Stroke Thrombectomy: New Devices, Imaging, Scoring System and Outcomes in the Older Population

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Abstract

In the past several years there have been major developments in the interventional treatment of acute ischaemic stroke. This thesis consists of four projects that I developed throughout my graduate studies.

I started by working on setting up a phase 2 multicentre, randomised, controlled trial to assess the technical safety and efficacy of two new devices to be used in endovascular treatment: the ERIC retriever and the SOFIA distal access catheter. The trial has not yet finished, but partial results are presented.

I went on to investigate the role of imaging in hyperacute stroke management. I developed a validated case archive of computed tomography angiography scans which was used for a radiological course. Assessing trainees reports pre- and post-training showed that there was a significant improvement in rates of major errors and this study concluded that an intensive hands-on radiological course was effective.

While the trial was running, I developed a new technical index of thrombectomy difficulty. This score uses computed tomography angiographic images to evaluate key factors for predicting the expected procedural difficulty. The results demonstrated an excellent inter-rater reliability making this potentially a powerful tool to help with decision making and procedural planning.

Due to limited evidence for mechanical thrombectomy in the older population, I worked on a study to assess the safety and efficacy of this treatment. Patients had more comorbidities, more tandem occlusions, but still good reperfusion rates with a similar safety profile to the younger population. Clinical results at 3 months were poorer than in the younger population, but milder presenting clinical deficits and good reperfusion rates were predictors of good outcomes.

This thesis will first discuss stroke with a review of the evidence for performing mechanical thrombectomy. The projects undertaken during my studies will be discussed and I will finish with a succinct conclusion.

Dedication

To my husband,

The reason of where I am today. Thanks for your ongoing support and unconditional love.

To my parents,

You have helped me succeed along the way with no specific advice, just love and encouragement when I needed it most.

To my late grandparents,

Who have helped raise me and shape my personality from a young age, I know you would be proud of my achievements.

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Working and writing on this thesis, was fascinating and very rewarding, but also challenging at times and I would like to thank a number of people who have helped me along the way.

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Lastly, I would like to thank my family for all their love and encouragement. To my parents who raised me and supported me in all my pursuits. To my sister who has been very helpful during my last two years of studies. I have a deep sense of gratitude to my grandparents who cared for me from a young age and always aimed to teach me what really matters in life. Most of all, I need to thank my loving, supportive and encouraging husband Afshin who put up with me throughout all these years of studies.

Thank you.

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List of Abbreviations

ACA – Anterior cerebral artery

ADAPT – A direct aspiration first pass technique

ADC - Apparent diffusion coefficient

ASCOD - A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: dissection

ASPECTS - Alberta Stroke Program Early CT Score

BASIS - Boston Acute Stroke Imaging Scale

BMI - Body mass index

CAA - Cerebral amyloid angiopathy

CBF – Cerebral blood flow

CBS - Clot Burden Score

CBV - Cerebral blood volume

COPD – Chronic obstructive pulmonary disease

CPD – Continuing professional development

CRF – Case report form

CT - Computed tomography

CTA - CT Angiography

CTP - CT perfusion

DAC - Distal access catheter

DALY - Disability-adjusted life year

DSA – Digital subtraction angiography

DWI - Diffusion weighted imaging

ECASS - European Cooperative Acute Stroke Study

EIS - Early infarct sign

ERIC - Embolus Retriever with Interlinked Cages

FLAIR - Fluid-attenuated inversion recovery

GRE – Gradient echo

HENE Radiology – Health Education North East Radiology

HSRC - Hyperacute stroke research centre

ICA – Internal carotid artery

ICA-T – Carotid terminus

ICC – Intraclass correlation coefficient

ICH - Intracranial haemorrhage

IMS – Interventional management of stroke

INR – Interventional neuroradiologist

IV - Intravenous

IVT – Intravenous thrombolysis

FR – Flow restoration

LACS - Lacunar syndrome

LVO – Large vessel occlusion

MCA – Middle cerebral artery

MDCT - Multidetector computed tomography

MeSH – Medical Subject Headings

MR - Magnetic resonance

MRI – Magnetic resonance imaging

MRP – Perfusion MRI

mRS - Modified Rankin Scale

mTICI – Modified treatment in cerebral ischemia

MTT - Mean transit time

NCCT - Non-contrast CT

NICE - National Institute for Health and Care Excellence

NIHSS - National Institutes of Health Stroke Scale

NINDS - National Institute of Neurological Disorders and Stroke

NHS - National Health Service

OCSP - Oxford Community Stroke Project Classification

PACS - Picture Archiving and Communication System

PCA- Posterior cerebral artery

PICA – Posterior inferior cerebellar artery

POCS - Posterior circulation syndrome

PVD – Peripheral vascular disease

PWI – Perfusion weighted imaging

RCR -Royal College of Radiologists

SAE – Serious adverse effect

SCA – Superior cerebellar artery

sICH - Symptomatic intracranial haemorrhage

SOFIA - Soft torqueable catheter Optimized for Intracranial Access

STABILISE - Stroke: an evaluation of Thrombectomy in the Ageing Brain - including where IV thrombolysis IS contraindicated

SWI – Susceptibility weighted imaging

TACS - Total anterior cerebral syndrome

TIA - Transient ischaemic attack

TICI - Thrombolysis in Cerebral Infarction

tPA - Tissue plasminogen activator

TTDI - Thrombectomy Technical Difficulty Index

TTP - Time to peak

US - Ultrasound scan

WHO - Word Health Organisation

Chapter 1. Introduction to Stroke and Thrombectomy

The World Health Organisation (WHO) stroke definition is: “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24h or leading to death with no apparent cause other than that of vascular origin” (Hatano, 1976).

1.1 History of Stroke

The earliest record of stroke being recognised as its own entity is from over 2400 years ago by Hippocrates of Kos, the father of western medicine (Grammaticos and Diamantis, 2008). The ancient Greeks called this disease cerebral apoplexy which means “struck by lightning” as they had no other reasonable explanation for these symptoms.

It was only many years later, in the 1600s, that Jacob Wepfer from Italy performed cadaveric dissections on patients affected by this disease process and discovered that the blood supply to the brain had been disrupted either in the form of a blocked or a ruptured intracranial artery (Pound, Bury and Ebrahim, 1997). Further research in the 1800s by Rudolf Virchow, the father of modern pathology, confirmed this theory and made advancements in the understanding of thromboembolic disease. It was Virchow who coined the more modern term cerebrovascular insult and from here on this was favoured instead of apoplexy (Leak *et al.*, 2014).

The layman term of “stroke” had been described in 1824 by a physician who noted that this term had been in use for centuries (Pound, Bury and Ebrahim, 1997). This word is likely to have its roots from one of the phrases: “the stroke of God’s hand”, “the mortal stroke”, “the stroke of God” or “the stroke of justice” (Pound, Bury and Ebrahim, 1997). All of these refer to the fact that people believed the patient afflicted by this disease had been struck by a higher power. The term stroke was used in a publication by the Chest and Heart Association in 1962 in a booklet put together by a multidisciplinary team titled: “Modern Views on “Stroke” Illness” (Pound, Bury and

Ebrahim, 1997). It is from this point forward that the term stroke as we know it has been in use regularly within the medical field.

Among famous people, there have been several which have passed away due to stroke. A few of the iconic stroke victims are: Louis Pasteur, Charles Dickens, Nicolaus Copernicus and Alfred Nobel (Leigh, 2007), Figure 1.

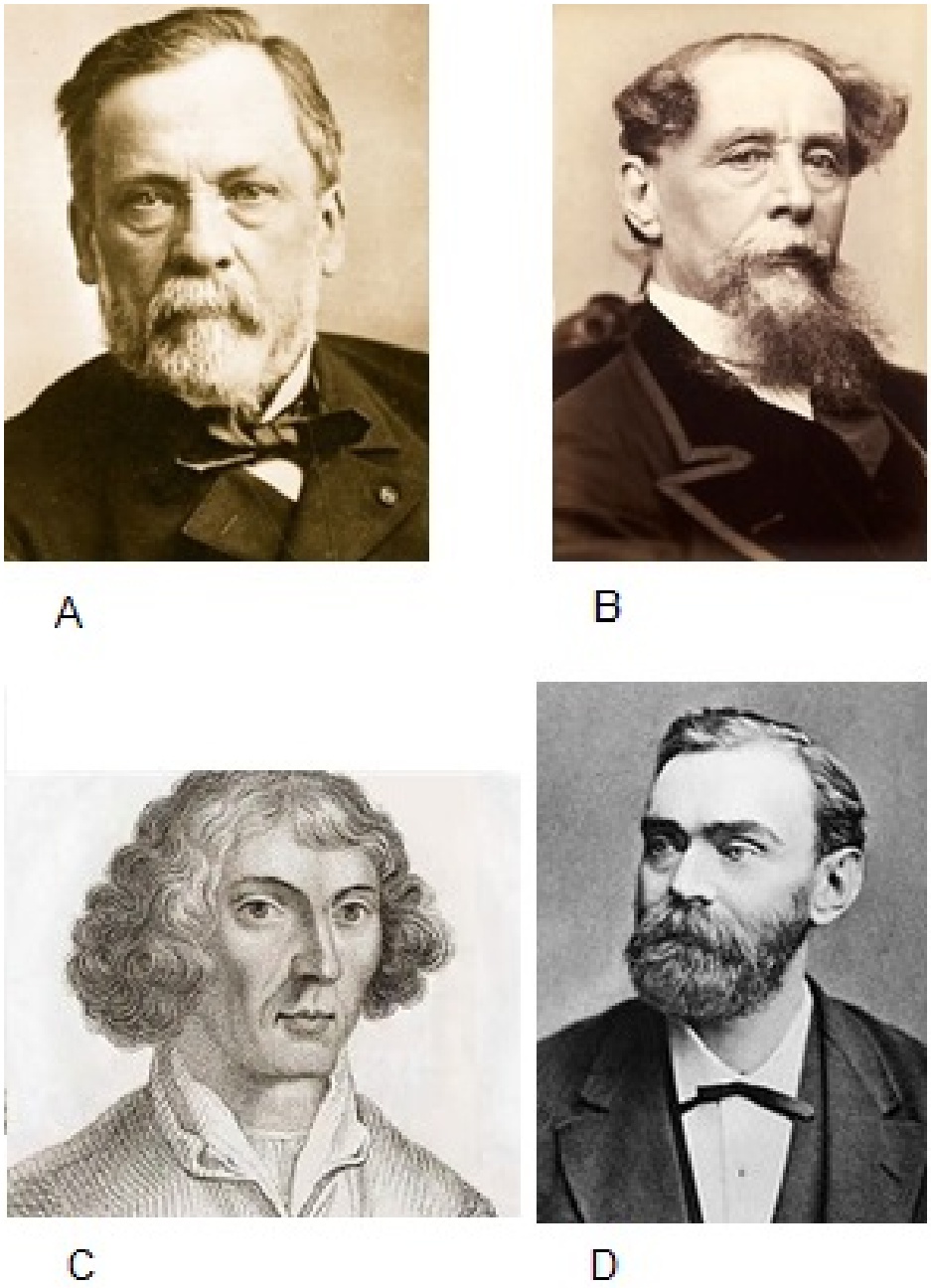


Figure 1 - Famous stroke sufferers

A - Louis Pasteur, B - Charles Dickens, C - Nicolaus Copernicus, D - Alfred Nobel

1.2 Epidemiology

Data from WHO shows that stroke was the 2nd most common cause of death worldwide in 2012, affecting 6.7 million people and representing 11.9% of all deaths (WHO, 2016), Table 1.

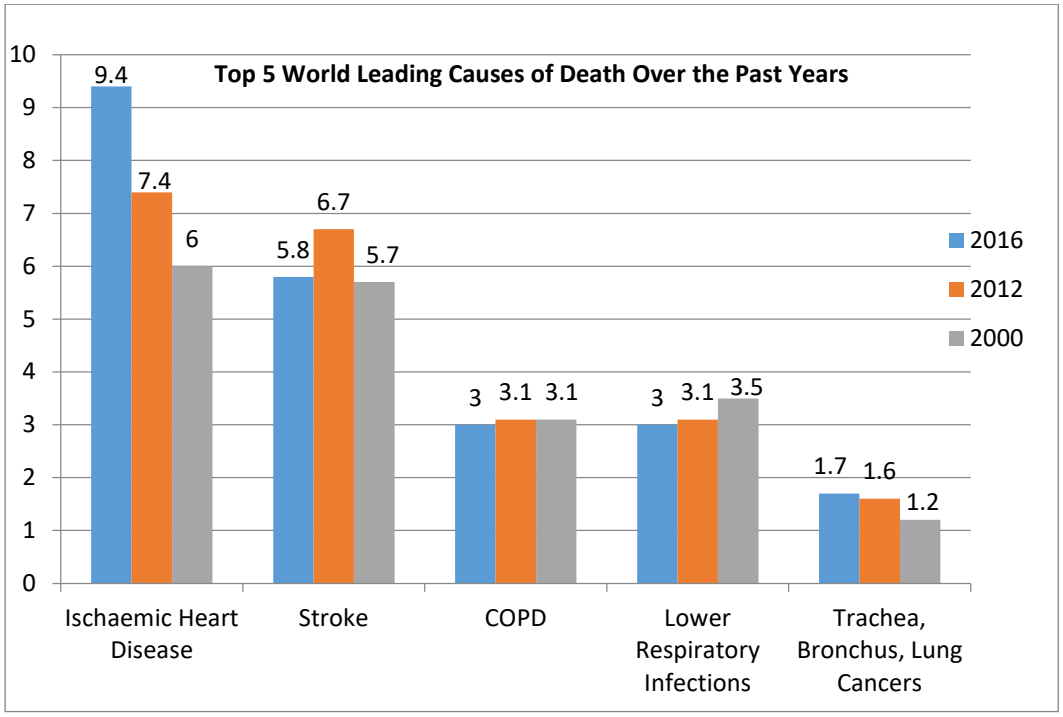


Table 1 - Top 5 causes of death from 2000 to 2016
Adapted from World Health Organization, (WHO, 2016)

A recent paper showed that the worldwide incidence of a first stroke in 2010 was 16.9 million and the prevalence 33 million (Feigin *et al.*, 2014). This is significant as it resulted in 102 million of years lost due to disability or death as measured by the disability-adjusted life years (DALYs). More worryingly however is the fact that over the past 20 years there has been an increase in stroke globally, especially in lower income countries. This is presumed to be due to an increase in the prevalence of risk factors for stroke such as: increasing population age, diabetes, high cholesterol, obesity and smoking (Giroud, Jacquin and Béjot, 2014). Feigin et al. estimate that if the current trends continue, in 2030 there will be almost 12 million deaths, 70 million survivors and over 200 million DALYs due to stroke.

In the UK alone, the yearly incidence of stroke is 152,000 times per year and the prevalence is 1.2 million. 20% of women and 17% of men will have a stroke by the age of 75 (The Stroke Association, 2015). Stroke is the largest cause of complex disability in adults and half of stroke survivors will be dependent on others - either family, friends or professional carers - with regard to their activities of daily living (NICE, 2008b). Similar to the worldwide data, stroke accounts for 11% of all deaths in England and Wales (NICE, 2008b).

It is important to focus efforts and develop innovations both on the preventive measures and the acute treatment of stroke to improve the outcome for this disease.

1.3 Economic Cost of Stroke

The most recent State of the Nation, Stroke Statistics publication from the Stroke Association gives a reliable and updated picture of the amount the UK government is spending on the acute and chronic management of stroke (The Stroke Association, 2015). The average cost for the initial acute and rehabilitation care for one stroke patient is between £23,315 and £26,700. The total yearly amount spent is approximately £9 billion and this is divided as follows:

- £4.4 billion (49%) – health and social care
- £2.4 billion (27%) – informal care costs
- £1.3 billion (15%) – productivity losses
- £841 million (9%) – benefits paid out

This represents ~6% of total NHS (National Health Service) expenditure, which for the financial year of 2014/2015 stood at approximately 140 billion. It is a significant cost to healthcare spending, especially under the current economic climate. Cost effective strategies to help reduce the amount spent on stroke by leading to an improvement in patient outcomes is at the interest of all parties involved.

1.4 Stroke Risk Factors

Identifying the risk factors present, especially modifiable ones, is important because if these can be improved, they may reduce the severity, incidence and overall prevalence of stroke.

The non-modifiable stroke risk factors cannot be altered and therefore can only be taken in consideration when reviewing everything else and assessing the risk of future stroke. There are multiple non-modifiable risk factors as recognised by the American Stroke and Heart Associations are (Meschia *et al.*, 2014) including age, genetics and family history of stroke.

The modifiable stroke risk factors however, could be improved with different medical or even surgical interventions. There have been several studies assessing these risk factors: hypertension, carotid stenosis, atrial fibrillation and diabetes mellitus, just to name a few, are among the medical conditions which are known to increase chances of stroke (Jamrozik *et al.*, 2000; Meschia *et al.*, 2014).

In addition, modifiable lifestyle stroke risk factors such as cigarette smoking, obesity, physical activity, diet, alcohol and drug use are also important to acknowledge (Zhang *et al.*, 2011; Meschia *et al.*, 2014).

If these conditions are identified and managed accordingly before any stroke or transient ischaemic attack (TIA) symptoms occur, that would be the ideal situation. However, many patients will present with TIA symptoms and these patients are at higher risk to have a recurrent event, which may well be a full-blown stroke.

A paper described that interventions aimed at improving blood pressure control and aggressive medical treatment of hyperlipidaemia in their study population led to a significant decrease in atherosclerotic disease and ischaemic stroke (Bogiatzi *et al.*, 2014). These findings confirm the importance of assessing and managing any risk factors which may lead to stroke.

1.5 Stroke Classification

Strokes can be either ischaemic or haemorrhagic in nature. It is largely recognised that approximately 87% of strokes are of ischaemic nature and the other approximately 13% are due to intracranial haemorrhage (Bogiatzi *et al.*, 2014).

1.5.1 Ischaemic stroke

Ischaemic strokes are caused by blockage of an intracranial vessel leading to decreased perfusion of the brain tissue in the supplied territory and ultimately in brain infarction. Ischaemic strokes can be further categorised according to the Oxford Community Stroke Project Classification (OCSP) which relies on the initial clinical signs and symptoms into the following categories (Dewey *et al.*, 2001; Donnan *et al.*, 2008):

TACS – Total Anterior Cerebral Syndrome

PACS – Partial Anterior Cerebral Syndrome

POCS – Posterior Circulation Syndrome

LACS – Lacunar Syndrome

These categories have been demonstrated to correlate well with the findings on CT (computed tomography) scans, as long as lacunar strokes were accepted to be represented within the negative CT scan category (Pittock *et al.*, 2003).

1.5.2 Haemorrhagic stroke

Haemorrhagic stroke accounts for approximately 13% of all strokes and this is further subcategorised into different causes (Feldmann *et al.*, 2005; England *et al.*, 2010). The most important of these are hypertensive haemorrhage, haemorrhagic transformation of a recent ischaemic infarct, aneurysmal subarachnoid haemorrhage, cerebral amyloid angiopathy and rupture of an intracranial vascular malformation.

Stroke symptoms due to intracranial haemorrhage may be indistinguishable from symptoms due to an ischaemic stroke. This is the reason why imaging plays an important role in the acute management of these patients and this will be further discussed in the imaging section.

1.6 Signs and Symptoms of Stroke

Clinical signs and symptoms are usually of sudden onset and will depend on the part of the brain affected. Generally, if a larger part of the brain is affected, patients will have more significant symptoms.

