additional costs charged currently). NB (If costed it would be £60/hr for Jnr doctor and £58/hr for Nurse).			Referred patients incurred two cost of transportation: the cost for ambulance transfer to primary hospital and transfer from primary hospital to Centre B.
ED attendance^ Time in ED (Centre B) Time in ED (referring hospitals)	152 129 146 146 151 218 151 160	Centre B Finance Department Referring Centre 1 Finance Department Referring Centre 2 Finance Department Referring Centre 3 Finance Department Referring Centre 4 Finance Department Referring Centre 5 Finance Department Referring Centre 6 Finance Department Referring Centre 7 ~~Finance~~ Department	The referred patients bypassed ED and were taken directly to the Radiology Department. The Stroke Team received the patient with an escort in Radiology.
The ED attendance costs covered the cost of routine blood investigations, all supportive care provided in ED and stroke team in attendance, excluding the cost of Imaging. Thrombectomy was only offered between 9 am to 9 pm weekdays and weekends. The Stroke Nurse was usually pre-alerted and present for up to a maximum of 1.5hours for the duration of the investigations and thrombolysis in the ED and subsequent transfer of eligible patients to the IRS for MT. The Stroke Consultant was not necessarily in ED for the initial assessment before imaging or thrombolysis, mainly when out of hours (20:00-08:00 hours).			Referred patients incurred a cost for emergency hospital attendance at the primary hospital and additional costs for the initial consultation by the stroke team on arrival at the Centre B Radiology Department.
Imaging ^			Referred patients incurred two costs for initial scan at primary hospital and for repeat scans at Centre B.
Non-Contrast CT Brain	100.00	Centre B Finance Department	
CT angiogram (CTA)	150.00	Centre B Finance Department	
CT Perfusion (CTP)	250.00	Centre B Finance Department	
The costs of imaging (CT and CTA) were based on the NHS costs for imaging. All patients had a combined CT and CTA and a CT perfusion in those with unknown time of onset. All the transferred patients got CT and CTA as well as CTP. Additionally, there was a repeat CT head 24 hours -post. Intervention, either IVT or MT. The imaging tariff included the cost of reporting by a diagnostic radiologist.			

Treatment			
Intravenous thrombolysis Alteplase Tariff for Intravenous thrombolysis **Item (s)- (Centre B)**	578 1671 **Unit Cost** (£)	British National Formulary (BNF) NHS reference Costs- 2018/19 AA23E **References**	 **Additional costs** (£)
Mechanical thrombectomy			
Thrombectomy Devices** <u>Stent retriever</u> ev3 SOLITAIRE ™ 2 ev3 SOLITAIRE ™ AB Trevo XP <u>Aspiration Catheter</u> SOFIA Distal Access Catheter **Thrombectomy ancillary** Microcatheters Microcatheter (Neuroslider21)- Headway DUO microcatheter- NeuroSlider micro catheters Traxcess Guidewire **Carotid Stenting** Carotid stenting (Casper RX) **Miscellaneous material** Drapes, syringes	 3144.75 2829.75 2400.00 640.00 359 410 395 954 200	Centre B Finance Department	Additional costs for patients with carotid stenosis.
ITU **HDU**	2282 1245	NHS reference Costs 2016/2017	
The ICU/HDU was costed per the number of organ systems being supported and was charged per day on the unit. The costs included both the medical and nursing care costs on the unit, together with other investigations and overheads.			
Stroke Unit^	255	NHS reference Costs 2016/2017	Total cost depended on the LOS
The costs for the stroke unit were charged per day and included ward-based nursing, allied staff and administrative staff. They also included the cost of routine ward-based investigations and consumables, but excluded the Stroke Consultant, or visits from other allied health professionals. Additionally, the costs for other members of the stroke team on the Stroke Unit, such as Speech and Language Therapy, Physiotherapy, Occupational Therapy and Dietician were based on an hourly rate.			
24-hour post treatment scan^ CT head	100.00	Centre B Finance Department	

Discharge/Transport			
Repatriation Home with ESD Transfer to a community hospital Transfer to a care home	210.00 50.00 50.00 50.00	Centre B Finance Department	
Patients were repatriated with Category 2 ambulances by the regional Ireland Ambulance Service NHS Foundation Trust. Most repatriated patients were without paramedic escort because they were stable. Transport to a community hospital or a care home was by a different transport service and discharge home was by hospital taxis or by relatives.			
Follow-up	265	NHS reference Costs 2016/2017	
All thrombectomy treated patients were followed-up, except those repatriated to their local hospitals, who may have been followed- up by their primary hospital**.**			
Others: Hidden costs: Cancellation of elective cases to use IRS for emergency MT, Others (overheads etc).			

Appendix 6.E (2) - Hospital specific unit costs for resource use in each phase in the treatment pathway at Centre C

Item(s) - (Centre C)	Unit Cost (£)	References	Additional costs (£)
Transport^	204.77	NHS Reference Costs 2016/2017	
An ambulance cost was based on ambulance's transfer from home and transfer from referring hospitals both of which fall under the category of 'Red type 2' meaning response within eight minutes. This cost was based on the West Midlands Ambulance Service NHS Foundation Trust. The transport cost is similar for both IVT and MT treated patients, but patients referred for MT were transported first to their primary stroke centre before the transfer to Centre C.			Referred patients incurred two costs of transportation: the cost for ambulance transfer to primary hospital and transfer from primary hospital to Centre C. Patients were usually transferred without any doctor or nurse escort.
ED attendance^ Time in ED (Centre C) Time in ED (referring centre)	 165 299	 Centre C NHS Trust Finance Department NHS reference Costs 2018/2019	
The cost of ED attendance at the referring hospitals was based on "Emergency Medicine, Category 3 Investigation with Category 4 Treatment" (NHS reference costs) and "Emergency Medicine, Any Investigation with Category 5 Treatment" for Centre C. The ED attendance costs covered the cost of routine blood investigations and all supportive care provided in ED, excluding the cost of imaging and stroke team attendance. The Stroke Team were pre-alerted, but the Stroke Consultant was not necessarily in ED for the initial assessment before imaging or thrombolysis, mainly out of hours (2000-0800 hours). The Stroke Nurse and Consultant attendance were costed for one hour for the investigations and interventions.			Referred patients incurred a cost for emergency hospital attendance at the primary hospital and additional costs for the initial consultation by the Stroke Team on arrival at Centre C Radiology Department.
Imaging ^			
Non-Contrast CT Brain	81.28	NHS reference Costs 2017/2018 RD20A	
CT angiogram (CTA)	93.78	NHS reference Costs 2017/2018 RD21A	
CT Perfusion (CTP)	120.39	Centre C Finance Department	
The costs of imaging were based on the NHS costs for imaging. All patients had a combined CT and CTA, and a CT perfusion for those with unknown time of onset. The Tariff included the cost of reporting by a diagnostic consultant radiologist. Additionally, there were repeated CT head scans immediately post-intervention and 24 hours-post MT and a CT head 24-hour after IVT.			Few referred patients incurred two costs for an initial scan at the primary hospital and repeat scans at Centre C.
Treatment			
Intravenous thrombolysis Alteplase Tariff for Intravenous thrombolysis	 578 1671	 British National Formulary (BNF) NHS reference Costs- 2018/19 AA23E	

Item (s)- (Centre B)	Unit Cost (£)	References	
Mechanical thrombectomy			
Thrombectomy Devices*		Centre B Finance Department Trust	
<u>Stent retriever</u>			
Solitaire 2	3720		
Solitaire Platinum	3720		
Tigertriever	3300		
Eric	3600		
EmboTrap II	3960		
pREset/pREset lite	2700		
<u>Aspiration Catheter</u>			
ARC	1619		
Sofia plus 6F =	780		
ACE60, ACE64, ACE68 reperfusion catheters	1608		
3 MAX Reperfusion Catheter	654		
<u>Thrombectomy ancillary</u>			
Headway micro delivery catheter	528		
Traxcess EX 14	240		
Traxcess Docking Wire	150		
Velocity micro delivery	420		
Echelon	544		
Max canister	114		
Synchro	240		
Angio-seal Vascular closure	144		
Carotid Stenting			
Stent Carotid CASPER RX = 954	954		
Miscellaneous material	200		
Drapes syringes			
Others			
ICU/HDU	1420	NHS reference Costs 2016/2017	
The ICU/HDU was costed per the number of organ systems being supported and was charged per day on the unit. The costs included both the medical and nursing staff on the unit and together with other investigations and overheads.			