The OCSP classification which has been described above is a good way of categorising the location of stroke. According to the different stroke categories, the main presenting clinical signs and symptoms were described in the original paper (Bamford *et al.*, 1991). Stroke signs and symptoms include: motor or sensory deficits, visual field defects, dysphasia, ataxia.

Total anterior circulation infarcts may present with higher cerebral dysfunction (e.g. dyspraxia), motor or sensory deficits and visual dysfunction.

Partial anterior circulation infarcts have similar symptoms to an anterior circulation stroke but can be milder in character.

Posterior circulation infarcts can present with ataxia, homonymous hemianopsia, cranial nerve palsies and possibly motor or sensory deficit.

Lacunar infarcts can present with motor, sensory or less commonly higher function deficits or ataxic hemiparesis.

In primary or secondary haemorrhagic stroke, the mass effect exerted by the haematoma may also exert compression of adjacent brain structures leading to additional neurological symptoms. There is also the issue that in some patients, there will be further haematoma expansion and development of adjacent brain oedema leading to progressive neurology.

1.7 Causes of Ischaemic Stroke

Determining the cause of stroke in each individual patient is important because this will influence both the short-term and the long-term treatment. One of the most cited studies that has looked at causes of ischaemic stroke and developed a validated method of classifying them was the Trial of Org 10172 in Acute Stroke Treatment (TOAST) (Adams *et al.*, 1993; Adams and Biller, 2015). Based on this system, the Causative Classification System has been developed and offers the advantage of taking into account recent improvements in assessing patients with ischaemic stroke (Ay *et al.*, 2007). Another system is the ASCOD (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: dissection), a phenotyping system which has been developed to also include dissection which is a more common cause in younger patients (Amarenco *et al.*, 2013). According to this system, the different causes of ischaemic stroke are presented next.

1.7.1 Atherothrombosis

Atherothrombotic stroke can be diagnosed if there is evidence of significant atherosclerotic disease causing at least 50%, but usually more than 70% stenosis of the ipsilateral internal carotid artery (ICA). This diagnosis should also be considered if there is evidence of atherosclerosis affecting the aortic arch or the origin of the ipsilateral common carotid artery (Amarenco *et al.*, 2013).

1.7.2 Small vessel disease

A stroke caused by small vessel disease can be diagnosed if there is evidence of two or more lacunar infarcts, which are deep strokes caused by a perforator artery. Microhaemorrhages and dilatation of perivascular spaces are also signs of small vessel disease which may help with reaching a diagnosis (Amarenco *et al.*, 2013).

1.7.3 Cardiac pathology

A cardiogenic stroke can be diagnosed if there is evidence of multi-territorial strokes (bilateral, supra and infra tentorial) and signs of systemic embolism due to a cardiac condition that may be due to atrial fibrillation, patent foramen ovale or a mechanical valve, just to name a few (Amarenco *et al.*, 2013).

1.7.4 Other Causes

There are multiple other causes of acute ischaemic stroke that were mentioned in the original article, the top three being: dolichoectasia with complicated aneurysm; polycythaemia vera and systemic lupus (Adams *et al.*, 1993).

1.7.5 Dissection

Finally, an acute dissection leading to stroke can be diagnosed either by CT or MRI (magnetic resonance imaging) as these can demonstrate the acute findings which range from subtle wall irregularity to a mural hematoma which can be flow limiting (Amarenco *et al.*, 2013).

Except for small vessel disease, the other causes of acute ischaemic stroke discussed above could potentially be treated with intravenous thrombolysis and/or mechanical thrombectomy if patients present early enough to hospital. Before discussing treatment however, it is important to be able to diagnose the type of stroke and imaging plays a key role in this regard.

1.8 Radiological Tests for Diagnosis

In the acute stroke setting it is important to determine as soon as possible whether the patient suffers from an ischaemic or a haemorrhagic stroke event. The subsequent acute and then the secondary management will depend on the type of stroke. In the last 20 years, CT and more recently MRI have been used to differentiate between these two types of stroke and to exclude a stroke mimic. These techniques are further discussed below.

1.8.1 Unenhanced CT Brain

Patients presenting with signs and symptoms of acute stroke need to have urgent imaging assessment to evaluate for evidence of any intracranial haemorrhage and stroke mimics versus an acute ischaemic event. Studies have shown that approximately 30% of patients presenting with suspected acute stroke will have another pathological cause for their symptoms such as seizures, subdural haematomas, infections, etc. (Merino *et al.*, 2013).

The majority of hospitals in the UK will perform a non-contrast CT (NCCT) as an initial assessment due to the fact that this is quick, available 24/7 and easy to obtain (Department of Health, 2008; NICE, 2008a). Current imaging guidelines in the UK recommend brain imaging to be performed as soon as possible and within one hour from arrival to hospital if out of hours (Department of Health, 2008).

The initial NCCT can demonstrate abnormalities at 3 hours from symptoms onset in up to 41% of patients having an acute ischaemic stroke (The IST-3 collaborative group, Wardlaw, 2015). Early infarct signs on CT can be difficult to appreciate as these changes can be very subtle. It is important to review for presence of brain swelling and sulcal effacement which could be reversed if there is timely reperfusion of the ischaemic brain tissue (Wardlaw and Mielke, 2005; Butcher *et al.*, 2007). Hypoattenuation of the cortex or the deep grey matter is more likely to represent irreversibly infarcted tissue (Butcher *et al.*, 2007). The presence of a hyper attenuated intracranial artery on NCCT, e.g. the dot sign, raises the suspicion of an intracranial thrombus (Wardlaw and Mielke, 2005).

To further improve detection of these subtle imaging findings, review of thin slices and using a narrower window width setting centred around 40 Hounsfield units with a window width around 10, a technique called “stroke window”, will help increase the contrast for the human eyes to be able to detect subtle pathology (Srinivasan *et al.*, 2006). The presence of underlying small vessel cerebrovascular disease, old infarctions or other brain pathology can make this assessment extremely challenging (Wardlaw *et al.*, 2007). Importantly, evidence of pathology such as old strokes, leukoaraiosis and brain atrophy should be considered when assessing patients for IVT (intra-venous thrombolysis) or thrombectomy, as they have been shown to predict poorer clinical outcomes and increased rates of intracranial haemorrhage post treatment (The IST-3 collaborative group, Wardlaw, 2015; Kongbunkiat *et al.*, 2017).

Specialist reporting by a neuroradiologist, although available only in certain centres, has been shown to be more accurate at detecting signs of acute stroke on NCCT (Wardlaw et al., 2010). Scoring systems have been developed to improve detection of these subtle findings, the most widely used one is the ASPECTS (Alberta Stroke Program Early CT Score) score, and routine use of this tool helps with report consistency (Wardlaw et al., 2010). A normal brain will have a total score of 10 and 1 point is subtracted for each part of the following MCA territory parts that shows acute signs of infarction: caudate head, lentiform nucleus, internal capsule, insula, and then 6 parts of the MCA cortex (M1 – M6) as illustrated in Figure 2 (Barber, Demchuk, Zhang, & Buchan, 2000).

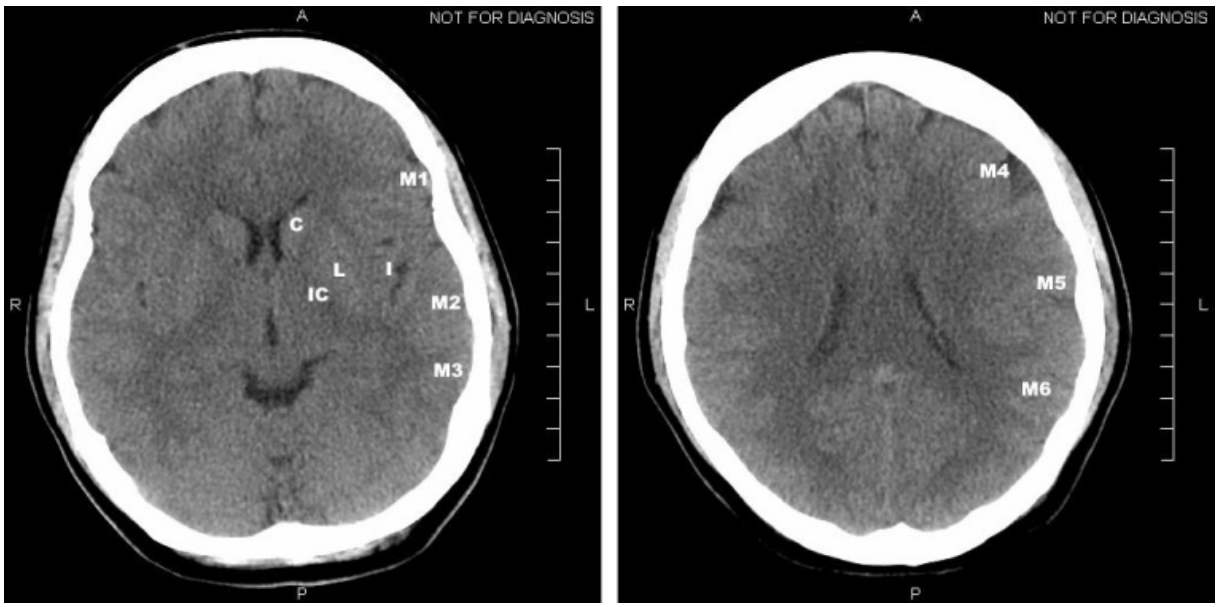


Figure 2 - The APECTS score.

This is composed of 10 regions. C=caudate, L=lentiform nucleus, IC=internal capsule, I=insular ribbon. M1 to M3 regions are at the level of the basal ganglia: M1=anterior MCA, M2=MCA lateral to insula, M3=posterior MCA. M4, M5 and M6 regions are at the level of the lateral ventricles, superior to M1 – M3.

With the advent of artificial intelligence, automated calculation of the ASPECTS score can be performed. A study on 132 patients analysed the performance of the e-ASPECTS software versus experienced neuroradiologists in assessing early ischaemic changes and concluded that e-ASPECTS is not inferior to neuroradiologists (Nagel et al., 2017).

The main purpose of the NCCT in patients presenting with acute signs and symptoms of stroke is to exclude intracranial haemorrhage and other stroke mimics. Although a very useful tool which can help with predicting outcomes, NCCT has its limitations. Because of these, further research has been undertaken to the evaluation of CT angiography (CTA) and CT perfusion (CTP), which will be discussed next.

1.8.2 CT Angiography

Following the initial NCCT, CTA is a fast and reliable method to accurately detect whether there is an intracranial large vessel occlusion (LVO). It allows to clarify whether a more subtle hyper-dense intracranial artery shown on the initial NCCT represents an embolus. Additionally, it shows the entire arterial tree from the aortic

arch to the circle of Willis, allowing to detect any other extracranial pathologies which may be important, e.g. significant carotid stenosis. This additional scan is important as it may lead to a different treatment plan (e.g. IVT followed by endovascular thrombectomy) (Butcher *et al.*, 2007; Berkhemer *et al.*, 2015; Goyal *et al.*, 2015). Some occlusion sites like the basilar artery, the M1 MCA (middle cerebral artery) or the ICA are well known to have poor recanalization rates and prognosis when only IVT is administered (Rha and Saver, 2007). In general, the recanalization rates with IVT are reported to be about 43%, but in some locations such as the carotid terminus (ICA-T) it can be 6% to 15% and in M1 MCA occlusions only 20% to 35% (Rha and Saver, 2007). Complete and fast recanalization is very important because this is what will ultimately affect long term clinical outcomes.

Another useful tool for assessing the brain parenchyma for any early ischaemic changes is the evaluation of the CTA source images (Bhatia *et al.*, 2011; Mortimer *et al.*, 2013). Although on its own it is more reliable than the ASPECTS score from the NCCT, when both are combined, they have a good correlation with the patient's clinical outcomes (Bhatia *et al.*, 2011; Mortimer *et al.*, 2013).

CTA has been shown to have a good specificity and sensitivity for the detection of intracranial LVO and arterial stenoses (Menon *et al.*, 2014). Additionally, this is important for the acute evaluation of the intracranial collateral circulation which is what will maintain the blood supply to the ischaemic penumbra potentially prolonging the time window to recanalization (Mortimer *et al.*, 2013). It has been shown that the patient's collateral status is an important factor influencing clinical outcomes after mechanical thrombectomy (Menon *et al.*, 2014).

Multiphase CTA has been developed to further assess the collateral status by providing additional temporal resolution. It is less affected by motion artefact and does not require any additional contrast administration (Goyal *et al.*, 2015). In addition, the actual thrombus is better estimated than on single phase CTA and it has been shown to improve the accuracy of detecting distal occlusions which may be missed on CTA (Yu *et al.*, 2016).

1.8.3 CT Perfusion

CTP is an additional tool available on most modern CT scanners which can provide additional information regarding the brain penumbra region, which is the salvageable ischaemic parenchyma, and the established ischaemic core, which represents the infarcted brain parenchyma (Schellinger, Fiebach and Hacke, 2003; Schramm *et al.*, 2004; Tan and Goddard, 2007; Department of Health, 2008; Lui *et al.*, 2010; Eastwood, Lev and Provenzale, 2012). The CTP data is obtained by repeatedly acquiring brain images after an initial contrast bolus from which typically the cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and time to peak (TTP) are calculated (Schellinger, Fiebach and Hacke, 2003; Tan and Goddard, 2007; Lui *et al.*, 2010; Eastwood, Lev and Provenzale, 2012). Acquiring the CTP data usually has a higher patient radiation dose, although a dose of about 2mSv, similar to the NCCT, can be achieved if the scanner settings are carefully adjusted (Cohnen *et al.*, 2006; Castillo, 2010).

CTP is especially useful in strokes affecting the posterior circulation as these regions are usually very difficult to evaluate on NCCT due to artefact (Lui *et al.*, 2010). To interpret CTP images, the MTT and/or TTP is evaluated as this demonstrates the amount of ischaemic brain parenchyma, while the CBV, if low, will correspond to already established infarction. The penumbral region will show a raised TTP, but a preserved or increased CBV; while the core infarct will show a raised TTP with a low CBV (Wardlaw *et al.*, 2014). To help with interpretation, there has been development of automated software (e.g. Olea, RAPID). A study on the use of RAPID software revealed rare technical failures, reliability in helping to make clinical decisions and showed this tool to be faster than using automated perfusion-diffusion MRI scans (B. C. V Campbell *et al.*, 2015).

Finally, the acquired CTP data can be used to obtain a CTA of the circle of Willis in a similar way to the multiphase CTA, but with a lower resolution. As there is a temporal component, this CTA could be reformatted to demonstrate time resolved images and better assess intracranial vascular flow. Further studies on this technique to assess reliability are still required.

1.8.4 MRI and MRA

MRI and MRA (magnetic resonance angiography) are both currently indicated in the UK in certain clinical situations (e.g. atypical strokes, dissections) and when there is uncertainty on the initial CT/CTA imaging (Department of Health, 2008; NICE, 2008a). When compared to CT, MRI is more expensive to perform and less available especially out of hours (Department of Health, 2008; Kane *et al.*, 2008). In addition, MRI takes a longer time compared to CT, there is the need to ensure all medical equipment is compatible with MRI, and overall is more difficult to tolerate by patients especially when they are unstable (Hand *et al.*, 2005). All these factors together with the fact that MRI scans are more difficult to interpret and may require a specialised neuroradiologist opinion, limit its utility in hyperacute stroke initial evaluation.

However, the possibility of using both DWI (diffusion weighted imaging) and PWI (perfusion weighted imaging) has significant advantages. PWI is able to demonstrate a focal area of hypoperfusion, while DWI can depict small areas of infarcted brain parenchyma, even in areas such as the posterior fossa that are usually more difficult to assess on CT/CTA. DWI abnormalities need to be assessed in conjunction with the ADC (apparent diffusion coefficient) map, because acute ischaemia will demonstrate a low ADC. Post stroke, the ADC values with gradually increase and return to normal over a period of 5 to 10 days (Lansberg *et al.*, 2001). A mismatch between the DWI and the PWI can be used to identify patients that will benefit from hyperacute treatment and this was utilised as part of the inclusion criteria in a few trials: MR RESCUE, DEDAS, DIAS 2 (Furlan *et al.*, 2006; Hacke *et al.*, 2009; Kidwell *et al.*, 2014).

Another important subgroup of patients are those with an unknown time onset or wake-up stroke which account for 25 to 30% of patients with acute ischaemic stroke (Rimmele and Thomalla, 2014). A mismatch between the DWI and FLAIR (fluid attenuated inversion recovery sequence) sequences has been used as a substitute to time the onset of stroke between <3 to 4.5 hours and this mismatch has high positive predicted value (Aoki *et al.*, 2010; Petkova *et al.*, 2010; Thomalla *et al.*, 2011). The MR WITNESS trial demonstrated that it is safe to administer intravenous thrombolysis within 4.5 hours of stroke symptoms discovery in patients with unknown stroke onset time when using DWI:FLAIR mismatch on MRI (Schwamm *et al.*, 2018). The WAKE-UP randomised control trial selected patients for thrombolysis

administration using DWI:FLAIR mismatch in patients with unknown time of symptom onset and concluded that they had better functional outcomes, but also more intracranial haemorrhages and deaths at 3 months (Thomalla *et al.*, 2018).

Other important MRI sequences which should be obtained in all stroke patients are a gradient echo (GRE) and/or susceptibility weighted imaging (SWI) as these can identify intracranial haemorrhage that could otherwise be overlooked on other standard sequences. GRE sequences can identify microhaemorrhages and this is important because if they are present, they may indicate a higher risk of haemorrhage, especially with IVT and may alter the hyperacute treatment (Linfante *et al.*, 1999; Kidwell *et al.*, 2002).

Susceptibility-weighted imaging (SWI) can more readily detect acute brain haemorrhage and micro-bleeding areas in acute ischaemic stroke or haemorrhagic consequences of intra-arterial thrombolysis. It can reveal abnormalities impossible to detect with other methods (Skalski, Kessler and Bhatt, 2018), but SWI sequences may be more difficult to interpret and radiologists need to be aware of its different appearances depending on the magnetic field strength, in states of low blood flow or low level of oxygenation (Bosemani *et al.*, 2014).

1.9 Acute Treatment

The long-term outcome for patients affected by acute ischaemic stroke depends on whether the affected ischaemic territory has been timely reperfused and to what extent. The possible outcomes range from full clinical recovery to death and this is commonly assessed on the modified Rankin Scale (mRS) (Banks and Marotta, 2007), see Appendix A - Modified Rankin Scale.

The introduction of stroke unit care has been shown to significantly benefit stroke patients with reduction in the odds of death, dependency or institutionalised care that was seen across all groups of patients (Trialists'Collaboration, 2013). Until a few years ago, the only approved acute treatment for acute ischaemic stroke has been intravenous thrombolysis. More recent advancements in technology have allowed for

endovascular treatments and devices to be developed and their efficacy have been proven in multiple recent clinical trials (Lackland *et al.*, 2018).

1.9.1 Intravenous Thrombolysis

The earliest records of using a medical thrombolytic drug was in 1958 when Sussman and Fitch started to administer intravenous fibrinolysis to several patients which had a confirmed LVO on angiography (Sussman and Fitch, 1958). They did demonstrate that complete or partial recanalization was achievable, but there were doubts about the usefulness of this intervention. However, this initial case series opened the gate for further research into this drug.

Subsequently, randomized controlled trials in patients presenting with acute ischaemic stroke started in the late 1980s. Different intravenous thrombolytic medications were used, but the earlier one which was streptokinase, did not demonstrate efficacy across several trials (Multicentre Acute Stroke Trial-Italy (MAST-I) Group, 1995; Donnan *et al.*, 1996; Group, 1996).

The search continued and in 1995 a trial comparing alteplase versus placebo demonstrated that the intervention group was at least 30% more likely to have mild or no disability at three months after the stroke event, when treated within three hours of symptom onset (The National Institute of Neurological Disorders and Stroke tPA Stroke Study Group (NINDS)., 1995). Compared to the other studies, the patients within this trial received faster treatment (<180 min).

Later, in 2008, the ECASS III trial (Hacke *et al.*, 2008) compared again alteplase versus placebo, but administered it 3 to 4.5 hours after the onset of symptoms. The findings showed a favourable outcome (OR 1.4) and concluded that alteplase is underused due to delayed patient presentation. Next, the IST-3 trial (Sandercock *et al.*, 2012) found that administration of IV tPa (intravenous tissue plasminogen activator) up to 6 hours after onset of symptoms is still beneficial, even for patients older than 80 years of age. In 2014 the VISTA meta-analysis underpinned the approval of intravenous thrombolysis with alteplase as a treatment for patients presenting with acute ischaemic stroke within three hours (Emberson *et al.*, 2014).

1.9.2 Thrombectomy Development

There is a significant number of patients for which IV tPA cannot be administered due to the time delay at presentation and to the long list of absolute and relative contraindications. In recent years there have been significant advancements in endovascular devices for clot retrieval and thrombectomy is now a proven treatment which has been approved by NICE (NICE, 2016).

The first historical usage of an intra-arterial treatment in acute ischaemic stroke was the local administration of a thrombolytic drug in the vessel of interest in order to promote clot lysis (Del Zoppo *et al.*, 1998; Suarez *et al.*, 1999; Ernst *et al.*, 2000). The PROACT II study was a randomized controlled trial comparing an intra-arterial infusion of recombinant prourokinase versus placebo in patients presenting with acute ischaemic stroke and with evidence of a proximal MCA occlusion on angiography (Furlan *et al.*, no date). This study demonstrated that patients within the intervention group had significantly higher recanalization and better long term outcomes (Furlan *et al.*, no date; Del Zoppo *et al.*, 1998). This type of treatment however was not recognized by NICE and if delivered, this was done off label. Some practitioners used other intra-arterial infusions in a similar fashion to try and improve clot lysis and other interactive agents administered were tPA, abciximab, etc (Abou-Chebl *et al.*, 2005). At that time, no advanced clot retrievers were available and later on the results of the SYNTHESIS trial (Ciccone *et al.*, 2013) performed in 362 patients, comparing endovascular therapy with IV tPA in patients presenting with acute ischaemic stroke within 4.5 hours showed that endovascular therapy is not superior to IV tPA treatment.

In addition to this type of treatment, some neurointerventionists used the method of clot disruption by using a microwire which had a J or C shape at its tip. This was done by blindly doing multiple passes through the clot and thus achieving a mechanical clot disruption. The results with this kind of technique were variable.

Together with the introduction of flexible intracranial balloons which were originally designed for angioplasty and / or coiling via the balloon remodelling technique, a new method emerged which was basically another type of mechanical clot disruption by performing angioplasty of the occluded segment (Ringer *et al.*, 2001).

After the development of intracranial stents which had their primary use for stent assisted coiling of aneurysms, it was incidentally discovered that they could potentially be used in thrombectomies. The SARIS trial (Roth *et al.*, 2010; Levy *et al.*, 2011), which was a pilot, study demonstrated that deploying a stent in an acutely occluded vessel had high recanalization rates and good clinical outcomes. This procedure however requires dual antiplatelets and this was a major disadvantage for the technique.

These different methods were used off-label by different groups to treat patients and as anecdotal evidence grew, eventually the understanding that mechanical thrombectomy could potentially result in significant improved outcomes in acute ischaemic stroke is what led the way to further progress. The belief that this treatment has the potential to change the potentially devastating outcomes in acute ischaemic stroke due to LVO is what led the way in the quest for the development of specific, purpose built thrombectomy devices.

1.10 Mechanical Thrombectomy Devices

1.10.1 First generation – Merci retriever

The first device made specifically for this purpose was the Merci retriever and this was approved by the FDA in 2004 (Gobin *et al.*, 2004). This device had basically a corkscrew at its distal tip which would be screwed into and so engage the clot before retrieving it. The catheter used to deliver this device was placed into the common carotid artery, at its bifurcation, and a balloon inflated to obtain blood flow reversal. Even with this precaution however, a relatively long course of catheter retraction was often necessary, and this was not ideal from a mechanical point of view as the captured thrombus could become disengaged and / or fragmented. Even allowing for these negative points, the Merci trials demonstrated an overall revascularisation rate of 43% to 55% (Smith *et al.*, 2005; W.S. Smith, 2006; Flint *et al.*, 2007). The IMS III trial (Broderick *et al.*, 2013) demonstrated that unfortunately this was not associated with a significant increase in good clinical outcomes, which were defined as patients being functionally independent and correlated to a post stroke mRS of ≤ 2.

The ultrasound assisted microcatheter devices (EkoSonic Endovascular System and EKOS MicroLysUS catheter) were first introduced in the early 2000's. The microcatheter was placed within the thrombus and allowed the thrombolytic agent to be infused inside the clot while at the same time the device would create ultrasound vibrations to reach clot thrombolysis faster (Mahon *et al.*, 2003). The idea is that this combination accelerates thrombolysis as the ultrasound generates radial pressure that speeds up the dispersion of the drug (Kuliha *et al.*, 2012). This system was considered less damaging than the rotational devices and after successful partial recanalization, further endovascular treatment with angioplasty and stenting was carried out.

1.10.2 Second generation – Penumbra aspiration system

The Penumbra aspiration system was marketed in 2008 and this technique involved macerating the thrombus by repeatedly passing a separator through the clot while at the same time applying suction to remove the dislodged fragments and to prevent distal embolization (The Penumbra Pivotal Stroke Trial Investigators, 2009). This technique used a large catheter (5 French) to deliver the system very close to the proximal aspect of the clot. To achieve this, a more flexible large bore catheter able to navigate through the intracranial vasculature was developed and used. This was essentially an intermediate catheter with a wide diameter which was delivered co-axially, its advantages being that it could deliver higher suction and thus remove more material, but because of its size it had also a major disadvantage in that it was more difficult to navigate distally. However, once this catheter was in position, the thrombectomy procedure could be performed without having to navigate again the device to the clot as was the case for the Merci device.

The Penumbra catheters were further improved and in 2012 the Max catheters were introduced. These are available in three different sizes and have a larger proximal lumen to increase aspiration efficiency while at the same time being more flexible to allow for easier navigation. Whereas previous catheters needed to be advanced over a microcatheter, especially when advancing past the ophthalmic artery, this catheter due to its multiple transition zones giving it greater support and flexibility, could be advanced with only a guiding microwire.

1.10.3 Third generation – Stent retrievers

The first case in which a stent retriever device was used, according to literature, was in 2007 in Cleveland (Kelly, Furlan and Fiorella, 2008) with an Enterprise stent and then this technique was again used in 2008 in Germany with a Solitaire stent (Pérez *et al.*, 2012). These devices are basically stents which are deployed intracranially, allowed to expand and engage the thrombus before being retrieved with concomitant suction via a large bore catheter, Figure 3 .

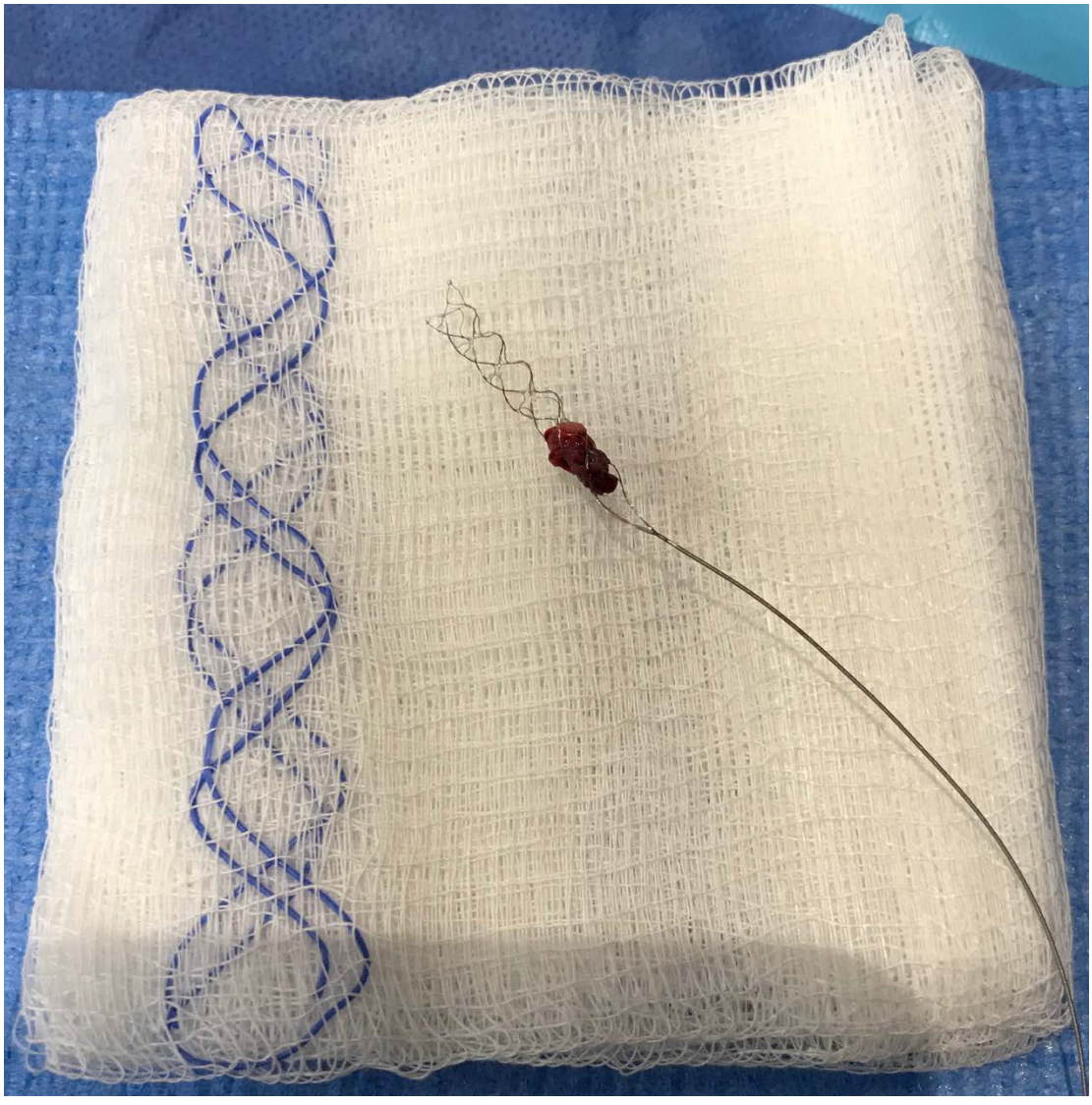


Figure 3 - Trevo stent with thrombus
This is a picture of a Trevo stent used to retrieve the shown thrombus in a patient who had an M1 MCA occlusion.

The microcatheter is first placed past the thrombus, then via unsheathing the stent is deployed and expanded with radial force applied externally as it engages the clot. While the stent is open, there is restoration of blood flow to the ischaemic brain territory, and once the clot is fully engaged, the stent is retrieved into the guiding catheter. The advantage of this technique is that there is no permanent stent deployed intracranially and the need for keeping patients on dual antiplatelets is avoided. The recanalization rate with stent retriever devices was found to be superior to the previous devices (primarily MERCI) in randomised controlled trials published as early as 2012 (Nogueira *et al.*, 2012; Saver *et al.*, 2012). The MR CLEAN trial compared endovascular treatment, done primarily with stent retrievers, with standard medical treatment and it was the first trial to favour endovascular treatment (Berkhemer et al. 2015). It showed improved outcomes in functional independence in the endovascular group (32.6% versus 19.1%) with a similar safety profile. Subsequent trials confirmed this benefit and a meta-analysis from 2016 with individual patient data from five trials showed that for every 2.6 patients treated endovascularly, disability was reduced by one point on the mRS (Goyal *et al.*, 2016). These findings marked a turning point in the treatment of acute ischaemic stroke with endovascular techniques.

1.10.4 Fourth generation – Aspiration technique

The newest thrombectomy technique has developed in part due to advancements being made with regards to the large bore distal access catheters. The developments of Distal Access Catheters (DAC) resulted in larger bore catheters, with improved flexibility, better tracking and a higher aspiration force, Figure 4.

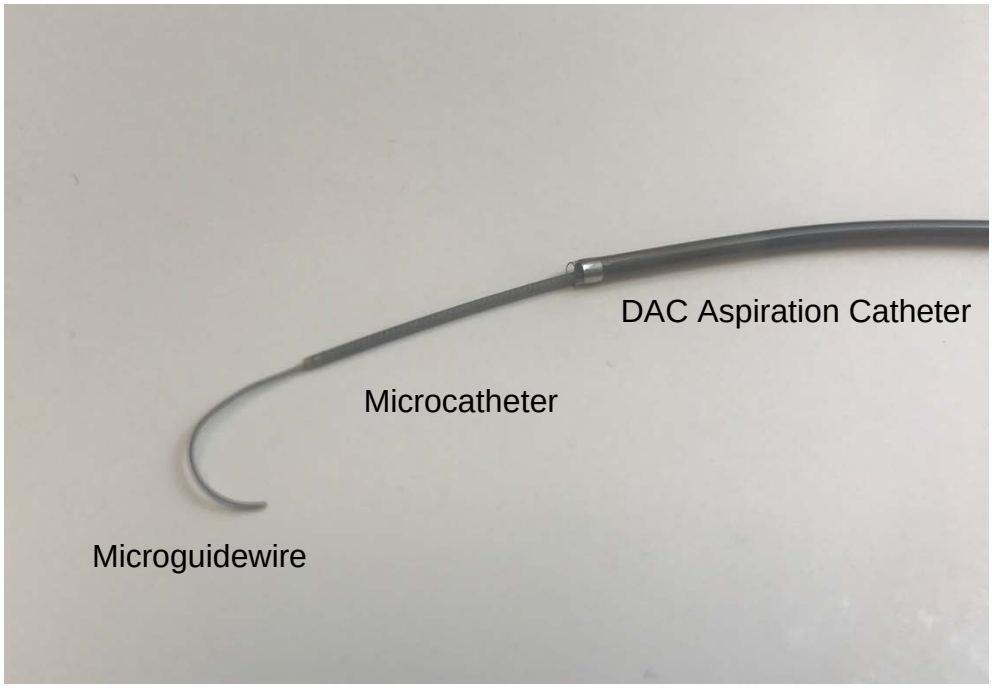


Figure 4 - Distal access catheter
Distal access catheter mounted over a delivery microcatheter and a microguidewire which are used to bring the DAC to the thrombus interface.

The aspiration technique uses the advantages of the DACs. The catheter size is chosen according to the vessel size, with the largest possible catheter chosen for the particular vessel which is occluded. The DAC is advanced to the proximal end of the thrombus and aspiration is applied to engage the clot. Once this is confirmed, the catheter is withdrawn under continuous aspiration via both the DAC and the guiding catheter with the expectation that the engaged clot will basically be “vacuumed” and sucked with the force applied. This technique has the advantage of being faster than the stent retriever technique and if it does not work, the guiding catheter is already in place and a stent retriever device can be placed swiftly and thrombectomy attempted again (Tsang *et al.*, 2018).

1.10.5 Future generations

This is a very rapidly developing field with multiple other purpose specific devices being developed and evaluated. Just over the past decade, at least four different types of devices have been used. The need to improve recanalization rates is what

has been driving these technological advancements, however it is important to remember that ischaemic brain tissue can only survive for a limited period of time and in all thrombectomy cases it is important to judiciously assess the patient and if ischaemic changes are already established, recanalization may be futile and may even lead to disastrous complications.

1.11 Acute Ischemic Stroke Treatment Pathway

In order for patients to achieve good outcomes after an acute ischaemic stroke due to an intracranial large vessel occlusion, there is an important sequence of events that needs to take place. This is very important and the sooner the steps in the patient's journey are done to enable acute treatment, such as administration of IV tPA and mechanical thrombectomy if suitable; the higher the chances of a good clinical recovery post stroke. Below are the steps involved in initial recognition and acute management of patients with acute stroke symptoms:

A) Acute stroke symptoms need to be recognized by the patient or bystanders
B) Call for help promptly
C) Ambulance needs to transfer patient rapidly to the correct medical facility
D) Once in hospital, a quick assessment by a team that has the correct skills is needed to correctly diagnose the type of clinical stroke
E) Rapid imaging to assess both the brain and vasculature
F) Correct radiological interpretation of the scan
G) Prompt delivery of appropriate hyperacute treatment (IV tPA +/- mechanical thrombectomy)

My thesis consists of multiple projects that are present along this pathway with an aim to research and improve delivery of care specifically affecting points E, F and G detailed above that are also modelled in Figure 5.

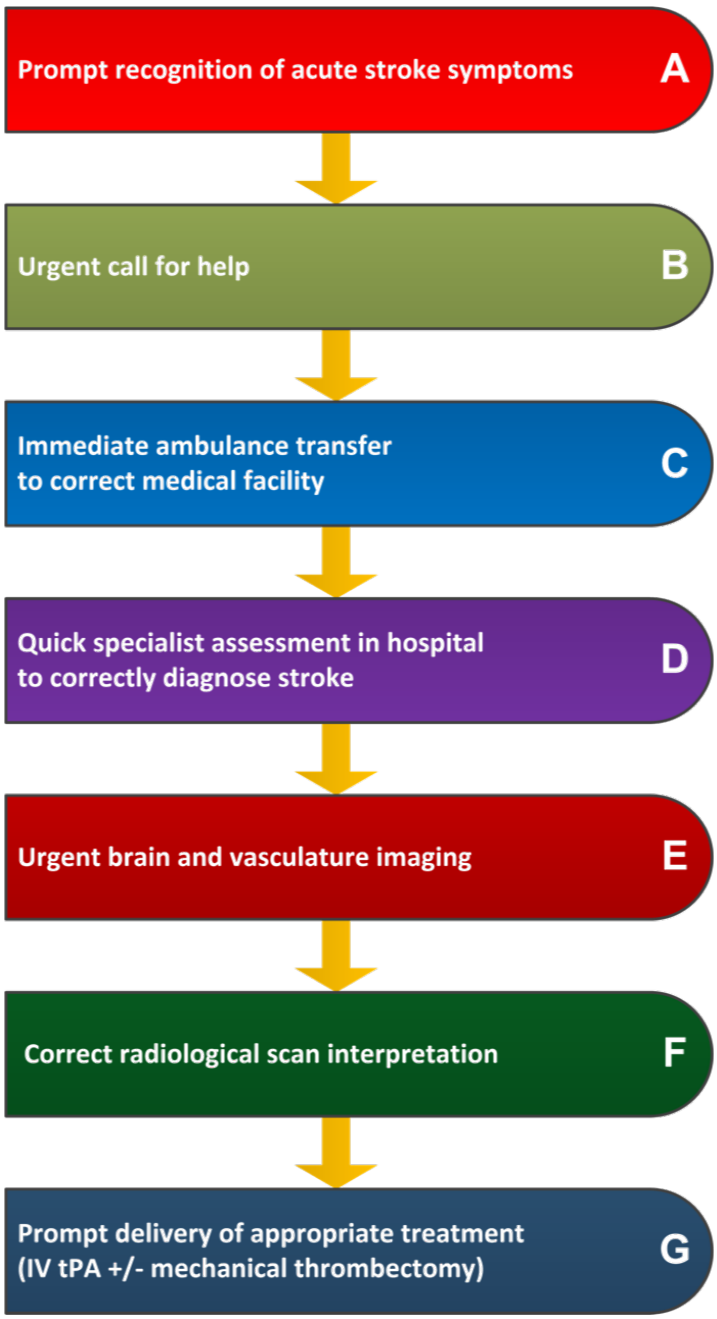


Figure 5 - Acute stroke care patient pathway

All the points demonstrated here are necessary to be done in a fast and efficient manner to achieve the best clinical results possible. The research presented in this thesis specifically affects points E, F and G along this pathway.