^ common to both IVT and MT** Thrombectomy devices provided in Appendix F

Item(s) -(Centre C)	Unit Cost (£)	References	Additional costs (£)
Stroke Unit^	300/day	Centre C **NHS** Trust Finance Department	Total costs were dependent on the length of stay.
The costs of stay on the Stroke Unit was between 450-600 for the first 48 hours and after that 300/day. The costs for the Stroke Unit was charged per day and included ward-based nursing, allied staff and administrative staff. It also covered the cost of routine ward-based investigations and consumables. The costs also included medical staffing or visits from other allied health professionals. Additionally, the costs for other members of the Stroke Team on the Stroke Unit such as Speech and Language Therapy, Physiotherapy, Occupational Therapy and Dietician were based on an hourly rate.			
Immediate post-intervention CT	81.28	Centre C **NHS** Trust Finance Department	
24-hour post treatment scan^ CT head MRI Others	81.28 342.14	Centre C **NHS** Trust Finance Department Centre C **NHS** Trust Finance Department	
Discharge			
Transport: Repatriation without paramedic escort	115.00	Centre C **NHS** Trust Finance Department	
Repatriation with paramedic escort	140.00	Centre C **NHS** Trust Finance Department	
Patients were repatriated by Category 2 ambulance by the West Midlands Ambulance Service NHS Foundation Trust. Most repatriated patients were without paramedic escort because they were stable. Transport to a community hospital or a care home was by a different transport service and discharge home was by hospital taxis or by relatives.			
Follow-up^	129	NHS reference Costs 2016/2017	
All thrombectomy treated patients were followed-up, except those repatriated to their local hospitals who may also be followed- up by the Primary Hospital. IVT treated patients were also followed up.			
Others: Other costs were obtained directly from the Centre C **NHS** Trust Finance Department			
Hidden costs: Others (overheads etc).			

^ common to both IVT and MT ** Thrombectomy devices provided in Appendix F

Appendix 6.E (3) - Hospital specific unit costs for resource use in each phase in the treatment pathway at Centre D

Item(s) -(Centre D)	Unit Cost (£)	References	Additional costs (£)
Transport^	196	NHS Reference Costs 2016/2017	
The ambulance cost was based on transfer by ambulance from home and transfer from referring hospitals both of which fall under the category of 'Red type 2' meaning response within eight minutes. This was the cost of the regional Ambulance NHS Trust. The transport cost is similar for both IVT and MT treated patients, but patients referred for MT would have been transported first to their Primary Stroke Centre before the transfer Centre **D.**			Referred patients incurred additional costs of transportation: the cost for ambulance transfer to primary hospital and transfer from primary hospital to Centre D. Patients are usually transferred without any junior doctor or nurse escort.
Stroke Unit first attendance^	273.36	Centre D NHS Foundation Trust Finance Department Personal Social Services Research Unit (PSSRU) Personal Social Services Research Unit (PSSRU) [Medical Consultant]	
First attendance at ED	328	NHS reference Costs 2018/2019- code VB02Z	
Time in ED (referring Centres)	299	NHS reference Costs 2018/2019- code VB02Z	
The Stroke Unit first attendance costs covered the cost of routine blood investigations and all supportive care provided on the Stroke Unit, excluding the cost for the Stroke Consultant. The Stroke Nurse was usually pre-alerted and with the patient for the duration of the investigations and thrombolysis and subsequent transfer of eligible patients to the Theatre for MT. The Stroke Consultant may not necessarily have been on the Stroke Unit for the initial assessment before imaging or thrombolysis, particularly out of hours (2000-0800 hours).			Referred patients incurred two costs for emergency hospital attendance: first for attendance at primary hospital and then on arrival at Centre D Stroke Unit for assessment, before transfer to the Radiology Department for repeat imaging or to the theatre.
Imaging ^			
Non-Contrast CT Brain	87.24	NHS reference Costs 2016/2017- code RD20A	
CT angiogram (CTA)	100	Centre D NHS Foundation Trust Finance Department	
CT Perfusion	133	NHS reference Costs 2016/2017-code RN20Z (Based on Myocardial Perfusion scan)	
The costs of imaging were based on the NHS costs for imaging. All patients had a combined CT and CTA, and a CT perfusion in those with unknown time of onset. The Tariff included the cost of reporting by the diagnostic radiologist. Additionally, there was a repeat CT head 24 hours-post intervention, either IVT or MT.			Some referred patients could have incurred two costs for initial scan at primary hospital and for repeat scans at Centre D if they arrived more than one hour after initial scan.
Treatment			
Intravenous thrombolysis			
Alteplase	578	British National Formulary (BNF)	
Tariff for Intravenous thrombolysis	1671	NHS reference Costs- 2018/19 AA23E	

Item (s)- (Centre D)	Unit Cost (£)	References	
Mechanical thrombectomy			
Thrombectomy Devices/**		Centre D NHS Foundation Trust	
Stent retriever			
Solitaire 2.	3100		
SOLITAIRE AB	3100		
Eric Retrieval Device	3100		
Aspiration Catheter			
Sofia PLUS Aspiration Catheter	495		
Catheter Distal Access Sofia	495		
ACE60, ACE64, ACE68 reperfusion catheters	1340		
3MAX, 4MAX,5MAX reperfusion	150		
Thrombectomy ancillary			
hybrid guide wires.	350		
Traxcess EX 14 =	150		
Neuron MAX 6F 088 Sheath	150		
Synchro	210		
PAPS2 SUCTION MAX CANNISTE	245		
Headway micro delivery catheter	395		
6F 070 Neuron Delivery Catheter 95/6 MP	245		
6F 070 Neuron Deliver Catheter 105/8 MP	350		
6F Benchmark 071 + BEE Select	450		
Pack Angioplasty MAP 20cm	150		
Guidecath Benchmark 071 6F MP-W/BERNTEIN Catheter 5F 130CM	450		
Catheter Guiding Neuron Select SIM 5F 9cmX040inX130cm	450		
Guidewire Hydrophilic Zipwire STD ANG	70		
ASAHI INTECC ASHAHI Neurovascular Guide Wire	245		
Echelon =	380		
INVATEC SUBMARINE RAPIDO	70		
Max canister.	95		
Angio-seal Vascular closure	93		
Carotid stenting			
CASPER Carotid Stent System	800	Additional costs for patients inserted with carotid stent due to carotid stenosis	
Miscellaneous material			
Drapes, syringes others etc	180.70		

Item(s) -(Centre D)	Unit Cost (£)	References	Additional costs (£)
ICU/HDU	1331	NHS reference Costs 2016/2017	
Stay on ICU/HDU was costed per the number of organ systems being supported and was charged per day on the unit. There was no distinction between HDU and ITU. The costs included both the medical and nursing staff, together with other investigations and overheads.			
Stroke Unit^ - (Centre D) Stroke Unit admission	269.57/day	Centre D NHS Foundation Trust Finance Department	Total cost depended on the length of stay.
The costs for the Stroke Unit was charged per day and included ward-based nursing, allied staff and administrative staff. It also included the cost of routine ward-based investigations and consumables. The costs also included medical staffing or visits from other allied health professionals. Additionally, the costs for other members of the Stroke Team on the Stroke Unit such as Speech and Language Therapy, Physiotherapy, Occupational Therapy and Dietician were based on an hourly rate.			
24-hour post treatment scan^ CT head MRI	71 140.86	NHS reference Costs 2016/2017 Centre D NHS Foundation Trust Finance Department	
Discharge			
Transport: Repatriation Home with ESD Transfer to a community hospital Transfer to a care home	 100 50 50 50	 Centre D NHS Foundation Trust Finance Department Centre D NHS Foundation Trust Finance Department Centre D NHS Foundation Trust Finance Department Centre D NHS Foundation Trust Finance Department	
Patients were repatriated with Category 2 ambulance by the regional NHS Ambulance Trust. Most repatriated patients were without paramedic escort because they were stable. Transport to a community hospital or care home was by a different transport service and discharge home was by hospital taxis or by relatives. It was estimated that patients discharged home with ESD would have therapy input for maximum up to six weeks.			
Follow-up	149.14	NHS reference Costs 2016/2017	
All thrombectomy treated patients were followed-up, except those repatriated back to their local hospitals; these patients may also have been followed-up by their primary hospital.			
Hidden costs: Cancellation of elective cases to use IRS for emergency MT. Others (overheads etc).			

^ common to both IVT and MT, ** Thrombectomy devices provided in Appendix F

Appendix 6.E (4) - Hospital specific unit costs for resource use in each phase in the treatment pathway at Centre E1/E2

Item(s) -(Centre E1/E2)	**Unit Cost** (£)	**References**	**Additional costs** (£)
Transport^	£291:84	NHS Reference Costs 2016/2017	**Centre E1/E2**
An ambulance cost was based on ambulance's transfer from home and secondary transfer from non-MT hospitals both of which fall under the category of 'Red type 2' meaning response within eight minutes. This cost was based on the London Ambulance Service NHS Foundation Trust. The transport cost is similar for both IVT and MT treated patients, but patients treated with MT were transported again to QS.			All patients incurred two costs of transportation: the cost for ambulance transfer to Centre E1 or primary hospital and secondary transfer to QS. Patients were usually transferred with a junior doctor escort from UCHL to QS Centre E1 to Centre E2
ED attendance^ Time in ED (QEHB) Time in ED (referring centre)	 328 299	 NHS reference Costs 2018/2019- code VB02Z NHS reference Costs 2018/2019- code VB02Z	
The cost of ED attendance at the referring hospitals was based on "Emergency Medicine, Category 3 Investigation with Category 4 Treatment" (NHS reference costs) and "Emergency Medicine, Any Investigation with Category 5 Treatment" for Centre E1. The ED attendance costs covered the cost of routine blood investigations and all supportive care provided in ED, excluding the cost of imaging and stroke team attendance. The Stroke Team were pre-alerted, but the Stroke Consultant was not necessarily in ED for the initial assessment before imaging or thrombolysis, mainly out of hours (1700-0800 hours). The Stroke Nurse, SpR and Consultant attendance were costed for one hour for the initial assessment and investigations and initiation of treatment.			Referred patients incurred a cost for emergency hospital attendance at the primary hospital and additional costs for the initial consultation by the Stroke Team on arrival at Centre E1
Imaging ^			
Non-Contrast CT Brain	91	NHS reference Costs 2018/2018	
CT angiogram (CTA)	105	NHS reference Costs 2017/2018	
The costs of imaging were based on the NHS costs for imaging. All patients had a combined CT and CTA, The Tariff included the cost of reporting by a diagnostic consultant radiologist. There were repeated CT head scans at 24 hours-post MT and at 24-hour after IVT only.			Few referred patients incurred two costs for an initial scan at the primary hospital and repeat scans at Centre E2.
Treatment			
Intravenous thrombolysis Alteplase Tariff for Intravenous thrombolysis	 578 1671	 British National Formulary (BNF) NHS reference Costs- 2018/19 AA23E	