1.12 Aims of Thesis

Now that the significance, potential outcomes, economic burden, newly developed acute interventional treatment for acute ischaemic stroke have been described, it is important to recognize the need for further research in this field.

As mentioned earlier, most thrombectomy retriever devices were not specifically developed to perform intra-arterial thrombectomy. A novel retriever device has been developed called ERIC (Embolus Retriever with Interlinked Cages) and this device may be more suitable for performing thrombectomy as it was developed specifically for this purpose. Another device which may also be used during thrombectomies called SOFIA (Soft torqueable catheter Optimized for Intracranial Access) distal access catheter (DAC) has also been recently developed by Microvention Terumo Inc. (Alisa Viejo California).

I will look at the technical efficacy and safety of these two devices as part of a phase 2 trial that I have worked on called STABILISE (**S**troke: an evaluation of **T**hrombectomy in the **A**geing **B**rain – including where **I**V thrombo**L**ysis **IS** contraindicat**E**d).

The acute interventions for acute ischaemic stroke have been developing very rapidly in the past few years and multiple studies have been published during the timespan of my thesis. As new evidence became available, this was incorporated and reflected in my work. There was the need to have a major amendment less than a year into the STABILISE trial to introduce the new SOFIA catheter and to allow for new techniques to be permitted that had developed since the start of the study.

Chapter 2 will look at the evidence for intra-arterial thrombectomy, discuss the main trials that have been published in the past few years and their results.

Chapter 3 will discuss the STABILISE trial, from the methods and aims of the study to the progress to date and the presentation of partial, blinded results.

Chapter 4 will present a project I worked on after new imaging guidelines were developed and will summarize a study focused on improving the CT Angiogram interpretation in AIS.

Chapter 5 is devoted to the development of a technical index of thrombectomy difficulty to facilitate rapid decision making for time critical thrombectomy assessment in AIS.

Chapter 6 will present a multi-centre study on acute thrombectomy performed in the older population, patients that are 80 years of age and older, looking at the efficacy and safety in this subgroup.

Chapter 7 will provide a short synthesis and summary discussion of the previously presented chapters and topics; conclusion and further research considerations.

Chapter 2. Literature Review

As discussed in the previous chapter, there has been recent growing evidence for the treatment of acute ischaemic stroke due to LVO. As this mounting evidence was being published, there were significant changes to the hyperacute management of patients and new societal guidelines published. The objective of this chapter is to determine whether the literature shows that performing mechanical thrombectomy in patients with acute ischemic stroke due to a large vessel occlusion leads to better overall clinical outcomes. I will present the evidence for performing acute intra-arterial thrombectomy in patients presenting with acute ischaemic stroke that is shown on imaging to be due to an intracranial LVO. The evidence for treating both early and late presenting patients will be discussed, especially with regards to the clinical efficacy at 90 days and the safety of this treatment.

During my studies I collaborated on a systematic review and meta-analysis of trials that compared intra-arterial thrombectomy with or without concomitant IV tPA administration with best medical care, including IV tPA (Flynn *et al.*, 2017). This allowed me to develop skills in data extraction, analysis planning and statistical analysis. This project also allowed me to develop my interpersonal skills and learn how to collaborate effectively with others as I was involved with the manuscript revision.

Working on this collaborative project has allowed me to develop the basic research skills and self-reliance to write this chapter of my thesis. I used the search strategy which I had learned from the systematic review paper to complete and update the presented work. Some of the papers presented here are also discussed in the project on which I collaborated, but the way the evidence is organised and presented is very different, making this chapter an original and up to date review of literature. Importantly, this chapter discusses the most recent trial evidence regarding mechanical thrombectomy in patients with stroke presenting later. Additionally, although the evidence is more limited, I also chose to discuss the evidence for performing mechanical thrombectomy in the posterior circulation because this can be very disabling, and patients can also show significant benefit from endovascular treatment.

2.1 Materials and Methods

For this systematic literature review, I selected the randomized controlled trials which had at least 10 adult patients with acute ischaemic stroke symptoms, who had imaging performed to demonstrate LVO and then received mechanical thrombectomy with modern devices or best standard medical care. If available, data on the comparator arm of the study, such as IV tPA or best supportive care, was also collected. For the outcomes assessed, studies needed to have a 90-day follow-up evaluated on a scale such as the mRS or NIHSS among others, and they also needed to report safety and mortality data at 90 days. From the studies that met the eligibility criteria, the secondary outcomes as reported were also collected.

2.1.1 Literature Search

The search strategy has been described in the meta-analysis paper on which I collaborated (Flynn *et al.*, 2017). This was performed with the help of an experienced information scientist and the search was performed up to mid-February 2015. The search strategy used relevant MeSH (Medical Subject Headings) and thesaurus keywords, such as acute stroke, intra-arterial, mechanical, thrombectomy, stent-retrievers, etc. The bibliographic databases and trial registries that were searched included MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, International Standard Randomised Controlled Trial Number Register and ClinicalTrials.gov. Studies that were published before January 2009 were not included as they used older mechanical thrombectomy devices. Selected papers were assessed for quality by looking at the study design, participants, intervention delivered, and outcomes assessed. For inclusion the study needed to be in one of the following categories: randomized control trial, non-randomised trial, controlled before-and-after study or cohort study with prospective assessment. Single center studies, case control studies, cross-sectional study or case series were excluded. Participants had to be adult patients presenting with acute ischaemic stroke. For the interventional arm at least 10 participants had to receive mechanical thrombectomy for the paper to be included. Finally, in the outcomes section papers selected had to

have a follow-up at 90 days on a standardised scale that could be either the mRS, Oxford Handicap Scale, Barthel Index or the NIHSS.

I extended my search and from February 2015 to December 2018 any additional relevant papers that were published were selected. This search was performed by me including all data extraction. My search was performed via MEDLINE and EMBASE using the same relevant keywords and MeSH terms as described above and all papers had to be in English. In addition, I also decided to discuss a few other relevant studies and have added a meta-analysis that included patient level data as it has data from five trials that were pooled together. The evidence for performing mechanical thrombectomy in the posterior circulation is more limited, but I also included a few studies on this as these are also important.

For all the studies that are presented next, I used a structured data extraction form to retrieve the information for each study group population, the intervention performed and then the outcomes.

2.2 Results

The 7 randomised controlled trials that have looked at patients presenting early, within 6 hours of symptom onset, each have had slightly different inclusion criteria, but overall, they have all shown benefit of mechanical thrombectomy with improved functional outcomes at 3 months.

The 3 randomised controlled trials that have included patients presenting later, from 8 up to 24 hours after initial symptoms onset, have also shown benefit of mechanical thrombectomy when using imaging criteria for patient selection.

Since the publication of these trials, there were a few meta-analyses performed, with the most crucial one being an individual patient meta-analysis which accumulated data from a total of 1287 patients that I will also discuss (Goyal *et al.*, 2016).

2.2.1 Anterior Circulation Thrombectomy Trials

MR CLEAN was the first prospective, multicentre, randomized trial of mechanical thrombectomy to demonstrate the beneficial effects of endovascular therapy when compared to the current best medical management (Berkhemer *et al.*, 2015). Patients were randomized either to mechanical thrombectomy plus medical treatment or medical treatment alone, with most patients in this category receiving IV tPA. To be eligible for the trial, patients had to have a proven LVO in the anterior cerebral circulation on imaging and to have the thrombectomy done within 6 hours from stroke symptom onset. The primary outcome of this trial was clinical outcome at 90 days as assessed on the mRS. A total of 500 patients were enrolled across 16 sites in the Netherlands with 233 patients assigned to mechanical thrombectomy and the other 267 patients to medical treatment. Most thrombectomies (82%) were performed using retrievable stents, which at the time had already been shown to be superior to the first-generation Merci device. Results demonstrated clinical independence at 90 days, as assessed by an mRS of 0-2, to be significantly in favour of endovascular treatment: 76/233 (32.6%) versus 51/267 (19.1%), OR 2.05, 95% CI 1.36 – 3.09. There was no significant difference in safety and mortality outcomes in the two groups during the follow-up period of 90 days.

Data from this trial was further analysed to determine whether there is a correlation between timelines to achieve reperfusion and clinical outcomes (Fransen *et al.*, 2016). Data for the patients enrolled in the trial was analysed in terms of procedural timelines: stroke symptom onset to groin puncture and then to reperfusion. The primary outcome was again based good functional outcomes with an mRS of 0 – 2. Their results showed significant positive correlation for a shorter time to reperfusion (p=0.04), but no significant correlation to the start of the procedure as assessed by the time of the groin puncture. In addition, they showed that the treatment effect of mechanical thrombectomy is highest the sooner patients are treated successfully. Further analysis suggested that the likelihood of achieving clinical independence at 3 months reduces by 5% per hour of treatment delay reaching 40% at 8 hours.

For patients originally enrolled in the MR CLEAN trial, long-term outcomes at 2 years after initial treatment have also been published (van den Berg *et al.*, 2017). Outcome data was available for 391 (78.2%) of the original 500 patients, while death information was available for 459 (91.8%) patients. Clinical outcomes at 2 years as

assessed on the mRS were statistically significant and positive for endovascular thrombectomy (adjusted cOR 1.68, 95% CI 1.15 to 2.45, p=0.007). In addition, as a secondary outcome they assessed the quality of life by using the European Quality of Life questionnaire (The EuroQol Group, 1990) and this was also statistically significant and in favour of patients that were treated acutely with mechanical thrombectomy (p=0.006). Mortality data at 2 years, although lower for patients treated with mechanical thrombectomy, was not statistically different among the two treatment groups. Overall, they concluded that the initial better outcomes with endovascular treatment versus best standard care at 3 months were maintained in the long-term at 2 years follow-up.

SWIFT PRIME was another multicentre randomized controlled study assessing mechanical thrombectomy and IV tPA versus IV tPA alone which was performed across 39 centres in North America and Europe (Saver *et al.*, 2015). To be eligible for the trial, patients had to have imaging performed to confirm a LVO in the anterior cerebral circulation and salvageable brain tissue as assessed on the ASPECTS score and CT perfusion. This is one of the first trials to use CT perfusion to assess the penumbral region that represents potentially salvageable brain tissue. Patients aged between 18 - 80 years old were enrolled in the trial and they had to have a good clinical baseline (mRS of 0 - 1). Patients with mild strokes were excluded as there was a trial requirement to have an NIHSS (National Institutes of Health Stroke Scale) of 8 - 30. Endovascular treatment was performed with the Solitaire stent retriever (Medtronic, Minneapolis, MN, USA) and had to be done within 6 hours from onset of acute ischaemic stroke symptoms. The primary outcome was assessment of independence using an mRS of 0 - 2 at 90 days. This study was stopped early due to efficacy with a total of 196 patients being enrolled, with 98 receiving endovascular treatment and another 98 receiving best medical treatment. Functional independence at 90 days was significantly higher in the interventional group as compared to the control group: 59/98 (60%) versus 33/93 (35%) (p<0.001). There were no significant differences in safety and mortality outcomes between the two groups.

EXTEND-IA was a prospective, multicentre, randomized trial of mechanical thrombectomy that enrolled a total of 70 patients with anterior circulation acute ischaemic stroke among 10 centres in New Zealand and Australia (B. C. V. Campbell *et al.*, 2015). Patients were eligible for the trial if they could receive IV tPA within 4.5

hours after onset of stroke symptoms, have a groin puncture within 6 hours with recanalization by 8 hours. They needed to have vascular imaging to demonstrate an occlusion in the anterior cerebral circulation and salvageable brain tissue on CT perfusion. There was no age or stroke severity restriction and patients enrolled needed to be independent at baseline, as assessed by a score of 2 or less on the mRS. This trial used the Solitaire stent retriever for performing mechanical thrombectomy. The study was stopped early, after the publication of the MR CLEAN trial results, due to efficacy. In the intervention group 35 patients received mechanical thrombectomy in addition to IV tPA and in the control group 35 patients received best medical management with IV tPA. Four patients initially randomised to mechanical thrombectomy, did not have this procedure done due to major deterioration or major improvement. The primary outcome showed that 25/29 (86%) patients that underwent endovascular treatment had good revascularization as assessed by an mTICI (modified treatment in cerebral ischemia) of 2b/3. For secondary outcomes, there were 25/35 (71%) patients in the endovascular group that achieved independence at 90 days compared to 14/35 (40%) patients in the IV tPA only group. Their analysis showed that 3.2 patients need to be treated with endovascular therapy for one patient to achieve independence at 90 days. No statistically significant differences were shown for safety and mortality outcomes between the two groups.

THRACE was another multicentre, prospective, randomized controlled trial comparing mechanical thrombectomy and IV tPA with IV tPA alone (Bracard *et al.*, 2016). This trial enrolled a total of 414 patients, 204 in the interventional group and 208 in the control group, across 26 centres in France. To be eligible for the study, adult patients aged 18 to 80 had to have a proven LVO on imaging, either in the anterior or posterior cerebral circulation, either on CTA or MRA. This trial did not have any other imaging-based criteria such as a minimal ASPECTS score or CT perfusion to demonstrate a significant penumbra. The primary outcome was to assess clinical functional independence at 3 months consisting of an mRS of 0-2. Ten patients were excluded from the final results: four due to being lost to follow-up and another six having missing data. Their results showed that patients in the interventional group who received mechanical thrombectomy in addition to IV tPA had better functional outcomes at 3 months when compared to the control group (OR 1.55, 95% CI 1.05–2.30, p=0.028). There was no statistically significant difference between the two groups in terms of safety or mortality.

REVASCAT was a prospective, randomized, multicentre controlled trial conducted in Spain and enrolled patients across 4 centres randomising them either to best medical treatment with IV tPA in the control group or mechanical thrombectomy in addition to best medical treatment, including IV tPA, in the interventional group (Jovin *et al.*, 2015). This trial was stopped early due to loss of equipoise after the positive results from the other thrombectomy trials were reported. Patients could be enrolled if they presented within 8 hours of stroke symptoms onset and had a presenting NIHSS ≥6. Patients needed to be adults aged 18 - 80 and have a baseline mRS ≤1. The LVO had to be confirmed on either a CTA or MRA scan and in addition they needed to have an ASPECTS score ≥7 on CT or 6≥ on DWI MRI. The mechanical thrombectomy procedure was performed with the Solitaire stent retriever. Their primary outcome was the clinical outcome at 90 days as assessed on the mRS and secondary outcomes included the infarct volume on CT or MRI at 24 hours. A total of 206 patients were enrolled with 103 in each group. Their results demonstrated that patients in the interventional group had significantly better outcomes when compared to the control group at 90 days with 45/103 (43.7%) vs 29/103 (28.2%) achieving independence (OR 2.1, 95% CI 1.1 – 4). Similarly, the follow-up imaging demonstrated that there was a statistically significant reduction in the volume of infarcted brain at 24 hours in between the two groups: 16 mls in the interventional group vs 39 mls in the control group, p=0.02. No statistically significant differences were demonstrated between the two groups with regards to either safety or mortality.

Patients that were enrolled in the REVASCAT trial have had their long-term outcomes at one year follow-up published (Dávalos *et al.*, 2017). Data was available for 205 out of the total 206 enrolled patients. Significantly better outcomes with mechanical thrombectomy were sustained to the 12 months end-point with both reduced disability and higher rates of functional independence as assessed on the mRS (mRS=0–2; 45/103 vs 31/103 patients; aOR 1·86, 95% CI 1·01–3·44). Patients quality of life at 1year follow-up was assessed using the European Quality of Life questionnaire and this also showed significantly better outcomes in the interventional group as compared to the control group (p=0·01). There was no statistically significant difference in mortality rates at 1 year. They concluded that these positive results are significant for the assessment of long-term cost-effectiveness of endovascular treatment in acute ischaemic stroke.

PISTE was a prospective, multicentre, randomized controlled trial enrolling patients across 10 UK centres and randomizing patients to either IV tPA alone or IV tPA with mechanical thrombectomy (Muir, Ford and Messow, 2017). Adult patients, with no upper age limit, needed to have either CTA or MRA to demonstrate a LVO on imaging with <1/3 of the MCA territory demonstrating early changes of acute infarction. In addition, there was a time limit of 90 minutes from imaging to groin puncture with a maximum of 6 hours from symptom onset to cannulation of the target occluded vessel. Operators could use any CE marked device for performing the mechanical thrombectomy. The primary outcome was functional independence at 90 days as assessed by an mRS of 0 - 2. A total of 65 patients were recruited in the study with 33 of them being assigned to the interventional group and another 32 to the control group. The trial was stopped early, and the primary outcome was not statistically significant in the intention to treat population, however the patients that were allocated to mechanical thrombectomy achieved independence in a greater proportion compared to those allocated to IV tPA alone 57% vs 35% and this was statistically significant (OR 4.92, 95% CI 1.23 – 19.69, p=0.021). Rates of post-procedural intracranial haemorrhage and mortality up to 90 days were not significantly different in the two groups.

THERAPY was a prospective, multicentre, international randomized controlled trial which enrolled patients in Germany and the United States and evaluated mechanical thrombectomy performed with the aspiration technique and concurrent IV tPA administration compared to treatment with IV tPA alone in patients with acute ischaemic stroke due to a proven LVO and a thrombus length of ≥8mm (Mocco *et al.*, 2016). Adult patients aged 18-85 with a proven LVO on CTA measuring ≥8 mm, with an NIHSS score of ≥8 and occlusion of the anterior cerebral circulation (ICA or MCA) were eligible for the study. The primary outcome was assessed in terms of percentage of patients achieving functional independence at 90 days as assessed by an mRS of 0-2, with an intention to treat analysis. Like other trials, this was stopped early due to the results of the MR CLEAN trial being presented and the concern that this was unethical to be continued. The study included 108 patients with 55 allocated to mechanical thrombectomy plus IV tPA and 53 patients to IV tPA alone. The results did not reach statistical significance however they were in favour of mechanical thrombectomy performed with aspiration and IV tPA (OR 1.76, 95% CI 0.86–3.59, P=0.12). There were no significant differences in between the two groups in terms of

safety outcomes: serious adverse events, symptomatic intracranial haemorrhage or mortality at 90 days.

EASI was a single centre randomized care trial in Canada which enrolled patients that were considered for endovascular thrombectomy treatment based on their clinical presentation (Khoury *et al.*, 2017). This was a pragmatic trial with a relatively broad inclusion criteria for adult patients presenting ≤ 5 hours from stroke symptom onset or evidence of clinical to imaging mismatch, having an NIHSS ≥ 8 and either a suspected or definitively proven proximal intracranial LVO in the anterior or posterior circulation. Patients were randomized either to best standard care or best standard care and mechanical thrombectomy. The primary outcome was assessing rates of functional independence at 3 months by an mRS ≤ 2. This study was stopped early after the publication of the MR CLEAN results. A total of 77 patients were enrolled, 40 patients in the mechanical thrombectomy intervention group and 37 patients in the control group. There was no statistically significant difference in reaching the primary outcome in between the two groups. No statistically significant difference was demonstrated between the two groups in terms of safety or mortality.

Table 2 outlines the main outcomes in the interventional arms of the presented trials.