Item (s)- (Centre E)	Unit Cost (£)	References	Additional costs (£)
Mechanical thrombectomy **Thrombectomy Devices/**** <u>Stent retriever</u> Solitaire ab Solitaire 2 ev3 solitaire ab 4*20 = **Aspiration Catheter** Penumbra ace 68 kit Penumbra neuron max 6f 088 Penumbra 3maxc reperfusion catheter 153 **Thrombectomy ancillary** Headway 27 microcatheter Traxcess 14 guidewire ASAHI CHIKA1 014 guidewire BOSTON SCIENTIFIC Transend EX PLATINUM Neuron Max 6F SHEATH CODMAN 6F ENVOY MPD Sychro 14 0.014* 200 Wire ABB0TT PERCLOSE PROGLIDE 67 Angioseal VIP **Carotid Stenting** Carotid WALLSTENT 7*10 135cn **Miscellaneous material** Drapes, syringes	 3729 3729 3729 1608 180 654 834 180 204 180 132 150 211 102 97.50 804 275	BOSTON SCIENTIFIC Transend EX PLATINUM	
Miscellaneous material	275	Expert Clinical Opinion	
ICU/HDU* **	1083-1420	NHS reference Costs 2017/2018	
The ICU/HDU was costed per the number of organ systems being supported and was charged per day on the unit. The costs included both the medical and nursing staff on the unit and together with other investigations and overheads			

*** cost dependent on number of organs supported, ** Cost plus VAT

Item(s)- (Centre E1/E2)	**Unit Cost** (£)	**References**	**Additional costs** (£)
Stroke Unit ^ **HASU (**Centre E1) **ASU (**Centre E2**)**	 583/day 321/day	 Centre E1/E2 NHS Trust Finance Department Centre E1/E2 NHS Trust Finance Department	Total costs were dependent on the length of stay.
The costs of stay on the Stroke Unit was 583/day. The costs for the Stroke Unit was charged per day and included ward-based nursing, allied staff and administrative staff. It also covered the cost of routine ward-based investigations and consumables. The costs also included medical staffing or visits from other allied health professionals. Additionally, the costs for other members of the Stroke Team on the Stroke Unit such as Speech and Language Therapy, Physiotherapy, Occupational Therapy and Dietician were based on an hourly rate.			
24-hour post treatment scan CT head MRI	 91 136	 NHS reference Costs 2018/2018 NHS reference Costs 2018/2018	
Discharge			
Transport: Repatriation without paramedic escort Home with ESD**^^** Transfer to a community**^^** hospital	 90-237^^ 90-118^^ 90-118^^	 NHS Trust Finance Department Centre E1/E2 NHS Trust Finance Department Centre E1/E2 NHS Trust Finance Department	
Patients were repatriated by Category 2 ambulance by the London Ambulance Service NHS Foundation without paramedic escort because they were stable. Transport to a community hospital or a care home was by a different transport service and discharge home was by hospital taxis or by relatives.			
Follow-up^	235	NHS reference Costs 2016/2017	
All thrombectomy treated patients were followed-up, including those repatriated to their local hospitals. IVT treated patients were also followed up.			
Others: Other costs were obtained directly from Centre E1/E2 NHS Trust Finance Department			
Hidden costs: Cancellation of elective cases to use NIRS for emergency MT. Others (overheads etc).			

^ common to both IVT and MT

^^ Cost per distance and type of transportation based on degree of disability

Appendix F - Comparison of costs of NICE Devices with other Centres.

Company	Devices	Accessories	NICE (£) (Excluding Vat)	Centre A (£) Excluding Vat)	Centre B (£) Excluding Vat)	Centre C (£) Excluding Vat)	Centre D (£) Excluding Vat)	Centre E (£) Excluding Vat)
	Stent retriever							
Acandis; UK Supplier: Neurologica	Aperio		2700					
		NeuroSlider Microcathers	495		395			
Balt; UK Supplier: Sela Medical	Catch+ Mini		3000					
	Catch+		1900					
	Catch+ Maxi		1900					
		VASCO delivery catheters	435					
		hybrid guide wires	290					
Cerenovus Johnson and Johnson	EmboTrap II		3500			3300		
	ReVive SE		4963					
		Revive Intermediate access catheters	648					
Medtronic	MindFrame,Capture LP		3190					
	Solitaire 2		3190	3100			3100	3100
	Solitaire Platinum		3349	3200		3100		
	ERIC		2500	3000		3000	3100	
Penumbra	3D Revascularization device		5000					
Phenox	pREset/pREset lite		1995			2250		
Rapid Medical;UK supplier: Neurologic	Tigertriever		3000			2750		
		NeuroSlider micro catheters	495					
Stryker	Trevo ProVue		3250					
	Trevo XP ProVue		3250					
		Trevo Pro 14/18 microcatheter	300					
		Flowgate balloon catheter	750					
		Infinity access catheter	350					
	Aspiration Catheter							
Medtronic	ARC		1349			1349		
	ARC Mini		1249					
	Navien		613					
Microvention	Sofia/Sofia Plus		550	595	640	650	495	
		Headway micro delivery catheter	440	395	410	440	395	695
Penumbra	ACE60, ACE64, ACE68 reperfusion catheter		1275			1340	1340	1340
	3MAX, 4MAX,5MAX DD		1090				1150	
		Max Pump	7500					
		Velocity micro delivery	700					
		Neuron access catheters	300					543

		Max canister	190					
Stryker	AXS Catalyst DAC		900					

6.4.1 Total patient data (TPD) costing

The details of the TPD costing for the other individual MT centres B to E are in Appendix 6.G (1-4)

Appendix 6.G (1) - Resources used and costs along the treatment pathway at Centre B

Resource item (s)	MT +IVT (323) (£)	IVT only (299) (£)	Total cost (622) (£	Percentage
Pre-hospital notification	2149	875	3024	0.1%
Transport	74068	57120	131188	3%
Emergency Hospital Attendance (ED)	134716	141174	275890	6%
Diagnostic Imaging	212773	110032	322805	7%
IVT only		499629	499629	11%
MT procedure	2848848		2848848	64%
• venue	261630			
• Staffing cost	635987			
• MT devices	1930248			
• Anaesthesia	20983			
MT +IVT	71094		71094	1.6%
Immediate post-op care	79722		79722	2%
HDU/ICU	17430		17430	0.4%
Stroke unit stay	78795	76245	155040	3.5%
Post treatment scan	32300	29900	62200	1.4%
Total cost (24 hours)	3551895 (80%)	914975 (20%)	4466870	
Average cost	10997	3060	7182	

Appendix 6.G (2) - Resources used and costs along the treatment pathway at Centre C

Resource item (s)	MT +IVT (88) (£)	IVT only (271) (£)	Total cost (359) (£)	Percentage
Pre-hospital notification	329	1806	2138	0.1%
Transport	17201	52831	70032	4%
Emergency Hospital Attendance (ED)	38344	109134	147478	8.4%
Diagnostic Imaging	23592	79419	103011	6%
IVT only		452841	452841	26%
MT procedure	688527		688527	40%
• venue	71280 (10%)			
• Staffing cost	173624(25%)			
• MT devices	431904(53%)			
• Anaesthesia	11719 (2%)			
MT +IVT	27166		27166	1.6%
Immediate post-op care	48991		48991	3%
HDU/ICU	24140		24140	1%
Stroke unit stay	21300	81300	102600	5.9%
Post treatment scan	17537	54005	71542	4%
Total cost (24 hours)	907127 52%	831336 48%	1755398 1738463	
Average cost	10308	3068	4843	

Appendix 6.G (3) - Resources used and costs along the treatment pathway at Centre D

Resource item (s)	MT +IVT (444) (£)	IVT only (368) (£)	Total cost (76) (£)	Percentage
Pre-hospital notification	231	1995	2226	0.1
Transport	12544	55860	68404	4
Emergency Hospital Attendance (ED)	51575	173656	225231	13
Diagnostic Imaging	22319	112328	134647	8
IVT only		614928	614928	35
MT procedure	475003		475003	27.1
• venue	61560 (13%)			
• Staffing cost	131708 (28%)			
• MT devices	270940 (57%)			
• Anaesthesia •	10795 (2%)			
MT +IVT	28322		28322	1.6
Immediate post-op care	27299		27299	1.6
HDU/ICU	19965		19965	1
Stroke unit stay	16444	99202	115646	6.6
Post treatment scan	7167	32104	39271	2
Total cost (24 hours)	660869 (38%)	1090073 (62%)	1750942	
Average cost	8696	2962	3944	