	MR CLEAN	SWIFT PRIME	EXTEND-IA	THRACE	REVASCAT	PISTE	THERAPY	EASI
n	500	196	70	414	206	65	108	77
Process times (min, median)								
Onset to IV tPA	85	110	127	150	117	120	108	145
Onset to reperfusion	332	N/A	248	303	355	251	N/A	N/A
TICI 2b-3	59%	88%	86%	69%	66%	87%	70%	77%
Outcomes								
mRS 0-2 at 90 days	33%	60%	71%	53%	44%	51%	38%	20%
Mortality	19%	9%	3%	12%	18%	9%	12%	11%

Table 2 - Comparison of early intra-arterial thrombectomy main outcomes in the interventional arms of the presented mechanical thrombectomy trials

2.2.2 Thrombectomy Trials Within an Extended Time Window

ESCAPE was a prospective, multicentre, randomized controlled trial performed across the world and recruiting from 22 centres (Goyal *et al.*, 2015). This study recruited adult patients with no upper age limit who had a good baseline as assessed on the Barthel Index (Mahoney and Barthel, 1965) with a score of ≥90. Patients needed to have an NIHSS ≥5, a large cerebral artery occlusion demonstrated on CTA and an ASPECTS score of ≥6. In addition, patients had to have good collateral circulation either shown on CTA or multiphase CTA. For patients that met these inclusion criteria, they could be enrolled up to 12 hours after the initial stroke symptoms onset. Most patients recruited and treated were within 6 hours, with only a small minority being within the 6 to 12 hours window. Their overall results reflect their whole population, but this was the first published trial who pushed the boundaries of mechanical thrombectomy to include patients presenting in a later time window. A total of 316 patients were included in the study with 165 being randomized to thrombectomy and another 150 patients being randomized to standard medical therapy. This trial was stopped early after preplanned statistical analysis of the first 300 patients which occurred after the results of the MR CLEAN study. Their results showed that mechanical thrombectomy, even in this slightly delayed timeline, had significantly better outcomes at 90 days: 87/164 (53%) versus 43/147 29.3% of patients achieving an mRS of 0 - 2. In addition, the study also showed lower death rates in the interventional group with 17/164 (10%) versus 28/147 (19%) in the control group, (p=0.004). Like other trials, there was no statistically significant difference in intracranial haemorrhage rates.

DAWN was a prospective, multicentre, randomized controlled trial randomizing ischaemic stroke patients who were last seen well in the past 6 - 24 hours either to mechanical thrombectomy or standard care (Nogueira *et al.*, 2017). Patients had to have a proven occlusion of the anterior cerebral circulation on imaging and a mismatch between the severity of the clinical deficit at presentation and the already established infarct volume as assessed either by DWI MRI or CT perfusion, both via automated software (RAPID, iSchemaView). Patients needed to have a good clinical baseline as assessed by an mRS of 0 – 1. Although there was no upper age limit, there were 3 groups of clinical to imaging mismatch in which patients were categorized according to their age. Patients younger than 80 years were allocated

either to a group with an NIHSS score ≥10 and an infarct volume <31 mls or to a second group with an NIHSS score ≥20 and an infarct volume of 31 - 50 mls. Patients of age 80 and older were placed in a separate group and they needed to have an NIHSS score ≥10 and an infarct volume <21 mls. The study had two primary end-points: the utility-weighted mRS at 90 days and the functional independence as assessed by an mRS of 0 – 2 at 90 days. This trial was also stopped early due to the results of a pre-specified interim analysis. Results demonstrated significantly better outcomes in the thrombectomy group as assessed by both co-primary endpoints: the utility-weighted mRS (adjusted difference 2.0 points; 95% credible interval 1.1 - 3.0; posterior probability of superiority >0.999) and the mRS with 49% vs 13% achieving independence in the thrombectomy group versus the control group (adjusted difference 33 percentage points; 95% credible interval 21 - 44; posterior probability of superiority >0.999). Reperfusion was achieved in 84% of the patients in the thrombectomy group with a median time of 13.6 hours (IQR 11.3 – 18.0) from when patients were last known well. Maintained recanalization at 24 hours was demonstrated in 77% of the patients within the thrombectomy group versus 36% for those in the standard care group. Safety and mortality were not statistically different between the interventional and control arms. One extra patient achieved functional independence at 90 days for every 2.8 patients that were treated with thrombectomy plus standard best medical care.

The DEFUSE-3 trial was a multicentre, randomised controlled trial similarly assessing the efficacy of mechanical thrombectomy in an extended time window, from 6 – 16 hours after patients were last known well (Albers et al., 2018). This was conducted across 38 centres in USA. Patients needed to have LVO in the anterior cerebral circulation, an established infarct of less than 70 mls, a penumbra to infarction ratio of 1.8 or more and at least 15mls of penumbral region as assessed by CT perfusion or MRI diffusion perfusion imaging with the aid of automated software (RAPID, iSchemaView). Imaging to groin puncture for patients randomized to endovascular treatment had to be within 90 minutes, similar to other previous trials. Thrombectomy was performed with any FDA approved device and operators were allowed to perform carotid angioplasty and/or stenting if necessary. The primary outcome was the mRS at 90 days. The trial was stopped early after an interim analysis due to efficacy with a total of 182 enrolled patients, 92 to the interventional arm and the other 90 to the control arm. The mRs at 90 days was more favourable for the group that received endovascular therapy plus standard medical treatment compared with

standard medical treatment alone with 45% versus 17% achieving functional independence at 90 days ($p < 0.0001$) respectively. The mechanical thrombectomy group had a mortality rate at 90 days of 14% compared to 26% for the medical therapy group and this did not reach statistical significance, $p=0.05$.
Table 3 outlines the main outcomes in the interventional arms of the presented late window trials.

	ESCAPE	DAWN	DEFUSE-3
n	315	206	182
Process times (min, median)			
Onset to IV tPA	110	N/A	N/A
Onset to reperfusion	241	816	726
mTICI 2b/3	72%	84%	76%
Outcomes			
mRS 0-2 at 90 days	53%	49%	45%
Mortality	10%	19%	14%

Table 3 - Comparison of late intra-arterial thrombectomy main outcomes in the interventional arms of the presented late window mechanical thrombectomy trials

2.2.3 Meta-analysis

A few meta-analyses comparing the outcomes in patients who have had mechanical thrombectomy versus those that were treated with best medical treatment have been published in the past few years. One of the most important ones is the one published by the HERMES collaborators which had individual patient level data (Goyal *et al.*, 2016). This included data from 5 trials: MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND IA, with these trials having data accumulated from December 2010 to December 2014. As presented previously, in these trials, patients with acute ischaemic stroke symptoms due to LVO secondary to a thrombus in the anterior circulation were assigned randomly to either receive endovascular thrombectomy up to a maximum of 12 hours from symptom onset or best medical management, including IV tPA administration. The primary outcome of this meta-analysis was to assess the clinical outcome at 90 days on the mRS. In addition, they also performed subgroup analysis for the primary outcome. A total of 1287 patients had their data

analysed with 634 receiving mechanical thrombectomy and the other 653 receiving best medical management. As expected from the previously published trials, this meta-analysis confirmed the efficacy of mechanical thrombectomy with significant reduced disability at 90 days in the endovascular group as compared with the control group ($p<0.0001$, adjusted cOR 2.49, 95% CI 1.76–3.53). Impressively, this meta-analysis showed that for every 2.6 patients that received endovascular treatment, one patient had a reduction in disability by 1 point at 90 days on the mRS. Further subgroup analysis also confirmed the benefit of mechanical thrombectomy for patients that were randomized later than 300 minutes from symptom onset (cOR 1.76, 95% CI 1.05 – 2.97), patients that could not be administered IV tPA (cOR 2.43, 95% CI 1.30 – 4.55), as well as patients that were aged 80 years and older (cOR 3.68, 95% CI 1.95 – 6.92). They concluded that endovascular thrombectomy is beneficial for most patients that present acutely with ischaemic stroke due to LVO in the anterior circulation. Safety data, including intracranial haemorrhage and mortality up to 3 months, did not significantly differ between the two groups.

The HERMES collaborators have used the same patient level data from the 5 trials to assess the effects of time to successful endovascular treatment and clinical outcomes at 3 months (Saver *et al.*, 2016). For this meta-analysis, the primary outcome was assessing the degree of clinical functional independence based on the mRS at 3 months. They had a total of 390 patients who achieved good reperfusion with mechanical thrombectomy. Their data analysis demonstrated that for each 1-hour delay to good reperfusion, outcomes were worsened both in terms of disability and functional independence. The faster the mechanical thrombectomy was successful, the better outcomes for the patients at 3 months. In this patient cohort, for every 9 minutes delay to good reperfusion, 1 in every 100 treated patients had a drop of 1 point on the mRS. The initial benefit of performing mechanical thrombectomy was shown to be obsolete in patients who had their groin puncture at 7.3 hours from initial stroke symptoms onset. There was however no significant change in the mortality rates.

2.2.4 Posterior Circulation Thrombectomy Evidence

The main endovascular thrombectomy trials focused on anterior circulation LVO with only limited data on this type of treatment in patients having acute, ischaemic posterior circulation strokes. One of the more recent studies published on mechanical thrombectomy in the posterior circulation was the ENDOSTROKE study which was a multicentre registry performed in Germany and Austria enrolling patients from the beginning of 2011 until June 2013 (Singer *et al.*, 2015). They enrolled all consecutive adult patients with a confirmed basilar artery occlusion on conventional cerebral angiography and they had a total of 148 patients. The registry had both prospective and retrospective data, as 21 of their patients were treated before the registry was started and data was entered subsequently. Although most procedures were done with modern devices such as stent retrievers and suction catheters, they still had a minority of patients that were treated with the MERCI device (n=9). Like other studies, their primary outcome was good clinical function as defined by an mRS of 0-2 at least 3 months after the initial thrombectomy procedure. Angiographic data was reviewed in a blinded core lab which assessed the collateral circulation and the recanalization using the TICI (Thrombolysis in Cerebral Infarction) score. They had overall good rates of recanalization with a TICI score of 2B/3 in 79% of cases. Their results demonstrated that 34% of patients had reached clinical independence after 90 days in keeping with a good clinical outcome. Predictive factors for recanalization were the use of a stent retriever and better collateral status. Independent predictors of clinical outcome on multivariate analysis were baseline NIHSS, collateral status and using MRI before performing mechanical thrombectomy. Intracranial haemorrhage post procedure occurred in 6% of patients and this was significantly higher in patients that were treated with both intra-venous and intra-arterial thrombolysis in addition to mechanical thrombectomy in comparison to other treatments strategies used (p=0.038). Another significant finding was that mortality was almost double (47% vs 28%) in patients with poor reperfusion as assessed by TICI score of 0-2 when compared to TICI 2b-3 recanalization (p=0.044).

There is also a meta-analysis which looked at basilar artery occlusion and treatment with mechanical thrombectomy, specifically assessing the use of modern stent retrievers (Phan *et al.*, 2016). They included a total of 17 studies: 6 being prospective single centres studies, 10 being retrospective single centres studies and

the final one being a retrospective multicentre study. Studies included had data on mechanical thrombectomies performed from 1998 to 2014 and included both older and newer devices and techniques. Treatment with a stent retriever was undertaken in 77% of procedures, IA thrombolytic medication only was used in 21% of procedures while the rest were done with other techniques (e.g. Merci device, Penumbra aspiration catheter). They demonstrated that good recanalization rates were achieved in 80% when performing thrombectomy with stent retrievers and clinically 42.8% of patients achieved good outcomes (mRS ≤2). When comparing stent retriever mechanical thrombectomy versus conservative medical treatment (antiplatelets/anticoagulants) they showed that good outcome rates are almost double with endovascular treatment. However, when looking at stent retriever thrombectomy versus treatment with IV tPA there was no significant difference in good clinical outcomes, although there is a suggestion that mortality rates are reduced by approximately 10-20%. Rates of symptomatic intracranial haemorrhage were similar in patients receiving IV tPA and patients treated with mechanical thrombectomy. They concluded that further randomized controlled trials are needed to assess the clinical efficacy of mechanical thrombectomy in the posterior circulation as compared to current best standard medical treatment.

2.3 Discussion and Limitations

With the publication of these trials in the past few years, the acute treatment of ischaemic stroke due to LVO has changed dramatically worldwide. Additionally, there have been campaigns to try and educate the general population about signs and symptoms of acute stroke such as the “Act Fast” campaign in the UK (Dombrowski *et al.*, 2013) to ensure that patients present quickly to the nearest emergency department so that they have the greatest chance at receiving the best evidence-based treatment. These campaigns have been shown to have an effect, however they need to be continuous as their effects may trail off after several months once they are stopped (Advani, Naess and Kurz, 2016). We know that the brain will infarct over a period of several hours and this is faster in certain people compared to others: fast progressors being patients in whom the brain will infarct generally within a 3 to 6 hour window and slow progressors where it is believed their collaterals are maintaining perfusion beyond 6 hours (Rocha and Jovin, 2017). There are different

randomised controlled trials assessing neuroprotective agents as these may be able to further extend our time window for mechanical thrombectomy; for example, the ESCAPE-NA1 trial (NCT02930018) will test NA-1 as a neuroprotective agent in patients selected for mechanical thrombectomy. For patients that are in the fast progressing category these agents may be able to slow down the rate of infarction until reperfusion is achieved. On this basis offering endovascular thrombectomy for patients with proven LVO is now shifting from a time-based decision to an imaging-based decision with the imaging of choice left to the local centres with options including the ASPECTS score, CTA or multiphase CTA to assess collaterals, CT or MRI perfusion imaging to assess the infarct core and penumbra.

Although the HERMES meta-analysis allowed for subgroup analyses to be performed, further data is still needed as these subgroups were under represented and there is ongoing research being performed. Older patients represented 15% of those within the HERMES meta-analysis and since it was published, further retrospective studies have been performed. Similarly, another 15% of the patients from the HERMES meta-analysis could not be given IV tPA and there are ongoing studies assessing this subgroup.

There is still further research to be done, as there is not yet enough evidence regarding mechanical thrombectomy in certain patients subgroups. Patients with a proximal LVO on imaging and mild clinical stroke symptoms as assessed by a lower NIHSS score may also benefit from mechanical thrombectomy. There are other patients who have a significant clinical deficit, but a more distal LVO for example in the distal M2 or even M3 MCA branches. There is another subgroup of patients with already established significant ischaemic changes, as assessed by a high ASPECTS score or large core infarct, and it is still unclear what is the best management for them. For patients that present with tandem occlusions, such as one in the cervical ICA and a simultaneous one in the MCA territory for example, it is still not clear whether the intracranial occlusion or the cervical occlusion should be treated first. In terms of the actual procedure, although most trials have used stent retrievers, first pass aspiration is now being used more frequent and further data is needed to guide us as to which technique should be attempted first. Finally, different centres use different types of anaesthesia and there is another debate whether conscious sedation or general anaesthetic is best.

2.4 Conclusion

After the publication of these trials, there was a huge impact on the management of patients presenting with acute stroke due to LVO worldwide. Changes to the European and North American guidelines have already been implemented and now reflect the findings of these trials by recommending mechanical thrombectomy in suitable patients, including patients presenting in the later window in the North American guidelines (Casaubon *et al.*, 2015; NICE, 2016; Wahlgren *et al.*, 2016; Powers *et al.*, 2018).

Chapter 3. STABILISE Trial

This chapter will focus on the STABILISE (*Stroke: an evaluation of Thrombectomy in the Ageing Brain-[including] where IV thrombolysis IS contraindicated*) trial which was developed to allow investigation of two new devices to be used in acute ischaemic stroke. These intracranial tools: ERIC, *Embolus Retriever with Interlinked Cages*, and SOFIA, *Soft torqueable catheter Optimized For Intracranial Access*, DAC are being investigated. All aspects of the trial will be discussed, including the development of the protocol, the ethical submission, the trial running, and initial blinded results will be presented.

3.1 Scientific Background and Rationale

As discussed in the previous chapters, an acute large vessel intracranial occlusion may lead to significant clinical deficits, including dependency and mortality. In patients that present within a relatively early time window, advanced imaging may show an irreversible central infarcted zone, surrounded by a territory with reduced blood flow, the penumbra. This salvageable area is the target for performing endovascular treatment, aiming to recanalize the occluded artery, restore blood perfusion to the brain and avoid further extension of the necrotic territory.

At the time of developing the protocol for the STABILISE study, the evidence of efficacy for thrombectomy devices had been limited to case series and prospective observational studies. These were set out to establish the mechanical characteristics and performance devices with respect to the limited end-point of vessel recanalization. Even though there were high rates of recanalization, clinical outcomes have been poorer than expected which could have been due to reperfusion of non-viable brain tissue as this has no clinical benefit and poses an increased risk of intracranial haemorrhage. Although now there is enough evidence demonstrating that mechanical thrombectomy is superior to IV tPA, at the time of developing the STABILISE protocol, some of these ground-breaking trials were still ongoing. In addition, the randomized controlled trials which had concluded by 2013 mostly excluded the older population (patients of age 80 and above) and included few patients with contraindications to IV tPA. Importantly, patients with contraindications

to IV tPA account for >50% of patients with LVO stroke in routine practice series/registries. Further studies more truly representative of the general patient population were needed. Additionally, at the time, the non-randomised literature in the real-world patient population was also very limited with published studies reporting average ages far younger than seen in routine clinical practice.

As discussed in the first chapter, initial thrombectomy devices were mostly based on stents designed as an adjunct to intracranial aneurysm endovascular coiling and unexpectedly found to be useful in stroke. As a result, they were not optimized to access distal and/or tortuous vessels or those with long occlusions. Tortuous vessels are more common in the older population and patients with hypertension, while longer clots are less likely to respond to IV tPA (Kamalian *et al.*, 2013).

The new ERIC retrieval device was specifically designed for thrombectomy and has potential advantages in older patients with tortuous vessels and long clots. It has been designed to be less traumatizing with lower radial pressure exerted on the arterial walls, the interlinked cages having more flexibility and leading to less clot fragmentation. ERIC is made from nitinol, an alloy composed of nickel and titanium in roughly equal proportions. This material is highly biocompatible, has good shape memory and super elasticity. One of the advantages of the ERIC device is that it is better adapted for distal access as it needs a smaller calibre delivery catheter of 0.017", while other stent retrievers require at least a 0.021" delivery microcatheter. Additionally, there is no requirement to wait a few minutes for the thrombus to integrate as is required for the standard stent retrievers. This can help with achieving an even faster recanalization and in cases where multiple passes are required, being able to save approximately 5 minutes per attempt is significant, keeping in mind that up to 1.9 million neurons can die per minute treatment is delayed (Saver, 2006).

The second device being assessed in this trial, the SOFIA DAC has an ultra-soft final segment, but still very good proximal support, allowing excellent navigation in challenging tortuous vessels and good steerability around bifurcations. Being available in either a 5-French or 6-French size this could be brought up to the clot interface intracranially and be used for clot aspiration either on its own or with concurrent use of the ERIC retriever device engaged in the thrombus, Figure 6.