Appendix 6.G (4) - Resources used and costs along the treatment pathway at Centre E1/E2

Resource item (s)	MT +IVT (84) (£)	IVT only (321) (£)	Total cost (405) (£)	Percentage
Pre-hospital notification	553	2191	2744	0.1%
Transport	52036	91346	143382	6.5%
Emergency Hospital Attendance (ED)	54315	199694	254009	11.6%
Diagnostic Imaging	27322.	99538	126860	6%
IVT only		536391	536391	24.4%
MT procedure	717337		717337	33%
• venue	68040			
• Staffing cost	145572			
• MT devices	489552			
• Anaesthesia	14173			
MT +IVT	32368		32368	1.4%
Immediate post-op care	33986		33986	1.5%
HDU/ICU	119280		119280	5%
Stroke unit stay		187143	187143	8.5%
Post treatment scan	7644	29211	36855	2%
Total cost (24 hours)	1044841	1145514	2190355	
Average cost	12439	3569	5408	

6.4.3 Individual patient data (IPD) costing

The cost breakdown of each point along the treatment pathway up to discharge for individual patient data at the other MT centres are in APPENDIX 6 H.

Appendix 6.H (1) - cost breakdown of each point in the treatment pathway up to discharge for a sample of cases (n= 65) at Centre B

Resource item(s)	Mean total cost (£)	SD (£)	95% CI (£)	Range
Pre-hospital notification	6.14	2.321	5.56-6.71	0-7
Transport	417	244	356- -477	0- 668
Emergency Hospital Attendance	463	37	454 -472	316-536
Diagnostic Imaging	650	189	604-697	350-850
MT procedure	7,958	2,275	7,395-8,522	3,051-13,926
• MT devices	5,976	2,252	5,418-6,534	1125-12000
• Staffing cost	1,137	132	1,105-1,170	1089-1560
Cost of anaesthesia	35	39	26-45	27-227
Cost immediate post-op care	507	0	507-507	507-507
Cost HDU/ICU	140	553	4-277	00-2282
Cost hospital stay 24 hours-post MT	990	464	875-1105	774-2789
Total Costs 24 hrs (MT only)	10,479	2,350	9,892 -11,066	5,902-16795
Total Costs 24 hrs (MT+IVT)	10,749	2,346	10163-11335	5911-16795
Up to discharge from MT centre	13,247	5,815 4	11,794-14,700	5,957- 47539

Appendix 6.H (2) - cost breakdown of each point in the treatment pathway up to discharge for a sample of cases (n= 60) at Centre C

Resource (items)	**Mean total cost (£)**	**SD £)**	**95% CI**	**Range**
Pre-hospital notification	6.53	1.76	6.08-.6.99	0-7
Transport	400	394	299 to 502	0- 3105
Emergency Hospital Attendance	503	98	4778-529	31-704
Diagnostic Imaging	369	77	349-389	244-633
MT procedure	7,966	2,644	7,283-8,649	3,873-15680
• MT devices	4,908	2,615	4,232-5,583	794-12400
• Staffing cost	2,028	276	1,957-2,099	1,269-2152
Cost of anaesthesia	136	95	112-161	00-227
Cost immediate post-op care	645	37	636-655	507-655
Cost HDU/ICU	1,980-	5,082	667-3,293	00-26400
Cost hospital stay 24 hours-post MT	1100	561	955-1244	807-2157
Total Costs 24 hrs (MT only)	10,3377	2,837	9,638-11,116	5,546-17780
Total Costs 24 hrs (MT+IVT)	10670	2,854	9926-11413	6122-18356
Up to discharge from MT centre	14,691	7,642	12,700-16,682	6,701-45146

Appendix 6.H (3) - cost breakdown of each point in the treatment pathway up to discharge for a sample of cases (n= 52) at the at Centre D

Resource item(s)	Mean total cost (£)	SD(£)	95% CI	Range
Pre-hospital notification	6.33	2.084	5.75-6.91	0-7
Transport	280	144	240—320	0- 492
Emergency Hospital Attendance	644	131	608-681	316-861
Diagnostic Imaging	293	34	283-302	275-462
MT procedure	6,262	1749	5,775-6,749	4090-11914
• MT devices	3,564	1760	3,074-4054	1,325-9055
• Staffing cost	1,664	166	1,618-1710	973-1792
Cost of anaesthesia	134	91	108-159	27-335
Cost immediate post-op care	655	0	655-655	507-507
Cost HDU/ICU	410	1104	102-717	00-6655
Cost hospital stay 24 hours-post MT	980	422	863-1098	777-1838
Total Costs 24 hrs (MT only)	8,466	1,701	7,9992-8,939	6,123-14,277
Total Costs 24 hrs (MT+IVT)	8864	1,727	8383-9345	6387-14853
Up to discharge from MT centre	11,087	4,245	9,905-12,269	6,066-30404

Appendix 6.H (4) - cost breakdown of each point in the treatment pathway up to discharge for a sample of cases (n= 65) at the at the at Centre E1/E2

Resource (items)	Mean total cost (£)	SD (£)	95% CI	Range
Pre-hospital notification	6.89	0.87	6.68-711	0-7
Transport	677	75	659-696	350-879
Emergency Hospital Attendance	611	84	589-632	489-882
Diagnostic Imaging	350	68	332-367	287-424
MT procedure	8,937	3,261	8,128-9,745	4,528-22,338
• MT devices	5,828	3,263	5,020-6,637	1,345-19,355
• Staffing cost	2,146	0	2,146-2,145	2,146-2,145
Cost of anaesthesia	153	97	129-177	27-227
Cost immediate post-op care	565	0	565 -565	565 -565
Cost HDU/ICU	4,761	3,654	3,855-5,666	1,019-2,0781
Cost hospital stay 24 hours-post MT	1994	857	1781-2206	1508-7943
Total Costs 24 hrs (MT only)	12,558	3,217	11,696-13,419	8,079-25,487
Total Costs 24 hrs (MT+IVT)	12949	3,246	12,079-13,818	8,079-26,063
Up to discharge from MT centre	18,896	5,047	17,545-20,248	12,274-35,452

Appendix Chapter 7

Appendix 7.A - Search Strategy

Key Term Search

The search terms relevant to the disease state, stroke (isch(a)emia, brain, cerebral, cerebrovascular accident, stroke, large artery occlusion) were combined using the Boolean operator AND, with terms reflecting the treatment, Endovascualar mechanical theombectomy (thrombectomy, mechanical thrombectomy, mechanical thrombus removal, endovascular therapy, endovascular intervention, clot retrieval, , clot disruption, clot aspiration, stent-assisted) and economic evaluation(cost, cost analysis, cost –effectiveness, cost benefit, economic(s), benefit, health care cost, cost savings, hospital cost). The developed search terms were first used in MEDLINE and then adjusted accordingly for other databases.

Search terms:
1, Brain ischaemia/ischemia, acute ischaemic/ischemic stroke, Cerebral infarction, cerebrovascular accident, CVA

2, Mechanical thrombolysis, endovascular therapy, endovascular treatment, endovascular embolectomy, endovascular thrombectomy, intra-arterial intervention, intraarterial intervention, intra-arterial treatment, intraarterial treatment, intra-arterial therapy, intraarterial therapy, intra-arterial thrombolysis, intraarterial thrombolysis, neurothrombectomy, neuro-thrombectomy

3, Cost-effectiveness analysis, cost-effectiveness, cost-utility analysis, cost utility, cost-benefit analysis, cost benefit, cost analysis, cost estimates, cost, benefit etc.

Appendix 7.B - Summary of Study characteristics of cost analyses and economic evaluations of EVT for acute ischaemic stroke patients