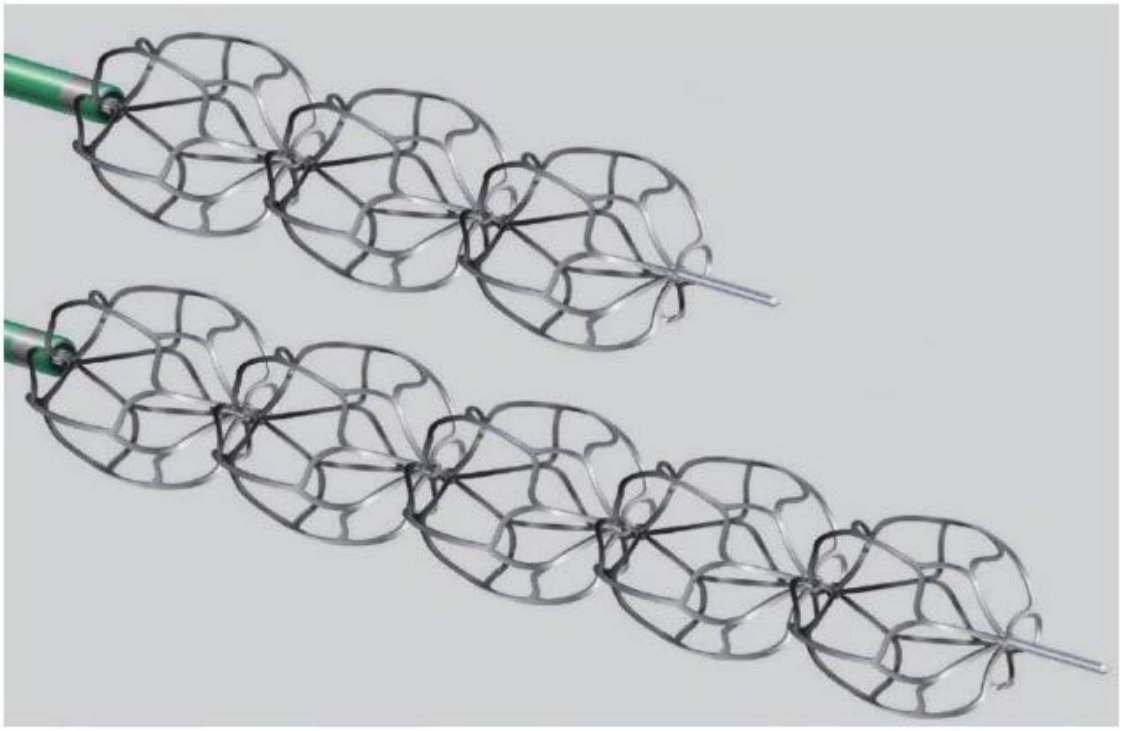


Figure 6 - ERIC Retrieval Device
Picture courtesy of Microvention Terumo Inc.

In addition, the ERIC retriever device offers more flexibility as there is the ability to select a device of smaller or larger diameter and the operator can decide how many clot retrieval baskets to deploy depending on the vessel diameter and the clot length, Figure 6. This may prove to be very effective in reaching more distal thrombi and offering a more personalized treatment approach depending on the patient's anatomy and thrombus length.

Figure 7 demonstrates how the ERIC device and SOFIA DAC work together to remove the thrombus. When the SOFIA device is placed under suction with an open ERIC device that is engaged in thrombus, it causes pinching of the thrombus between the two devices and plunges the clot into the inner lumen effectively trapping it before proceeding to retrieval.

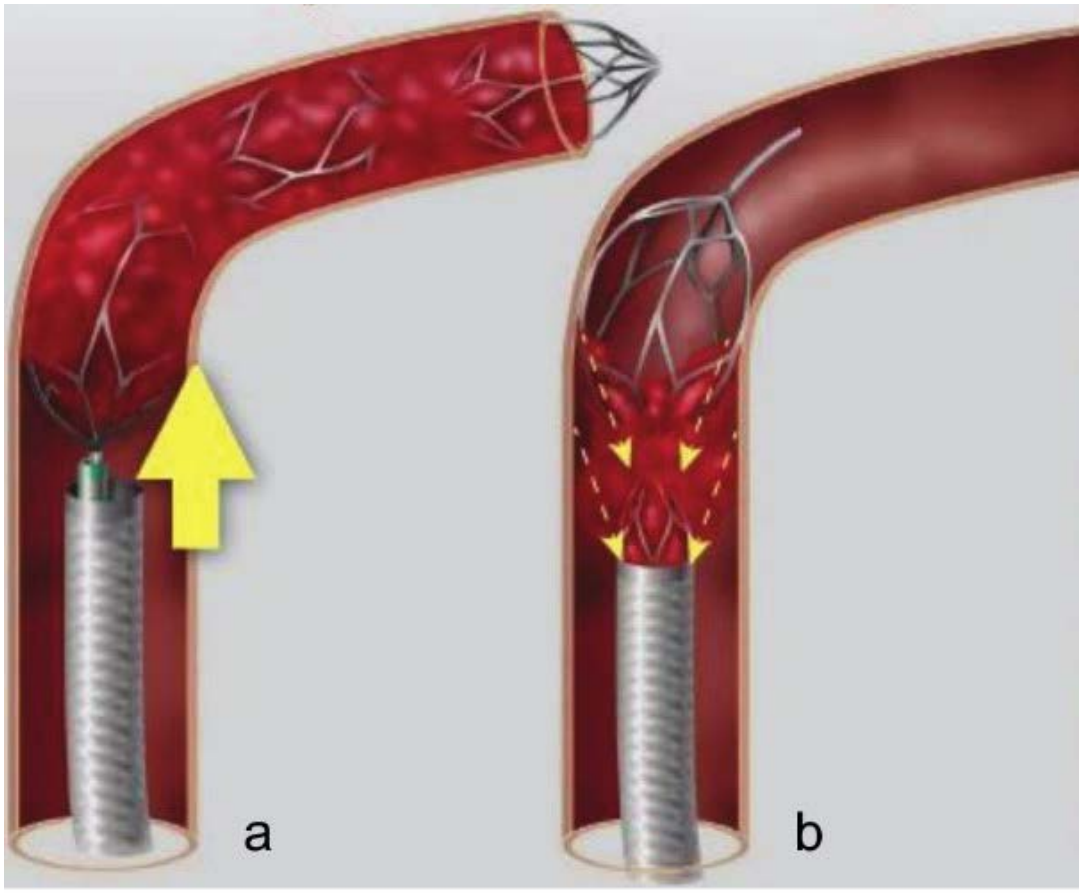


Figure 7 - ERIC and SOFIA Thrombectomy
a - SOFIA DAC advancing toward the ERIC device which is integrated with the thrombus
b - SOFIA DAC partially engaging the ERIC retrieval device and capturing the thrombus before retrieval
Picture courtesy of Microvention Terumo Inc.

3.2 Scientific Trial Objective

It is hypothesised that mechanical thrombectomy using the new ERIC retriever and SOFIA DAC will have at least an equivalent rate of occluded vessel recanalization as other standard modern thrombectomy devices. The clinical functional recovery in this group of patients will be assessed at long term using the mRS at 3 and 12 months. The primary objective of the trial is to determine if these new thrombectomy devices can be used successfully in the general population presenting with LVO acute ischaemic stroke. The mTICI recanalization rate as assessed by a blinded core lab is the primary efficacy assessment.

It is hypothesized that vessel tortuosity and/or brain collaterals are linked to outcomes of mechanical thrombectomy and if a link can be established, the aim is to develop a clinically useful assessment tool. The use of early MRI post LVO stroke to determine complications of mechanical thrombectomy and to direct patient management will be investigated. Finally, it is hypothesised that outcomes are independently linked to patients age and will assess if there is any influence regarding the type of device used to perform mechanical thrombectomy. These formed the basis for the secondary objectives of this trial: to determine the safety of these thrombectomy devices and plan the design of a phase III clinical trial, to determine mechanical thrombectomy procedure safety in the general stroke population including the older population patients, and finally to assess the use of early MR imaging after thrombectomy as a biomarker of clinical outcome.

The primary outcome was recanalization rate by using the mTCI scale as assessed by an independent, blinded core laboratory assessment. This primary outcome was selected as it was thought to best represent the ability of the new thrombectomy devices to retrieve the thrombus. The strength of this primary outcome is that it is assessed on a standardized scale that is already commonly used by neurointerventionists and it can be relatively easy to assess in a blinded fashion. The primary outcome is also relevant as it assesses the actual ability of the clot retrieval device to successfully remove the intracranial thrombus. The weakness of this assessment is that it may not necessarily correlate with the final clinical outcomes of these patients.

Due to the above, the secondary outcomes also included clinical patient outcomes, procedural safety and study feasibility. The study feasibility was important as this

being a pilot project, it would help guide whether further investigation of these devices in a trial can be feasible in terms of patient recruitment. Both clinical outcomes and procedural safety are also very important to assess, as being able to perform a safe procedure with the new devices was of paramount importance. If the devices proved to have more unexpected complications, then that could lead to these devices not being utilised because they could negatively affect clinical outcomes. Finally, clinical outcomes at 3 and 12 months were collected, and this is very important as that is the ultimate measure of the intervention, but the weakness of this outcome is that many other factors other than the devices used can potentially influence it.

3.3 Ethics and Trial Funding

I worked on the ethics submission at the beginning of my studies, and with help from my supervisor and the rest of the team from the Newcastle Institute of Ageing and Stroke research, this was submitted in 2014, Appendix B – STABILISE Ethics Application. After a meeting with the ethics committee, where a few changes to the protocol were requested, we received confirmation that the ethics committee approved the study from the NRES Committee North East – Newcastle & North Tyneside, 04/07/2014, ref: 14/NE/0113 see Appendix C – STABILISE Ethics Approval Letter. The trial's ISRCTN (International Standard Registered Clinical/Social Study Number) registration number is 15698516.

This trial was jointly and equally funded by the National Institute for Health (NIHR) Newcastle University Biomedicine Research Centre based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University; and MicroVention Terumo Inc.

3.4 Methods

Below I will synthetize the STABILISE trial methodology. In chapter 7, I will further discuss other types of possible methods that could have been used for this study.

3.4.1 Trial Design and Running

This is a UK multicentric, prospective, phase II, single-blinded, randomised controlled trial comparing novel thrombectomy devices, ERIC retriever and SOFIA distal access catheter, with standard aspiration and/or stent based thrombectomy in male and female patients aged ≥18 years with acute LVO ischaemic stroke. Patients were randomised to either the novel thrombectomy devices or to standard thrombectomy devices in a 2:1 ratio.

Potential participants were identified on referral to participating acute stroke services and were assessed for study suitability using the inclusion and exclusion criteria, see Appendix D – STABILISE Inclusion and Exclusion Criteria. Data collected for routine clinical care was used for clinical trial documentation and I worked on developing the Case Report Form for collecting all required data, Appendix E – STABILISE Study Workbook. Once this was finalised, I worked together with the trial statistician and IT developer to make an electronic case report form, capturing the same data, for ease of use for the enrolling sites. This was available via secure login from: https://macro.infermed.com/NewcastleCTU/Login/LoginForm.aspx?IsUniInstance=true.

Additionally, I worked on a thrombectomy procedural sheet to capture data that was required during the procedure, Appendix F – STABILISE Thrombectomy Treatment Details. Consent was obtained either from the patient or their family or in cases where this was not possible from an appropriate consultee. I have had the chance to work on the patient and consultee information and consent forms as well, Appendix G – STABILISE Patient Information Sheet, Appendix H – STABILISE Consent Form, Appendix, Appendix I –STABILISE Consultee Information Sheet, Appendix J – STABILISE Consultee Declaration. Please also refer to Appendix K – STABILISE Protocol, Appendix L - Stabilise Trial - Patient Pathway Flowchart.

The data monitoring committee was established, and I developed a charter to ensure these external experts are able to assess the progress of the trial and assess the trial safety data, Appendix M – STABILISE DMC Charter.

3.4.2 Trial Protocol Amendments

During the STABILISE trial, there was one protocol amendment which covered multiple issues. One of the most important modifications made were due to changes with regards to the technical aspect of thrombectomy as this is a very rapidly changing field. At the beginning of the trial, distal access catheters were not widely used, but as these started to be used more regularly in clinical practice, there was difficulty with recruiting other centres and a lag in patient recruitment. Other changes were related to the trial inclusion criteria to allow inclusion of patients aged 18-50 years, initially excluded, and also patients with lower NIHSS score between 6-9, initially only NIHSS of 10+, as there was newly published data during the course of the trial which did not demonstrate any age or NIHSS specific cut off effects for clinical benefit from mechanical thrombectomy. These changes have been made to allow extension of the trial to other centres and to increase the recruitment rate which was slower than initially predicted. Due to the overall slow recruitment the trial was extended, and it will be finalised on the 30th of April 2019.

3.4.3 Eligibility Criteria

The trial recruited male and female patients aged ≥18 years with clinically significant acute ischaemic stroke. Eligible patients had to have vascular imaging in the form of either a CTA, MRA or DSA (digital subtraction angiography) to demonstrate an intracranial LVO. Patients that were also eligible for IV tPA had this additional treatment initiated as per standard clinical practice. After ensuring that mechanical thrombectomy is feasible within the trial timescale, consent for the trial was obtained and the patient was then randomized. Details of both the inclusion and exclusion criteria are in Appendix C – STABILISE Inclusion and Exclusion Criteria.

3.4.4 Participant sites

This trial was run at 4 UK sites: Addenbrookes Hospital in Cambridge, Royal Victoria Infirmary in Newcastle, Queen's Medical Centre Campus in Nottingham and University College London in London. Centres selected were from HSRCs (hyperacute stroke research centres) who were all approached and invited to participate in this trial and who expressed a willingness to join. All centres had to demonstrate that neurointerventionists had the level of experience necessary for performing neuroendovascular procedures as delineated for the PISTE trial that was ongoing in the UK when STABILISE started. This stated specifically that operators needed to have performed at least 120 neurovascular procedures per operator in the last 3 years with at least 10 mechanical thrombectomy procedures in the last 18 months for all site operators. All operators had to be comfortable with using both the ERIC and SOFIA devices, which were already available for use across the country and extra training, if required, was made available. A thrombectomy pathway had to be already in place plus evidence of mechanical thrombectomy outcomes documented (eg. local audit). In addition, there was a requirement to have IV thrombolysis available during extended hours, consultant stroke/neurology cover for administering IV tPA, an established local protocol for advanced stroke imaging and regular multidisciplinary stroke/neuroradiology meetings in operation.

Recruitment started in October 2014 and the last patient was recruited in January 2018. Figure 8 shows the recruitment of patients in the STABILISE trial. Recruitment was slower than anticipated and overall challenging. Many different issues combined together lead to those difficulties and the trial had to be extended. Once the trial opened at the first site in Newcastle, there was a plan to rapidly expand it to other sites. Unfortunately, there were changes to the documentation needed for enrolling new sites that happened concomitantly and this resulted in significant delays in obtaining the required paperwork for getting the trial started at other sites. Because this is such a fast-moving field, the type of mechanical thrombectomy preferred by operators had slightly changed during the course of the trial. Because of this it was necessary to allow for different techniques to be performed as part of the trial, leading to a protocol amendment, and this also contributed to further delays and slower recruitment rates. At the beginning of the trial, thrombectomy being not yet proven or within guidelines, consenting was also challenging due to clinical equipoise and

constraints of staff being able to explain everything and gain consent in an emergency situation. Finally, patient preference may also have proved a part in the slow recruitment, initially because the treatment was not proven yet and later on during the course of the trial because the procedure was potentially done with a new device.

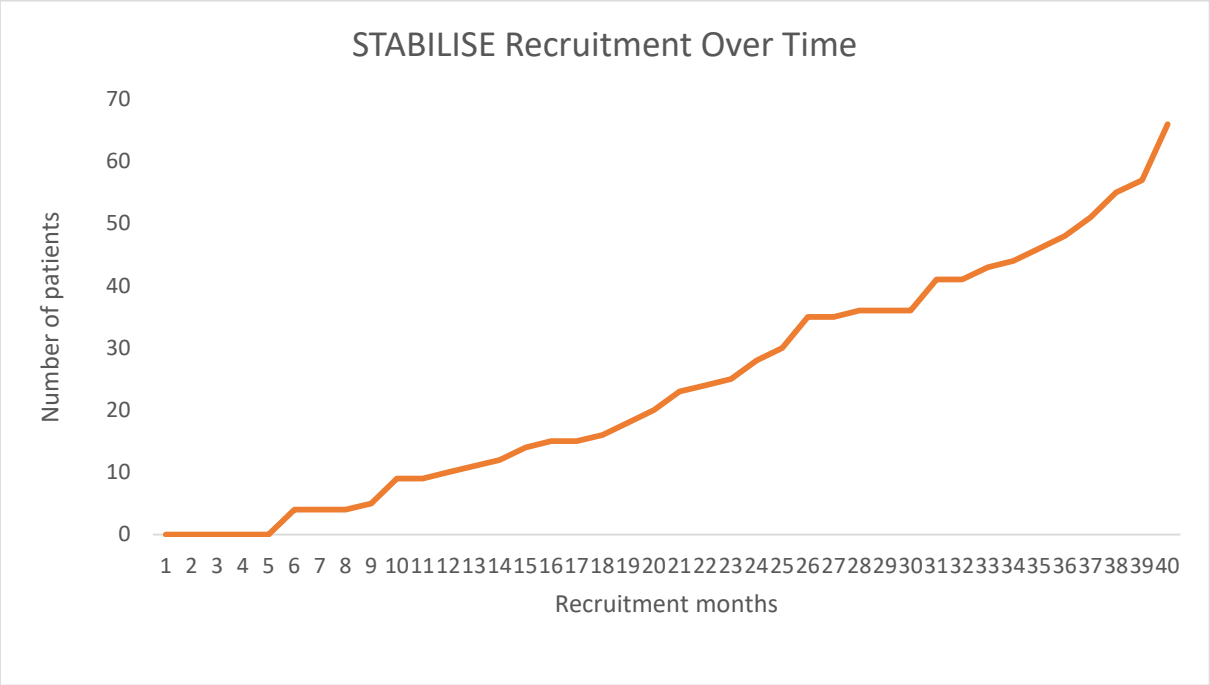


Figure 8 - STABILISE Trial Recruitment

3.4.5 Consent and Randomisation Methods

Patients were first screened if eligible for the trial and then consented before proceeding to randomisation. If patients were able to give consent themselves, this was performed and the Patient Information Sheet and STABILISE Consent Form were used (Appendix G – STABILISE Patient Information Sheet, Appendix H – STABILISE Consent Form). For patients unable to give consent due to lack of capacity, appropriate consent was taken from their next of kin or if no family member was available, an assent process followed where a medical doctor that was not involved in performing the trial and had the patient's best interests at hand signed the consent form; in these cases the STABILISE Consultee Information Sheet and the

STABILISE Consultee Declaration forms were used (Appendix I –STABILISE Consultee Information Sheet, Appendix J – STABILISE Consultee Declaration).

Patients were randomised to either the novel thrombectomy devices or standard thrombectomy devices in a 2:1 ratio (SOFIA/ERIC to control) by using stratification by age (18-65 vs >65 years) and NIHSS severity of stroke at presentation (NIHSS scores of 6-15 versus 16+). The randomization system was based at the Newcastle Clinical Trials Unit (NCTU) and the randomisation was web based and accessed using a secure password protected website link: https://apps.ncl.ac.uk/random.

3.4.6 Statistical Method

The STABILISE trial has a comprehensive Statistical Analysis Plan that was authored by the Trial Statistician and has to be agreed by the Trial Steering Committee (TSC) before any comparative analysis is undertaken or any unblinded data is released. Due to this being an early clinical phase trial, most of the analyses were planned to be descriptive, on an intention to treat basis.

The sample size calculation was performed by the trial statistician. The number of patients required in the trial was determined by achieving a specified recanalization rate in the interventional arm, with an acceptable error level, that would justify a subsequent larger scale trial. If a recanalization rate lower than 75% is used to reject, while a recanalization rate higher than 90% is used to further investigate the ERIC^{TM} or SOFIA^{TM} devices, a minimum recruitment of 67 patients to the interventional arm will permit α and β error levels of 2.5% and 10% respectively by using the Fleming-A'Hern single stage early phase trial methodology. If there is a higher than expected drop-out rate of 20%, this would increase the recruitment target to the interventional arm to 80 patients.

The primary outcome is based on an independent core lab judgement that is blinded to treatment and defined as STIR II modified TICI grade 2b/3.

3.5 Trial Results

3.5.1 Patient Population

A total of 68 participants were recruited to the study with the baseline clinical characteristics presented in Table 4. Two patients were initially included in the study, but were removed, one because consent had not been obtained prior to the procedure and the other one withdrew. Once these 2 were removed, there was a total of 66 patients included in the trial, see Figure 9.

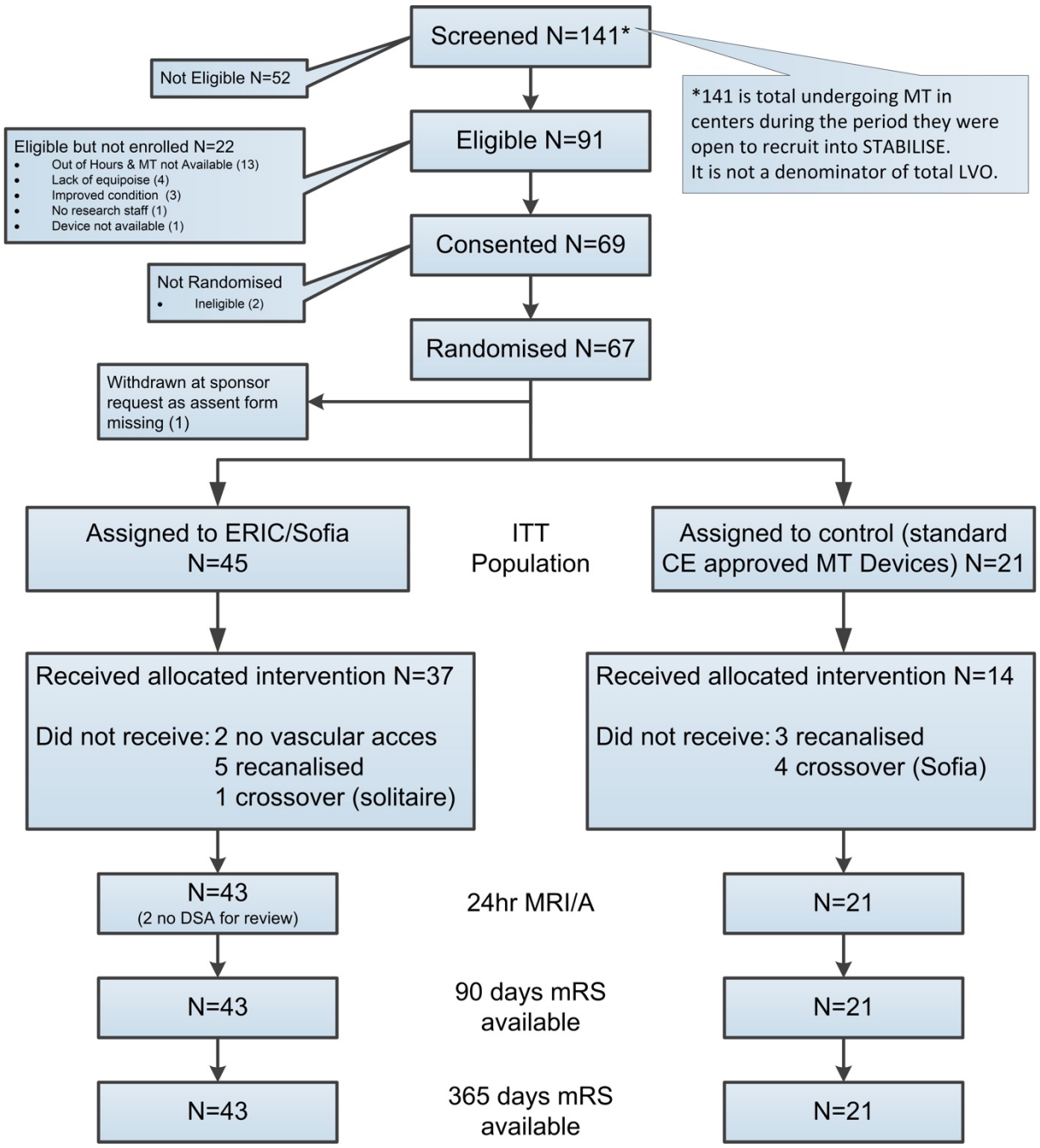


Figure 9 - STABILISE trial flow chart (CONSORT diagram)

3.5.2 Demographics and Baseline Imaging Data

There were 26/68 (38%) females and 42/68 (62%) males with a median age of 72 (IQR 59 - 79), Table 4, a total of 15/68 (22%) participants were aged 80 or more. The prevalence of hypertension was 37/66 (56%), atrial fibrillation was present in 22/66 (33%) and current or prior smoking history in 37/66 (56%).

The median NIHSS score at presentation was 18 (IQR 13–23). All participants had vascular assessment in the form of a CTA to establish evidence of LVO. In addition, 3/66 (5%) patients had MRI and 2/66 (3%) patients had MRA on initial imaging assessment. The most common location of the target occlusion was the proximal M1 MCA segment in 49% (32/66) of patients, next the distal M1 MCA segment in 29% (19/66) followed by the proximal M2 MCA in 28% (18/66), Table 5. An ICA occlusion was present in 23% (15/66) patients and tandem type ICA-T occlusions were present in 14% (9/66) of patients. There were an additional 9% (6/66) of participants who had a posterior circulation large arterial occlusion. The intracranial occlusion location in a certain patient could be in one or more of these regions and the number of patients with additional tandem occlusions, e.g. ICA and M1 MCA, will only be available once unblinded data is released. The median baseline ASPECTS score is not yet available as images need to be processed by the core lab.

Basic Demographics	**Total Population (n=68)**
Median Age (years)	72 (59-79)
Men	42 (62%)
Women	26 (38%)
Past Medical History	**Population (n=66)**
Hypertension	37 (56%)
Diabetes Mellitus	9 (14%)
Atrial Fibrillation	22 (33%)
Heart Disease	18 (27%)
Previous Stroke	7 (10%)
Previous Endarterectomy / Carotid stent	1 (2%)
Smoking (current)	9 (14%)
Smoking (former)	28 (42%)
Clinical Characteristics	**Population (n=65)**
Baseline mRS	
0	35 (54%)
1	25 (38%)
2	5 (8%)
Baseline NIHSS	18 (13 – 23)
Baseline Systolic Blood Pressure	146 (132 – 166)

Table 4 - STABILISE Patient Characteristics
(n varies due to partial data being available)

Imaging and Treatment Characteristics	**Population (n=66)**
Intracranial Occlusion Location (>1 in certain patients)	
ICA	15 (23%)
ICA-T	9 (14%)
M1 Proximal	32 (49%)
M1 Distal	19 (29%)
M2	18 (28%)
VA	2 (3%)
Basilar distal	3 (5%)
PCA	1 (2%)
Other	1 (1%)

Table 5 - STABILISE Trial Patients Imaging and Treatment Characteristics

3.5.3 Treatment Details

IV tPA was administered in 90% (55/61) of patients at a median time of 115 (IQR 89 – 159) minutes from symptom onset. Procedures were performed under conscious sedation in 79% (52/66) of patients. General anaesthesia was used in 21% (14/66) of patients, Table 6.

Treatment Details and Process Times	**Population (n=61)**
Treatment with intravenous alteplase	55 (90%)
Process times (min)	
Onset to IV tPA (min)	115 (89 - 159)
Onset to Reperfusion (min)	258 (215 - 311)
Anaesthesia details	**Population (n=66)**
CS (conscious sedation)	52 (79%)
GA (general anaesthetic)	14 (21%)
Reperfusion (mTICI)	**Population (n=59)**
0	3 (5%)
1/2a	9 (15%)
2b/3	47 (80%)

Table 6 - STABILISE Treatment Details and Timelines
(n varies due to partial data being available)

3.5.4 Radiological Outcomes

Good grade reperfusion as assessed by an mTICI 2b or 3, was achieved in 80% (47/59) of participants for which data is available, within a median time of 258 minutes (IQR 215 - 311) from symptom onset.

3.5.5 Clinical Outcomes

The median NIHSS at 24 hours improved to 9 (IQR 4-19) from 18 at initial presentation. A good functional outcome as assessed by an mRS of 0 - 2 was achieved at 3 months in 44% (25/57) of participants and in 36% (20/55) at 12 months, Table 7 and Table 8.

Outcomes	**Population (n=66)**
NIHSS at 24 hours	9 (4-19)
mRS at 90 days	**Population (n=57)**
0-2	25 (44%)
3-6	32 (56%)
mRS at 12 months	**Population (n=55)**
0-2	20 (36%)
3-6	35 (64%)
Safety outcomes	**Population (n=66)**
Asymptomatic intracranial haemorrhage	13 (20%)
Symptomatic intracranial haemorrhage	3 (5%)
Mortality at 12 months	12 (18%)

Table 7 - STABILISE Trial Clinical and Safety Outcomes

(n varies due to partial data being available)

3.5.6 Safety and Mortality

Symptomatic intracranial haemorrhage was present in 5% (3/66) of patients. Asymptomatic intracranial haemorrhage was detected in 20% (13/66). Other procedural and peri-procedural complications include: intracranial vessel rupture in 1/66 (2%), new ischaemia in a different intracranial arterial territory in 12/66 (18%), groin haematoma in 3/66 (5%), common femoral artery pseudoaneurysm in 1/66 (2%) and limb ischemia in 1/66 (2%). The 12 months mortality rate was 18% (12/66).

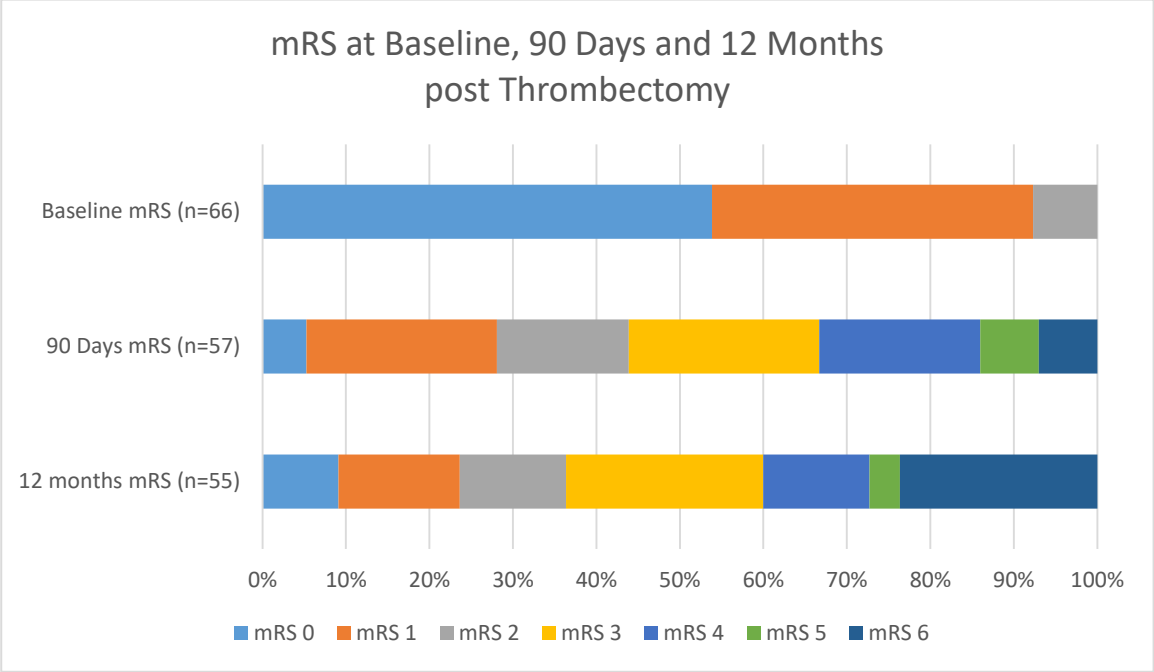


Table 8 - STABILISE Trial mRS from Baseline to 12 Months

(n varies due to partial data being available)

3.6 Discussion and Limitations

After the market release of the SOFIA DAC and ERIC retrieval device, while the STABILISE trial was ongoing, there have been a few studies that reported on the efficacy, safety and clinical outcomes in patients who had mechanical thrombectomy with these devices.

A pilot study from one centre in Switzerland evaluated the safety and efficacy of the ERIC device on 36 consecutive patients who underwent mechanical thrombectomy and in which this was used as either a single (28 patients) or rescue (8 patients) device (Nedeltchev *et al.*, 2015). Their results showed good recanalization rates as assessed by a TICI 2b/3 result in 30/36 (83%) of patients and favourable outcomes (mRs ≤2) at 90 days in 33% of patients. Symptomatic intracranial haemorrhage was present in 8.3% (3/36) of patients and mortality at 90 days was 27.8% (10/36). They concluded that performing mechanical thrombectomy with the new ERIC retriever is safe and effective.

A multicentre, prospective study enrolling patients from 3 different centres in France assessed 34 consecutive patients with LVO who underwent thrombectomy with the ERIC device (Raoult *et al.*, 2016). As a first line device, ERIC achieved successful recanalization (TICI 2b/3) in 20/24 (83.3%) patients and the overall recanalization rate when ERIC was used either as a first- or second-line device was 27/34 (79.4%), which is similar with the results of the Switzerland study. Clinical independence at 90 days as assessed by an mRS of 0 – 2 was achieved in 15/31 patients (48.4%). This study also commented on the fact that the ERIC retrieval device has the advantage of capturing and removing the thrombus without the extra time delay required by the usual stent retrievers which once deployed need a few minutes for clot integration before retrieval.

The largest study was performed at one centre, in Copenhagen, in a retrospective fashion and included a total of 316 patients, 59 of which had mechanical thrombectomy with the ERIC device (Steglich-Arnholm *et al.*, 2017). Using a propensity score matched analysis they found 57 matched pairs and procedures done with the ERIC devices versus classic stent retrievers were then analysed. The rates of recanalization achieved with the ERIC device were 86% and were similar to the 81% rate achieved with the classic stent retrievers. A good 90 days clinical outcome as assessed by an mRS of 0-2 was achieved in 46% of patients treated with

the ERIC device versus 40% with other stent retrievers. Adverse events were also compared and were similar with 28% for ERIC versus 30% for other stent retrievers. Interestingly ERIC was significantly faster at achieving recanalization, this was reported at 67 minutes versus 98 minutes for other stent retrievers (p=0.009); furthermore, another rescue device was used less often in patients where ERIC was initially used; 18% versus 39%, p=0.02.

Another prospective study based on a multicentre registry from France had patient data from 8 centres and they assessed all patients treated with the new ERIC device over a 13 months period (Pierot *et al.*, 2017). The findings of this study are similar with the other ERIC studies showing a high rate of good recanalization TICI 2b/3 in 27/31 (87.1%) and excellent recanalization TICI 3 in 22/31 (71.0%). They compared their results with THRACE and HERMES studies and even though they had a higher rate of ICA and tandem occlusions, poorer ASPECTS scores but slightly less severe NIHSS scores, they showed that ERIC performed well overall despite these factors.

A retrospective study performed in Germany and Switzerland collected data from two centres from patients that were treated with mechanical thrombectomy due to an anterior circulation thrombus and were treated either with the new ERIC device or other stent retrievers (Gruber *et al.*, 2018). They had a total of 183 patients with the 1st device in 49% (90/183) of procedures being performed being the ERIC device and in the other 51% (93/183) a standard stent retriever. Good recanalization, mTICI 2b/3, was achieved in 82% (74/90) patients treated with ERIC versus 57% (53/93) in the other group, which was statistically significant with p<0.001. Additionally, switching to another device (ERIC or another stent retriever) after failed recanalization with the 1st device of choice was shown to increase final recanalization rates, up to 87% if the 1st device of choice was ERIC and up to 79% if the 1st device of choice a standard stent retriever. Good clinical outcomes (mRS ≤2) were reported in 50% (45/90) when the procedure was started with the ERIC device and 35% (32/93) for standard stent retrievers. After adjusting for baseline patient data and procedural characteristics, the rates of good clinical outcome were found to be associated with the patient's age, baseline NIHSS, carotid-T occlusion and the requirement for general anaesthesia; rather than the type of device used. Safety and mortality data were comparable in both groups.

An interesting case report showed that the ERIC retrieval device achieved successful recanalization of a calcified clot located in the MCA in an 82 years old patient (Kwak

and Park, 2018). They reported that imaging showed a 3,7 mm calcified occlusive thrombus and a first attempt to remove this via aspiration failed. Retrieval with the ERIC device was successful on the first attempt and the patient did well achieving clinical independence with an mRS of 1 at 90 days. Calcified intracranial thrombi are rare, but can be challenging to recanalize once lodged in the intracranial arterial vasculature, being more resistant to IV tPA and having lower recanalization rates (up to 13%) compared to atherogenic or cardiogenic emboli (Dobrocky *et al.*, 2018).

A retrospective study using the direct aspiration first pass technique (ADAPT) collected data from 52 patients with M2 occlusion who underwent thrombectomy by direct aspiration with large distal access catheters: SOFIA 5 - 0,055” / AXS Catalyst 6 – 0,060” (Grieb *et al.*, 2019).The successful revascularization rate was 92,3%, achieved with the use of additional stent retrievers in 6 patients. Good recanalization mTICI 2b-3 was reached in 86.5% (45/52) patients and excellent mTICI 3 recanalization in 61,5% (32/45) patients. At 90 days, 55,8% (29/52) patients had achieved independence with an mRS between 0 and 2. Their conclusion was that DACs used alone are safe and effective for mechanical thrombectomy in acute M2 MCA occlusions. They emphasized the advantage of not deploying stent retrievers in smaller vessels to avoid distal embolization and vasospasm. No cases of sICH (symptomatic intracranial haemorrhage) occurred, and the asymptomatic ICH (intracranial haemorrhage) rate was low at 3.9% (2/52).

These studies affirmed the need for a larger study to evaluate the ERIC retriever and SOFIA DAC. Preliminary blinded results from the STABILISE trial are very limited. When looking at the older people recruited into the study, this was 22% (15/68) which is not a very low rate, higher that other prior studies, but possibly more could have been recruited. Although the STABILISE trial did not have an upper age limit, lower overall recruitment into this age group could represent numbers of older patients being referred for thrombectomy from other hospitals, as well as patients having a good function at baseline as assessed by the clinical team, as only patients with a baseline mRS of 0 to 2 could be enrolled. Older people living in nursing homes with significant comorbidities leading to a lower mRS were most likely not considered for this trial and there is the potential that due to these stringent requirements, especially when rushing to make a decision, some potentially suitable patients were not identified.

Partial results in the present study show that the majority of patients had M1 51/66 (77%) and M2 18/66 (28%) MCA occlusions, 22/66 (33%) had atrial fibrillation and 37/66 (56%) were hypertensive, comparable to previous studies (Goyal *et al.*, 2016). The STABILISE trial achieved good mTICI 2b - 3 reperfusion in 80% (47/59) of patients in a median time of 258 minutes (IQR 215 - 311). The blinded STABILISE trial results show that thrombectomy performed either with a combination of ERIC/SOFIA devices or contemporary stent retriever or aspiration devices is efficient, and our results appear to be comparable with the recently published ERIC and SOFIA studies, but final unblinded data from the trial is still awaited. Our patients had a higher total rate of intracranial haemorrhage of 25% (16/66) compared to 10% (60/629) in the data from the HERMES meta-analysis and this may be due to the fact that patients were assessed at 24 hours with MRI including a GRE or SWI sequence that can show microhaemorrhage which could be easily missed on an unenhanced CT, which is routinely performed in clinical practice. The rates of sICH were 3/66 (5%) similar to data from other studies, e.g. 4.4% (28/634) in the HERMES meta-analysis (Goyal *et al.*, 2016). Preliminary results show that a good functional outcome with an mRS of 0-2 was achieved in 44% (25/57) at 90 days, and 36% (20/55) at 12 months, but again this data is incomplete.