Author Year Country	Population	Interventions comparator	Type of analysis Study design Perspective Time horizon	Costing Year Currency Discount rate	Data Sources for model inputs					
					Efficacy outcomes	Death probabilities	Transitional probabilities	Recurrent Strokes	Utilities	Costs input
Cost effectiveness										
Heggie 2019 UK	Patients with acute ischaemic stroke	MT plus IV tPA compared with IV tPA alone	Decision tree analysis and Markov model Healthcare system Time horizon: (90 days, I-5yrs, lifetime)	GBP 2015/16 3.5%	PISTE 201	Davis 2012	HERMES PISTE THRACE	Davis 2012	Dorman P 2000	Ganesalingam 2015 Division IS SHSC.2016 Committee JF BNF 2016 Youman P 2003
Pizzo 2019 UK	Patients with acute ischaemic stroke	MT plus IV tPA compared with IV tPA alone	Markov model Healthcare system Time horizon: 20 Years	GBP 3.5%	DEFUSE 3 and DAWN		DEFUSE 3 and DAWN			
Kabore 2019 France	Patients with AIS	MT+IV tPA IV tPA alone	Decision tree analysis and Markov model Healthcare system Time horizon: (90 days, 10 years	Euros 2015 4%		Magalhaes 2014	HERMES THRACE	Rivero-Arias 2010	Rivero-Arias 2010	
Arora 2018 Australia	Adults with acute large vessel occlusion (LAO) stroke Mean Age: 66	MT plus IV tPA compared with IV tPA/ usual care	Decision tree analysis and Markov model Healthcare system Time horizon: Lifetime (1-7day, 90 days, I year)	2016 Australian dollars. 5%	HERMES 2016	Australian Bureau of Statistics (ABS) life tables 2013	HERMES	Mohan 2011	Sturm 2002 [NEMESIS]	Tan 2013 Gloede 2014 Baeten 2010
Ruggeri 2018 Italy	Age: 66	MT+IV tPA IV tPA alone	Markov model Healthcare system Time horizon: 5 years Lifetime	Euros 3.5%	SWIFT PRIME	Slot et al. (2009)	SWIFT PRIME	SWIFT PRIME	Rivero-Arias et al. (2010)	Lucioni 2010 Fattore 2012
Pan 2018 China	AIS due to LAO Mean Age: 63 years	MT+IV tPA IV tPA alone	Decision tree and Markov model Healthcare payer Time horizon: 30 years (1, 5, 6)	2013 Chinese yuan renminbi (CNY) 3%	EAST study TIMS-CHINA 9 MT RCTs	China Health Statistics Yearbook 2014 Samsa 1999	Leppert 2015 Kim 2011	CNSR study 2011 Pennlert 2014	Leppert 2015 Kim 2011	EAST study CNSR study TIMS-CHINA
Frønsdal 2018 Norway	AIS due to LAO 68 years	MT+IV tPA IV tPA alone	CUA Markov model Healthcare payer 25 years	2016 Norwegian kroner (NOK)4%	HERMES	Kristoffersen 2016. SSB Life Tables 2015	Frønsdal 2016		Ganesalingam 2015	Swedish Dental and Pharmaceuticals Agency (TLV) (Thunman 2015)

CUA= Cost utility analysis, MT= Mechanical thrombectomy, IVT = Intravenous thrombolysis, **(Trippoli 2018) = reported QALYS, Net monetary benefit (NMB) and tender-based scores for four thrombectomy devices, SHSC= Scottish Health Services Costs,

Study Country	Population	Intervention/ comparator	Type of analysis Study design Perspective Time horizon	Currency Discount Rate	Sources of Data for model inputs				
					Efficacy outcomes	Death probabilities	Recurrent Strokes	Utilities	Costs input
Cost effectiveness									
Trippoli 2018 Italy**	Patients with acute ischaemic stroke	MT+IV tPA IV tPA alone	Net monetary benefit Markov model Time horizon: 5 years	3.5%	MR CLEAN Saver (HERMES) 2017 Almondoz 2016 FDA 2017	ISTAT 2005	MR CLEAN Saver (HERMES) 2017 Almondoz 2016 FDA 2017	Leppert	Ganesalingham 2015
Achit 2017 France ♦	Age:62.8	MT+IV tPA IV tPA alone	Economic evaluation along clinical trail Healthcare system Time horizon: 1 year	Euros Not discounted	THRACE trial ♦	THRACE trial♦	THRACE trial♦	THRACE trial♦	THRACE trial♦
Carlsson 2017 Sweden	Age 18-84	MT+IV tPA IV tPA alone	Decision-analytic model and Markov model Societal perspective Time horizon: Lifetime (25 years)	2015Swedish Krona (SEK) converted to British Pounds (GBP 3% discount	Riksstroke Pooled RCTS	Riksstroke Pooled RCTs	Riksstroke Ganesalingham Leppert	Rivero-Arias 2010	Riksstroke Skane Hospital records (10 patients)
de Andres-Nogales 2017 Spain	Patients with LVO Age: 66	MT+IV tPA IV tPA alone	CUA Markov Model. Healthcare system Time horizon: Lifetime (275 days, then I year afterwards)	Euros Cost year 2016 Discount rate: 3%	SWIFT PRIME	Instituto Nacional de Spanish mortality table 2013 Slot 2009	Mohan 2011	(Luengo-Fernandez 2013, Rivero-Arias 2010)	Rubio-Terre´s Mar 2011 Pin˜ol 2007 Oblikue 2016 Consejo 2016
Irish HTA 2017 Ireland	>18 Years Mean age 70 years	MT+IV tPA IV tPA/standard care alone	CUA, Markov decision-analysis model, Publicly funded health and social care system. Time horizon: 5, 10 years	Euros Discount rate: 5%	Six RCTs	Ontario HTA 2016	Ontario HTA 2016	Samsa 1999 Dorman 2000 Rivero-Arias 2010, Dewilde 2014	Finance Procurement BH Dublin 2016 HIQA (AF) 2015 Giraud 2016 Lightfoot Solutions UK 2015
Simpson 2017 USA	Adult stroke patients	MT+IV tPA IV tPA alone	CUA Decision-analytic model Perspective: payer (Healthcare System), Sweden Time horizon: 30 years	US dollars 2012	Palesch 2015 IMS III	IMS III trial	IMS III trial	IMS III trial	IMS III patients enrolled from USA, Australia and Canada Medicare 2012 billing database

CUA= Cost utility analysis, MT= Mechanical thrombectomy, IVT = Intravenous thrombolysis, ♦not a model-based economic evaluation, performed along the THRACE trial, Ψ= prospective economic evaluation conducted along the SWIFT PRIME trial.

Study Country	Population	Intervention/ comparator	Type of analysis Study design Perspective Time horizon	Currency Discount rate	Sources of Data for model inputs					
					Efficacy outcomes	Death probabilities	Transitional probabilities	Recurrent Strokes	Utilities	Costs input
Cost-effectiveness analysis										
Shireman 2017Ψ USA	Patients with LVO AIS 66	MT+IV tPA IV tPA alone	Prospective designed economic analysis Markov Model Healthcare system	US dollars 2015 3% discount	SWIFT PRIME (2015)	National Death Index (NDI) Hankey 2007	Cohort of US patients linked to NDI	SWIFT PRIME (2015)	SWIFT PRIME Mitchell 1995 cohort of USA patients inked to NDI	
Aronsson 2016, Sweden	Stimulated cohort of patients with AIS. Mean Age 67.2 years	MT Compared with Standard care (Including IV tPA) Stent retrievers	CUA Decision-analytic model Markov Model Healthcare System Time horizon: Lifetime and 30 years	US dollars 2015 3% discount	MR CLEAN, ESCAPE, EXTEND IA, SWIFT-PRIME, REVASCAT (2015)	SCB. Statistics Sweden (2014) Fang 2014 Hankey 2007		Pennlert 2014	Samsa 1999 Burstrom 2006 Dewilde 2014	Ghatnekar 2013, Earnshaw 2009
Kunz 2016 USA	Age:68	MT+IVT (SC) IVT (SC)	Decision-analytic model Markov Model Healthcare System Time horizon: 30 years,	US dollars 2015 3% discount	HERMES (2016)[a,b]	Samsa 1999 Arias 2011	Samsa 1999	Pennlert 2014	Chaisinanunkul 2015, Rivero-Arias 2010 Hong 2009	Reed 2001, Earnshaw 2009, Chambers 2002, Earnshaw 2009, NIS 2012
Lobotesis 2016, United Kingdom	Age:66 Confirmed occlusion in proximal vessel occlusion	MT (SR) + IVT compared with IV tPA alone CE-marked devices	Markov Model CUA Decision analytic model Healthcare System Lifetime (1/2/5 yrs)	2013/14-GBP 3.5% discount	SWIFT PRIME (2015	Slot et al. (2009) Office for National Statistics, UK (2014)	Slot 2009 Jung 2011	Mohan 2011	Rivero-Arias 2010	Multiple UK sources Luengo-Fernandez 2013
Xie 2016, Canada	Patients with LVOS Age:65-71	MT+IV tPA IV tPA alone	CUA Decision-analytic model Markov Public payer Time horizon: 5	2015 Canadian dollars 5% discount	5RCT Health quality Ontario review (2015)	Luengo-Fernandez 2013, Hankey 2007 Mortality, life table 2004, UK (2013)	Oxford Vas-cular Study	Not mentioned Oxford Vas-cular Study	Dorman et al. (2000)	Mittmann 2012, Rai 2015 Leppert 2015, Simpson 2014, Chen 2012, Nguyen-Huynh 2011, Kim 2011, Patil 2009

Author, Year And Country	Population	Intervention/ comparator	Type of analysis Study design Perspective Time horizon	Cost Year Currency Discount rate (%)		Sources of Data for model inputs				
					Efficacy outcomes	Death probabilities	Transitional probabilities	Recurrent Strokes	Utilities	Costs input
Cost effectiveness analysis										
Ontario HTA 2016 Canada	Age 65 to 70 years with LVO stroke	MT with or without IVT IVT tPA alone	CUA Markov decision -analytical model Payer and societal Time horizon 5, 10 and 15 years	2015 Canadian dollars 5% discount	MR CLEAN, ESCAPE, EXTEND IA, SWIFT-PRIME, REVASCAT	Luengo-Fernandez Stroke (2013) Neuro (2013)	Luengo-Fernandez Stroke (2013) Neuro (2013)	Luengo-Fernandez Stroke (2013) Neuro (2013)	Dorman 2000	Mittmann 2012
Medtronic 2016 Australia	Patients with AIS Age Unknown	MT +IVT compared with IV tPA Stent retrievers-	CUA Decision tree analysis Markov Model Healthcare Payer Time horizon, lifetime (I yr)	5% discount	Gensicke 2013 HERMES	Australian life table	Gensicke 2013	Mohan 2011 Hardie 2004	Sturm 2002 Rivero-Arias 2010 Noto 2011 Murphy 200	Tanny 2013 Gloede 2014 Cadilhac 2009 Dewey 2003, 2004, 2001 SWIFT PRIME
Ganesalingam 2015, United Kingdom	Patients with AIS Age Unknown	MT +IVT compared with IV tPA Stent retrievers-	CUA decision-analytic model Markov Healthcare payer System) Time horizon: 20 years	Costs were calculated in 2013–2014 UK pounds and presented in US$ 3.5%	MR CLEAN, ESCAPE, EXTEND IA, SWIFT-PRIME, REVASCAT	ScHARR 2014	ScHARR 2014 Morris 2011 Wahlgren 2007	ScHARR (2014) Morris 2011	Dorman 1997 Morris 2011 Sandercock 2002	British National Formulary ScHARR. 2014 Curtis 2013. Codman 2013
Leppert 2015 United States	Age 66	MT+IV tPA IV tPA	CUA Decision- analytic model Perspective: Societal Time horizon: lifetime	2012 3% discount	MR CLEAN 2015	MR CLEAN 2015 Arias 2010 Samsa 1999	Samsa 1999	Fagan 1998	?MR CLEAN	Reed 2001 Earnshaw 2009
Thurman 2015 Sweden	Age 67 with AIS	MT (Mainly SR) +IVT compared with IVT alone New generation devices	CUA Markov Societal 20 years	2015 Swedish kroner Discount rate not reported /not applied	MR CLEAN, ESCAPE, EXTEND IA, SWIFT-PRIME, REVASCAT (2015)					

Author Year Country	Population	Interventions comparator	Type of analysis Study design Perspective Time horizon	Costing Year Currency Discount rate	Data Sources for model inputs					
					Efficacy outcomes	Death probabilities	Transitional probabilities	Recurrent Strokes	Utilities	Costs input
Cost-benefit										
Mangla 2016 USA	Patients (>18 Years) with AIS due to LVO	MT+IVT compared with IV tPA alone	Cost -benefit analysis Payer Discount not applied Lifetime	**2015** US$	MR CLEAN	Based on Medicare Severity DRG, the				MS-DRG (Medicare Severity Diagnostic-Related Group Godwin 2011 Genworth Financial. 2015
Cost analysis										
Author Year Country	Population	Interventions comparator	Type of study	Currency	Pre-Intervention	Intervention	Post-intervention	Total cost	Others	Hospital/setting
Vega-Valdes 2018 Spain	Adult stroke patients with AIS Average age 71.1years	MT IIVT	Cost-analysis Retrospective data analysis	Euros 2016	Emergency admission, imaging, physician consultation			MT-€6,574.14 IVT: € 636.76		Clinical Costs Management Service of the hospital
Campbell 2017 Australia	Adult stroke patients with LVO AIS mean age of 69	MT+IV tPA IV tPA	Economic analysis Potential impact on resource cost (alongside EXTEND-1A)	Australian dollar 2014converted into US dollars	Interhospital transfer	Alteplase MT consumables MT Staffing	Inpatient care cost	In=patient cost MT- US$15,689. IVT- US$30,569 Total cost MT US$29,371. IVT $33,736		Royal Melbourne Hospital Finance Department
Vidal 2016 USA			Cost savings Retrospective			Devices 5MAX ACE SR				
Rai 2015 USA	Adult stroke patients with LVO Mean age 74.1	MT+IV tPA IV tPA	Financial analysis	US dollars		Devices				Diagnosis related group (DRG) code used for billing the hospital admission.
Comai 2015 Italy	Adult stroke patients with LVO		Cost analysis Prospective data analysis			Devices (ADAPT, SR) Procedure				Bolzano Central Hospital Bolzano, Italy
Kass-Hout 2015, United States	Adult stroke patients with LVO		Retrospective data analysis			Devices Procedure				Marcus Stroke and Neuroscience Center at Grady Memorial Hospital

ADAPT: a direct aspiration first-pass technique, SR: stent retriever

Appendix 7.C - Summary of results (Base case analyses) of MT for acute ischaemic stroke patients within 6 hours of stroke

Author, Year Country		Cost of procedure	Total cost		Incremental costs	QALY		Incremental QALY	ICER	Probability of being cost effective	Conclusion
	Time Horizon		MT+IVT	IVT/ alone		MT+ IVT	IVT alone				
Heggie 2019 UK	Lifetime		£46,684	£39,035	£7649	7.614	5.408	2.207	3466	WTP threshold £í20,000 76% probability of MT being cost-effective, compared with best medical care alone	
Pizzo 2019 UK	20 Years				12hrs- £1995 >16hrs- £6919 >.24hrs- £6466			12hrs- 1.63 >16hrs-1.69 >.24hrs- 2.23	12hrs- $1564 16hrs-$5253 24hrs - $3712	99.9% probability of being cost effective	
Kabore 2019 France	10 Years		€40,195,893	€35,198,650		€2584	€1462		€14715	probability of MT-IV-TPA being cost-effective was 85.4% at threshold WTP of s30,000 per QALY gained, reaching 98% at s50,000 per QALY gained.	
Arora 2018 Australia	Lifetime	£8871 $12438 (Aus$18308)	£49415 $69278 (Aus $101977)*	£44246 $62032 (Aus$91311)*	£5168 $7246 (Aus$10666)*	2.7182	1.8902	0.8281	£6203 $8696 (Aus$12,880)*	Life time cost savings estimated at £3877 [$5434 (Aus$8000)*]	Dominant
Ruggeri 2018 Italy	5 year	£6606 $9279 (€6660)*	£31537 $44214 (€31798)*	£ 34569 $48465 (€34,855)*	£3032 $4259 (€3,057)*	2.52	1.75	0.77	£23793 $33358 (€23,990)* per QALY gained	WTP** £7934 $11124 (€8000)*	Dominant
Pan 2018 China	I year		£15613 $21889 (CNY 77700)	£5470 $76681 (CNY 27220)	-£10143 $14221 (-CNY 50480)	0.405	0.326	0.079	£128397 $180009 (CNY 638987)	WTP** £25260 ($35411) [CNY 125700 US ($19300)]*	
Stoinska - Schneider 2018 Norway	25 years	£10729 $15042 (NOK152 965)*	£5915 $8293 (NOK 84,331)*	£4818 $6749 (NOK 68 634)*	£957 $1342 (NOK 13 645)*				£844.1 $1183 (NOK 12,034)*/ QALY gained	WTP** £35070 $49167 (SEK 500000)*	
Achit 2017 France	1 year		£3806 $5336 (€ 4813)	£2444 $3426 (€3090)	£1362 $1910 (€1723)	0.58	0.46	0.12	£10614 $14881 (€13423)	WTP £30251 $42412 (€33,051)	
Simpson 2017 USA	I year		£43218* $60 590	£34914* $48 948	£8304* $11642	0.5181	0.4737	0.0444	£187028* $ 262207	£187027* $262 207	
Shireman 2017 USA	Lifetime		£153913 ($215781) * (€175882)*	£176463 ($238 984) * (€194795)	- £16550 (-$23 203)* (-€18.913)*	6.79	5.05	1.74	£3481 ($4881) * per QALY gained	£18837 ($22203)* and higher QALYs SR remained under the threshold of £35664(US$50,000)*/QALY	**Dominant** Savings: £16550 ($23 203)*

Author, Year And Country	Time Horizon	Cost of procedure Per case	Total cost		Incremental costs	QALY		Incremental QALY	ICER	Probability of MT being cost effective	Conclusion
			MT+IVT	IVT/ alone		MT + IVT	IVT alone				
Carlsson 2017 Sweden	Long-term	£9352 ($13111)*	£175.210 ($245639)*	£204.886 ($287244)	-£29.677 (-$41606)*	3.637	2.616	1.022	<£ 10,000 ($14020)* per QALY gained		Dominant Savings: £-35 000 ($49069)*
de Andre´s-Nogales 2017 Spain	Life-time	£9142 $12817 (€8428)*	£134360 $188369 (€123,866)*	£182477 $255826 (€168224)	-£48 -$68 (-€44)*	7.62	5.11	2.51	£16319 [$22878 (€15044)*] per QALY gained	savings of £48138 $67488 (€44378)*	**Dominant** £129889 $182101 (€119744)
Irish HTA 2017	5 years		£55932 $78415 (€ 63774)*	£53630 $75187 (€ 61149)*	£2302 $3228 (€ 2626)*	1.306	1.119	0.187	£12293 $17234 €14,016)*	70.1% and 99.2%, at thresholds of < £14265 ($20,000) and < £32098 ($45,000)/ QALY gained,	
Aronsson 2016 Sweden	30 years	£5641 ($7,908*) (€ 6373)*	£49,993 ($70,088)* (€56,482)*	£50,150 ($70309)* (€56660)*	-£158 (-$221)* (-€178)*	2.59	1.6	0.99	£159 ($223)* per QALY gained	At the WTP threshold of £ 7133 (US$ 10,000)*/QALY, MT was cost-effective in 100% of cases cost savings of £158 ($221)*	**Dominant**
Kunz 2016 USA	30 years		-	-	£3509 $4919 €4025			1.59	£2208 ($3096) per QALY gained*	100% probability of being below the WTP threshold of £35664 (US$50,000) /QALY	
Lobotesis 2016 UK	Lifetime	£8480* $12896 €9935	£110,322* $ 154668 €129.247	£143512* $201199 €168.130	-£33,190 -$46531 - €38.884	7.01	4.7	2.31	£79,402* $111319 per QALY gained	99% WTP threshold of £30,000 ($42059)/QALY gained*	Dominant (£-14368) (less costly and more effective) than IVT alone Cost savings of £33,190 ($46531)*
Xie 2016 Canada	5 Years		£72362 $10499 ($CAD126 939) (€82484)*	£70925 $99435 ($CAD124 419)* (€80.846)*	£1437 $2014 ($CAD 2520)* (€1637)*	1.48	1.27	0.21	£6835 $9582 ($CAD11990)* per QALY gained	89.7% and 99.6% at thresholds of £28503 [$39960 (Can$50000)*] and £57005[$7992 (Can$100000)*]per QALY gained,	
Ontario 2016 Canada	5 years		£72362 $101449 (Can$12693 9)*	£70925 $99435 (Can$12441 9)*	£5654 $ 7926 (Can$252 0)*	1.484	1.273	0.210	£5654 $7926 (Can$11,990) per QALY*	57.5%, 89.7%, and 99.6%, at thresholds of £14266 ($20,000)*, £35664 ($50,000)*, and £71328 ($100,000)*/ QALY gained, respectively.	

*Reported currency, *WTP= Willingness to pay. Other currencies converted to United States (US) dollars using 2017 OECD purchasing power parity and then finally converted to United Kingdom pounds

Author, Year And Country	Time Horizon	Cost of procedure	Total cost/ MT+IVT	Total cost/ IVT/ alone	Incremental costs	QALY MT +IVT	QALY IVT alone	Incremental QALY	ICER	Probability of MT being cost effective	Conclusion
Medronic 2016 Australia	Lifetime	£8872 $12438 (Aus$18,308 .49)*	£49415 $69278 (Aus$101,977)*	£44246 $62031 (Aus$91311)	£5168 $7246 (Aus$10,666)	2.7183	1.8902	0.8281	£6241 $8750 (Aus$12,880)* per QALY		The life-time cost savings estimated to be > £3877, $5435 (Aus $8000)*/ patient
Ganesalingham 2015 UK	20 Years	£9,846 ($13, 803)* (€11,206)*	£ 46 190 268 ($64757281)* (€29,735)*	£46190277 ($52 494 730)* (€52,680)*	£8746 669 ($12 262.551)* (€9,955)*	4.84	3.7	1.05	£7061 ($11651)* (€9463)*]per QALY gained	100% probability of cost-effectiveness at WTP threshold of £23538 (US$ 33,000)*/QALY	
Leppert 2015 USA	Lifetime		£ 99899 ($ 140,055)* (€119,957)*	£ 92830 ($130144)* (€111468)*	£7070 ($ 9,911)* (€8489)*	3.80	3.10	0.70	£ 10084 [($14,137)* (€12,921)*]/ QALY gained	98% probability of being below the WTP threshold of ≤£ 35664 (US$50,000)*/QALY	
Thurman 2015 Sweden	20 years				£ 6146 $8616 (78,400 kroner)* (€7,372)*				£3527,$4945 (SEK45,000)* (€4,231)* per QALY gained		
Mangla 2016 USA			£14530 ($20,371)* (€17,291)*	£4129 ($5,788)* (€4,913)*					QALYs were valued at £92,078 $129,090 (€109,574)*]/ year	The direct benefit of MT was valued at £1275 $1,788 (€1,518)* per patient, and the indirect benefit was valued at £115435 [$161,836 (€137,370)]* per patient	
Vega-Valdes 2018 Spain		£7,131 $9,998 (€6,574)*	£17,420 $2,4421 (€16,059)*	£8,861 $12,423 (€8,169)*	£8,559 $11,999 (€7,890)*	NA	NA	NA	NA	NA	
Campbell 2017 Australia	Up to discharge from hospital		£ 20950 ($29,371)	£ 24063 ($33,736)	-£3114 -($4365)	NA	NA	NA			Average cost savings for treatment with MT £3114. US $4,365
Rai 2015	Up to discharge from hospital		£15,117 $21193* (SD£7966) (SD$11168)*	£10,185 $14,279* (SD£5887) (SD$8254)	NA	NA	NA	NA	NA	NA	Net financial gain of £340(±15 089) $476 (±$21 154)* for the EV group and a net financial loss of £250 (± £8677) $1752 (±$12 166)* for the IV group (p=0.3)

* Reported currency, *WTP= Willingness to pay.

Other currencies converted to United States (US) dollars using 2017 OECD purchasing power parity (0.xxxx) and then finally converted to United Kingdom pounds

Appendix 7.D - Summary of results (Base Case Analyses) of MT for acute ischaemic stroke patients within 12 hours, 16 hours and over 24 hours

Author, Year Country	Time Horizon	Time of treatment	Total cost		Incremental costs	QALY		Incremental QALY	ICER	Probability of being cost effective
			MT+IVT	IVT/ alone		MT+ IVT	IVT alone			
Pizzo 2019 UK	20 Years	Within 12 hrs	$37,943,267	$35,397,797	$1564 (£1219)	4698	3071	1.62	£1219	99.9% probability of being cost effective
		Within 16 hrs	$49,419,626	$40,601,040	$5253 (£4096)	4802	3123	1.68	£4903	
		Within 24 hrs	$42,653,404	$34,363,561	$3712(£2894)	4555	2322	2.23	£2894	

Appendix 7.E - Summary of Systematic Reviews of Economic Evaluations

Study	Population	Intervention/Comparators	Types of studies	Economic conclusion
Teljeur 2019 Ireland	Adults with AIS		12 cost utility studies 1 cost utility	
Boudour 2018 France	Adults with AIS	MT with or without IVT Compared with IV tPA/Standard medical therapy	8 studies: 7 cost-utility 1 cost-effectiveness	MT with or without IV tPA was likely to be cost-effective or even dominant.in patients with LAO AIS
Ryu 2018 Calgary, Alberta, Canada				MT was economically dominant (both in cost savings and better outcomes) in patients with LAO AIS
Sevick 2016 Alberta Canada	Adults with AIS	MT with or without IVT Compared with IV tPA/Standard medical therapy	17 studies: 7 Cost- Analyses 10 Cost-utility studies	MT relative to IVT/ standard care was found to be cost-effective using a willingness to pay threshold of $50,000/ QALY

Appendix 7.F Quality assessment of studies

Author Year Country	Type of study	Applicability	Limitations
Heggie 2019 UK	Cost-utility	Partially applicable	Minor limitations
Pizzo 2019 UK	Cost-utility	Directly applicable	Minor limitations
Kabore 2019 France	Cost-utility	Partially applicable	Minor limitations
Arora 2018 Australia	Cost-utility	Partially applicable	Potentially Minor limitations
Ruggeri 2018 Italy	Cost-utility	Partially applicable	Minor limitations
Pan 2018 China	Cost-utility	Partially applicable	Potentially Minor limitations
Frønsdal 2018 Norway	Cost-utility	Partially applicable	Potentially Minor limitations
Trippoli 2018 Italy**	Cost-utility	Partially applicable	Minor limitations
Achit 2017 France	Cost-utility	Partially applicable	Minor limitations
Carlsson 2017 Sweden	Cost-utility	Partially applicable	Minor limitations
de Andres-Nogales 2017 Spain	Cost-utility	Partially applicable	Potential serious limitations
Irish HTA 2017 Ireland	Cost-utility	Directly applicable	Minor limitations
Simpson 2017 USA	Cost-utility	Partially applicable	Potential serious limitations

Shireman 2017Ψ USA	Cost-utility	Partially applicable	Potential serious limitations
Aronsson 2016, Sweden	Cost-utility	Partially applicable	Minor limitations
Kunz 2016 USA	Cost-utility	Partially applicable	Minor limitations
Lobotesis 2016, United Kingdom	Cost-utilty	Directly applicable	Minor limitations
Xie 2016, Canada	Cost-utility	Partially applicable	Minor limitations
Ontario HTA 2016 Canada	Cost-utility	Directly applicable	Minor limitations
Medtronic 2016 Australia	Cost-utility	Partially applicable	Minor limitations
Ganesalingam 2015, United Kingdom	Cost-utility	Directly applicable	Minor limitations
Leppert 2015 United States	Cost-utility	Partially applicable	Minor limitations
Thurman 2015 Sweden	Cost-utility	Partially applicable	Potential serious limitations
Mangla 2016 USA	Cost-benefit	Partially applicable	Very serious limitations

Appendix 7.G - Resource use and Unit cost

Resource use items and costs	Lobotesis Protocol	Balami micro-costing (All Patients) N=310	Centre A	Centre B	Centre C	Centre D	Centre E
Primary intervention device							
Stent-retrievers							
Unit (mean)	1.2	0.57	0.78	0.92	0.28	0.33	0.46
Std error	NA	0.028	0.051	0.033	0.059	0.066	0.062
95% CI	NA	0.52 - 0.63	0.68 - 0.88	0.86 - 0.99	0.17- 0.40	0.20 - 0.46	0.34 - 0.59
Unit cost	£3,190	£3,120	£3100	£3,100	£3,200	£3,100	£3,100
Total cost	£3,828	£1,778	**£2,418**	**£2,852**	**£896**	**£1,023**	**£1,426**
Thrombo-Aspirators							
Unit (mean)	NA	0.72	0.65	0.32	0.87	0.87	0.92
Std error	NA	0.026	0.058	0.058	0.044	0.048	0.033
95% CI	NA	0.67 - 0.77	0.53 - 0.76	0.21 - 0.44	0.78 - 0.96	0.77 - 0.96	0.86 - 0.99
Unit cost	NA	£921	£872	£880	£1,000	£854	£997
Total cost	**£0**	**£663**	**£567**	**£282**	**£870**	**£743**	**£917**
Total cost of Primary intervention devices	**£3,828**	**£2,442**	**£2,985**	**£3,134**	**£1,766**	**£1,766**	**£2,343**
Catheters and support kits							
Catheter/support kit							
Unit (mean)	**1**	NA	NA	NA	NA	NA	NA
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	NA	NA	NA	NA	NA	NA
Total cost	**£920**	**£0**	**£0**	**£0**	**£0**	**£0**	**£0**
Direct Access Catheter							
Unit (mean)	NA	0.42	0.65	0.23	0.07	0.48	0.66
Std error	NA	0.028	0.058	0.053	0.032	0.070	0.059
95% CI	NA	0.37 - 0.48	0.53 - 0.76	0.13 - 0.34	0.00 - 0.13	0.34 - 0.62	0.54 - 0.78
Unit cost	NA	£595	£595	£595	£595	£595	£595
Total cost	**£0**	**£250**	**£387**	**£137**	**£42**	**£286**	**£393**
Proximal Balloon Flow Arrest Guide Catheter							
Unit (mean)	NA	0.08	0.16	0.06	0.00	0.06	0.09
Std error	NA	0.015	0.045	0.030	0.000	0.033	0.036
95% CI	NA	0.05 - 0.11	0.07 - 0.25	0.00 - 0.12	0.00 - 0.00	-0.1 to 0.12	0.02 - 0.16
Unit cost	NA	£595	£595	£595	£595	£595	£595
Total cost	**£0**	**£48**	**£95**	**£36**	**£0**	**£36**	**£54**
Carotid Stent							
Unit (mean)	NA	0.09	0.18	0.06	0.08	0.06	0.05
Std error	NA	0.016	0.047	0.030	0.036	0.033	0.026
95% CI	NA	0.06 -0.12	0.08 - 0.27	0.00 - 0.12	0.02 - 0.16	-0.01 to 0.12	-0.01 to 0.10
Unit cost	NA	£800	£800	£800	£800	£800	£800
Total cost	**£0**	**£72**	**£144**	**£48**	**£64**	**£48**	**£40**
Total cost of Catheters and supportive kits	**£920**	**£370**	**£626**	**£221**	**£106**	**£369**	**£486**
Consumables							
Procedure Pack							
Unit (mean)	**1**	NA	NA	NA	NA	NA	NA
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	£35	NA	NA	NA	NA	NA	NA
Total cost	**£35**	**£0**	**£0**	**£0**	**£0**	**£0**	**£0**
Drapes/Gowns/Gloves							
Unit (mean)	**1**	NA	NA	NA	NA	NA	NA
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	NA	NA	NA	NA	NA	NA

Total cost	**£80**	**£0**	**£0**	**£0**	**£0**	**£0**	**£0**
Sheath							
Unit (mean)	**1**	NA	NA	NA	NA	NA	NA
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	NA	NA	NA	NA	NA	NA
Total cost	**£15**	**£0**	**£0**	**£0**	**£0**	**£0**	**£0**
Drapes/Gowns/Gloves, procedure pack and others							
Unit (mean)	NA	**1**	1	1	1	1	1
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	NA	£200	£100	£200	£181	£275
Total cost	**£0**	**£191**	**£200**	**£100**	**£200**	**£181**	**£275**
Total cost of Consumables	**£130**	**£191**	**£200**	**£100**	**£200**	**£181**	**£275**
Venue							
Interventional Suite							
Unit (mean)	3	2	2	2	2	2	2
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	£150	£405	£405	£405	£405	£405	£405
Total cost of Venue	**£450**	**£810**	**£810**	**£810**	**£810**	**£810**	**£810**
Recovery post-MT							
Recovery Area							
Unit (mean)	NA	0.60	1	NA	1	1	NA
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	90.2	90.2	NA	90.2	90.2	NA
Total cost	**£0**	**£54**	**£90**	**£0**	**£90**	**£90**	**£0**
Recovery Nurse							
Unit (mean)	NA	**0.4**	1	NA	NA	1	NA
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	£49	£49	NA	NA	£49	NA
Total cost	**£0**	£20	**£49**	**£0**	**£0**	**£49**	**£0**
Total cost of Recovery post-MT	**£0**	**£74**	**£139**	**£0**	**£90**	**£139**	**£0**
Staffing							
Anaesthetist (Consultant)							
Unit (mean)	4	3	3	3	3	3	3
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	£157	£157	£157	£157	£157	£157	£157
Total cost	**£628**	**£471**	**£471**	**£471**	**£471**	**£471**	**£471**
Anaesthetist assistant							
Unit (mean)	4	3	3	3	3	3	3
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	£58	£58	£58	£58	£58	£58	£58
Total cost	**£232**	**£174**	**£174**	**£174**	**£174**	**£174**	**£174**
Anaesthetist SpR							
Unit (mean)	NA	0.40	NA	NA	£3	NA	£3
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	£60	NA	NA	£60	NA	£60
Total cost	**£0**	**£24**	**£0**	**£0**	**£180**	**£0**	**£180**
Radiographer Band (1)							
Unit (mean)	**3**	**2**	**2**	**2**	**2**	**2**	**2**

Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	£58	£58	£58	£58	£58	£58	£58
Total cost	**£174**	**£116**	**£116**	**£116**	**£116**	**£116**	**£116**
Radiographer Band (2)							
Unit (mean)	NA	0.6	2	NA	2	NA	2
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	£58	£58	NA	£58	NA	£58
Total cost	**£0**	**£35**	**£116**	**£0**	**£116**	**£0**	**£116**
Consultant INR							
Unit (mean)	3	3	3	3	3	3	3
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	£140	£140	£140	£140	£140	£140	£140
Total cost	**£420**	**£420**	**£420**	**£420**	**£420**	**£420**	**£420**
Registrar							
Unit (mean)	3	0.4	NA	NA	3	NA	3
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	£60	£60	NA	NA	£60	NA	£60
Total cost	**£180**	**£24**	**£0**	**£0**	**£180**	**£0**	**£180**
Nurse Band 7							
Unit (mean)	3	3	3	3	3	3	3
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	£58	£58	£58	£58	£58	£58	£58
Total cost	**£174**	**£174**	**£174**	**£174**	**£174**	**£174**	**£174**
Scrub Nurse Band 5							
Unit (mean)	3	3	3	3	3	3	3
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	£49	£49	£49	£49	£49	£49	£49
Total cost	**£147**	**£147**	**£147**	**£147**	**£147**	**£147**	**£147**
Scrub Nurse Band 6							
Unit (mean)	NA	0.4	3	NA	NA	NA	3
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	£58	£58	NA	NA	NA	£58
Total cost	**£0**	**£23**	**£174**	**£0**	**£0**	**£0**	**£174**
Stroke Consultant							
Unit (mean)	NA	3	3	3	3	3	3
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	£140	£140	£140	£140	£140	£140
Total cost	**£0**	**£420**	**£420**	**£420**	**£420**	**£420**	**£420**
Stroke Nurse							
Unit (mean)	NA	3	3	3	3	3	3
Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	£58	£58	£58	£58	£58	£58
Total cost	**£0**	**£174**	**£174**	**£174**	**£174**	**£174**	**£174**
Stroke SpR							
Unit (mean)	NA	0.6	NA	3	3	NA	3

Std error	NA	NA	NA	NA	NA	NA	NA
95% CI	NA	NA	NA	NA	NA	NA	NA
Unit cost	NA	£60	NA	£60	£60	NA	£60
Total cost	**£0**	**£36**	**£0**	**£180**	**£180**	**£0**	**£180**
*FY2/CTI***							
Unit (mean)	NA	0.2	NA		NA	NA	NA
Std error	NA	NA	NA		NA	NA	NA
95% CI	NA	NA	NA		NA	NA	NA
Unit cost	NA	£58	NA		NA	NA	NA
Total cost	**£0**	**£12**	**£0**		**£0**	**£0**	**£0**
Total cost of Staffing	**£1,955**	**£2,250**	**£2,386**	**£2,392**	**£2,752**	**£2,096**	**£2,926**
Total cost of MT intervention	**£7,283**	**£6,135**	**£7,146**	**£6,656**	**£5,724**	**£5,361**	**£6,840**

**Foundation Year 2/Core medical trainee doctor