The final data from the STABILISE trial is still in the process of being finalised, after which it will be analysed by the trial statistician and then I will be involved with writing the paper so that the results from the trial can be disseminated.

3.7 Conclusion

To my knowledge, the STABILISE trial will be the first multicentric, randomized control trial to assess the new ERIC and SOFIA devices. Preliminary, blinded data shows overall good recanalization rates in this study and a good clinical outcome at 90 days similar to other major trials. Once the trial results are finalized and access to the unblinded data given, I plan to work on writing up the trial paper and submitting it to a journal for world-wide dissemination.

Chapter 4. CTA Project

Once the STABILISE trial was open to recruitment at the Royal Victoria Infirmary in Newcastle, it became apparent that the initial CTA imaging for patients which could potentially have a LVO infarct is of utmost importance. No patients had been recruited in the trial in the first three months and a central point to be considered was the importance of obtaining the initial required CT/CTA imaging within a limited time window post symptom onset. As the benefits of thrombectomy were already proven, the diagnosis of LVO stroke needed to be urgently improved so that patients could be swiftly referred to the neurointerventionists for treatment. This was especially important for general district hospitals which would first need to fully assess the patient and perform the required imaging before arranging transfer to a tertiary centre. The STABILISE trial highlighted the fact that there was a lack of patients being referred for mechanical thrombectomy from the neighbouring district general hospitals. One of the problems was that their local radiology departments were not comfortable with performing and interpreting acute CTA scans to assess for signs of acute stroke and / or LVO. This is what motivated me to start the CTA project to see whether the imaging diagnosis of these patients and then their subsequent management can be improved.

4.1 Audit of CTA Practice

4.1.1 Introduction

In the North East teaching hospitals, out of hours CT/CTA scans are provisionally reported by a specialist radiology trainee before being reviewed by a consultant. At the Royal Victoria Infirmary, the supervising on call neuroradiology consultant, although available for giving a second opinion at any time, will generally review all scans and document any disparities within one to twelve hours. Local imaging guidelines for patients presenting with acute ischaemic stroke symptoms were introduced at the Royal Victoria Infirmary in 2013. These guidelines recommend that patients with a suspected LVO should have their imaging prioritised and that the CT

angiogram should be performed immediately after the unenhanced CT brain. A fast and accurate assessment of all patients potentially suitable for acute interventional management is critical to offer the best possible treatment and I was interested to find out whether the imaging was performed adequately and within the expected timeframe.

4.1.2 Aims

I performed an audit to assess the performance against the local Royal Victoria Infirmary guidelines for CT/CTA imaging in patients presenting with acute ischaemic stroke symptoms. The guidelines had five points which were used as criteria for the audit:

I. All patients with acute ischaemic stroke symptoms
II. Presenting within <9 hours of symptom onset
III. Suitable for thrombolysis and/or thrombectomy
IV. Immediate CT and CTA needs to be performed
V. CTA to cover from the aortic arch through to the circle of Willis

The three main aims of the audit were to:

I. Assess compliance with the local guidelines
II. Evaluate the rate of clinically relevant imaging findings
III. Consider using the data to develop a validated case archive of CTAs

4.1.3 Methods

A retrospective review was performed by assessing all consecutive patients identified from the stroke electronic database admitted with possible ischaemic stroke from 01/07/2013 to 31/01/2014. Data was extracted by using electronic sources and reviewing patient notes in selected cases. The data extracted and collated into an Excel file included the following fields for every patient assessed: patient ID, age, sex, stroke symptom onset, stroke type and side, date and time of CT scan, CT findings, whether CTA was indicated and whether it was performed, explanation if CTA was indicated but not performed, CTA timing, adequacy of CTA scan, CT scan

radiation dose, timing of CT/CTA report, report changes after consultant neuroradiology review, other imaging obtained (ultrasound or MRI), whether the patient had thrombolysis, thrombectomy, carotid endarterectomies/stenting, medical treatment and any other relevant information.

4.1.4 Results

The audit period was for a total period of seven months, from 01/07/2013 to 31/01/2014. In total 364 patients were assessed, 174 (48%) females and 190 (52%) males with a median age of 77, range 27 – 101.

CTA was indicated in 42% (153/364) and from those, it was performed in 75% (115/153) of those patients, Figure 10.

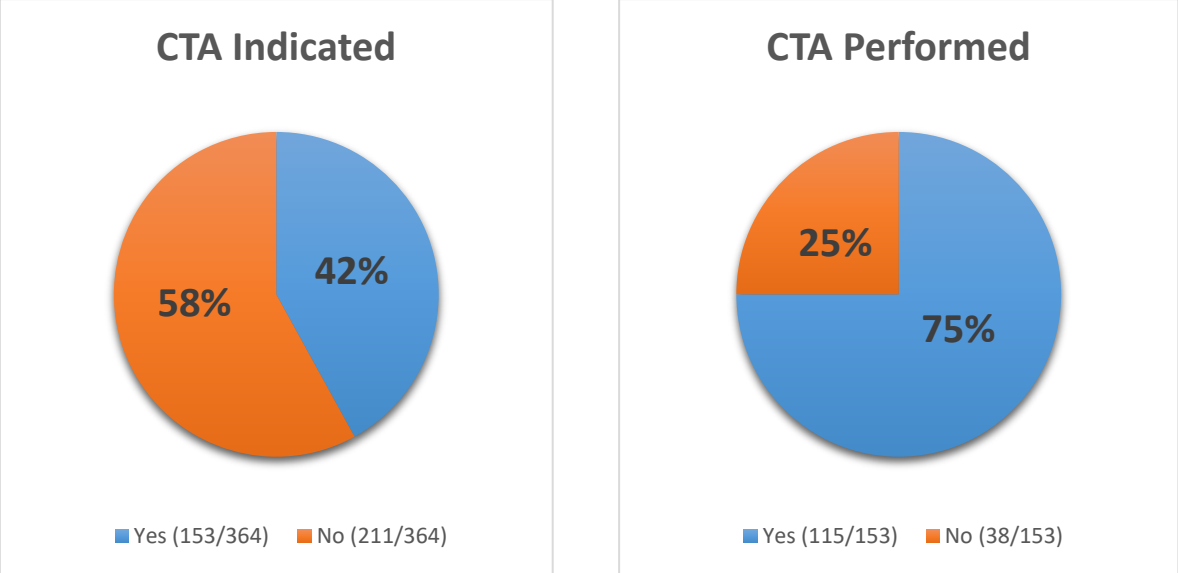


Figure 10 - Acute CTAs

Acute CTA was indicated in 42% and from these patients, it was performed in 75%.

Results showed that CTA was indicated but not performed in 38/153 (25%) of patients and the reason for this was assessed, Figure 11. For the majority of patients which did not have a CTA, although this was indicated according to the local

guidelines, there was a valid reason such as a contraindication to thrombolysis, improving symptoms, already established stroke, etc. For 7/38 (19%) of these patients, no valid reason was identified, Figure 11. Overall compliance with performing acute CT/CTA imaging was very good with 95% (146/153) of patients having immediate imaging as per local guidelines.

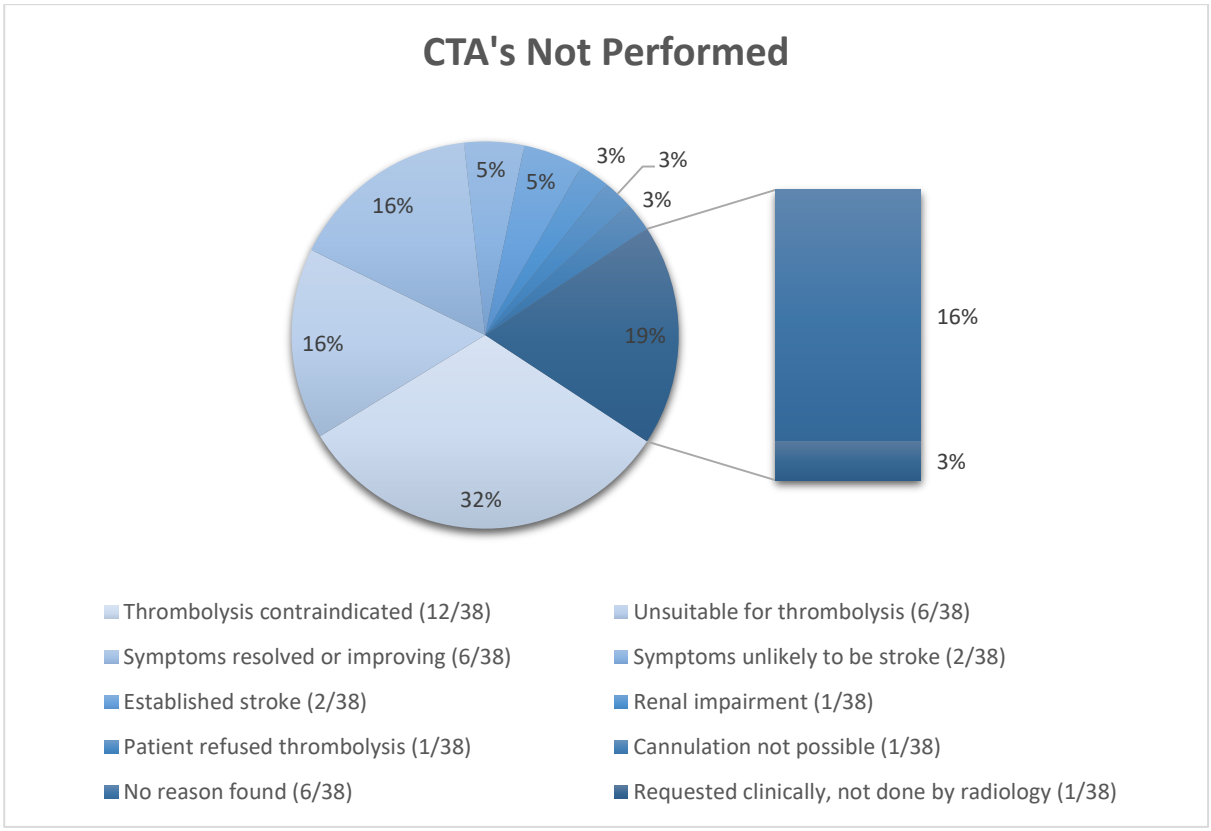


Figure 11 - Reasons for CTA not being performed acutely

Further analysis was performed to assess the adequacy of the CTA scans, in particular to assess whether all the vascular territory was imaged according to guidelines, from the aortic arch through to the circle of Willis. After reviewing all the CTA images on our local PACS (Picture Archiving and Communication System), results showed that the arch was not visualised in 20% (23/115) patients, Figure 12.

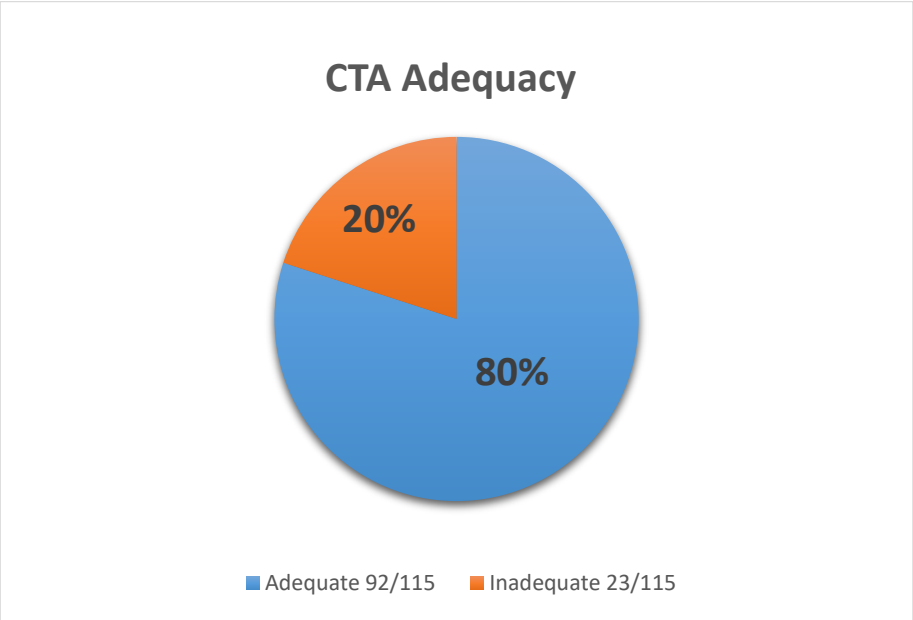


Figure 12 - Adequacy of CTA imaging

Percentage of adequate CTA scans with coverage from the aortic arch through to the circle of Willis.

Assessing when the scans were performed, showed that the majority 58%, (210/364) were done out of hours (outside of normal office hours, from 9AM to 5PM), see Figure 13.

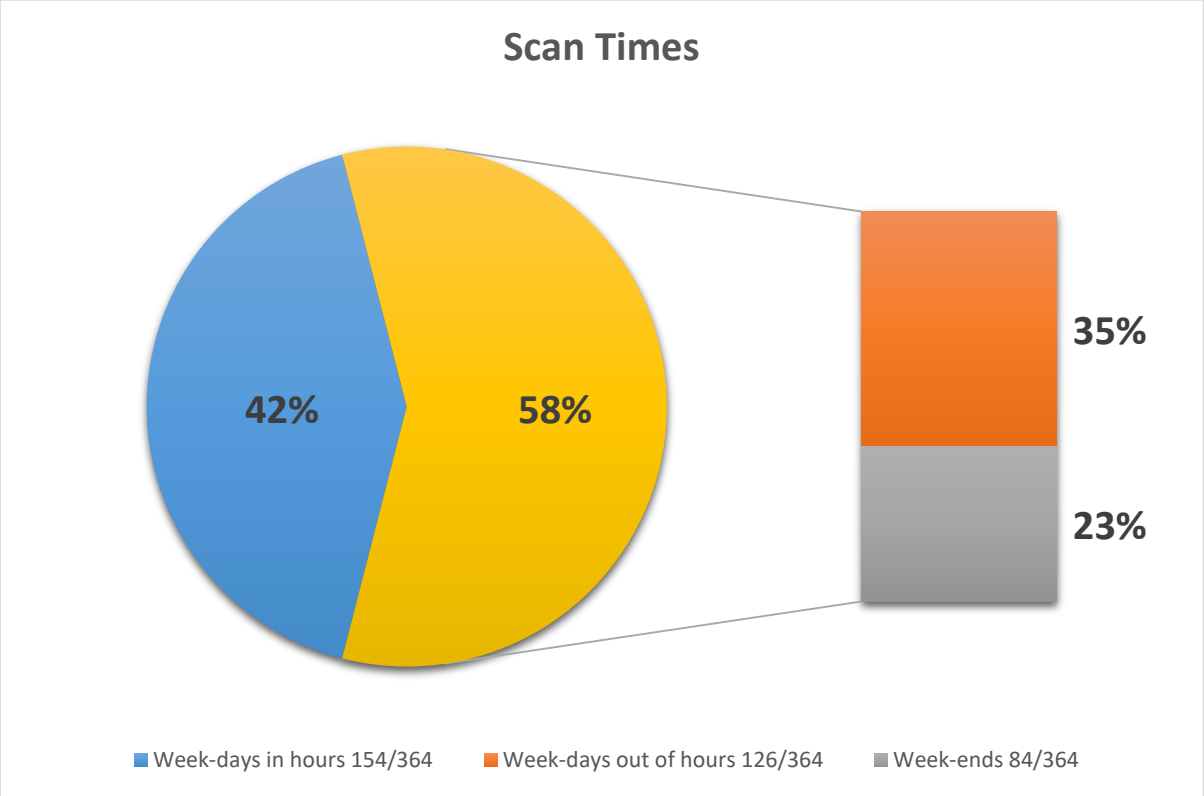


Figure 13 - CT/CTA scan times

As expected based on this, most scans (57%) were initially reported by the on-call radiology registrar before being reviewed and attended by a neuroradiology consultant, typically within 1 to 12 hours; Figure 14.

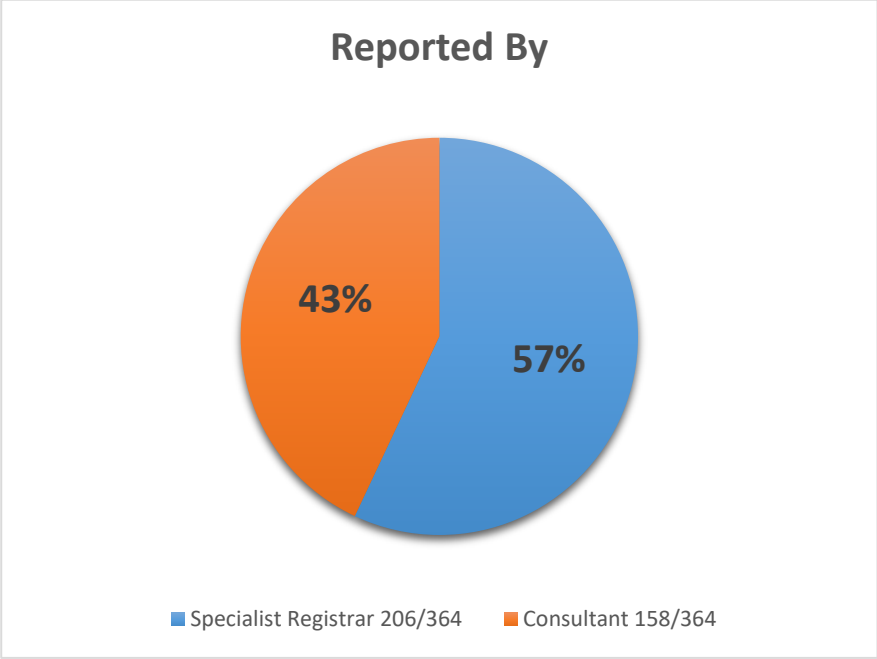


Figure 14 - CT/CTA scans reporting

The initial report was provided in the majority by the on-call specialist radiology registrars.

Out of a total of 206 scans initially reported by the radiology registrars, 11 (5%) of them had not been reviewed at the audit time by a consultant. The rest of the scans had all been reviewed by a neuroradiology consultant and an amendment was documented on the PACS system. From these, 25% (48/195) had a documented discrepancy, which was further classified as minor or major. A minor discrepancy was a finding on the scan which would not affect immediate patient management, while a major discrepancy would impact on the acute care of the patient. 12% (24/195) of the reports, after being reviewed by a neuroradiology consultant, had a documented major discrepancy.

Important incidental findings are also significant when reviewing scans. Out of the 115 CTA scans reviewed, 2 patients (2%) were found to have an incidental lung cancer which was not known to the clinical team.

Assessing how long it took for reports to be available on PACS after the imaging was performed, showed that it was faster to have a report at the weekends, with an average time of 54 minutes, Figure 15. This is most likely because out of hours reports are finalised by the on-call registrar, while during normal office hours, the radiology registrar will put a provisional report which will be reviewed and then finalised by a neuroradiologist, thus taking longer to complete.

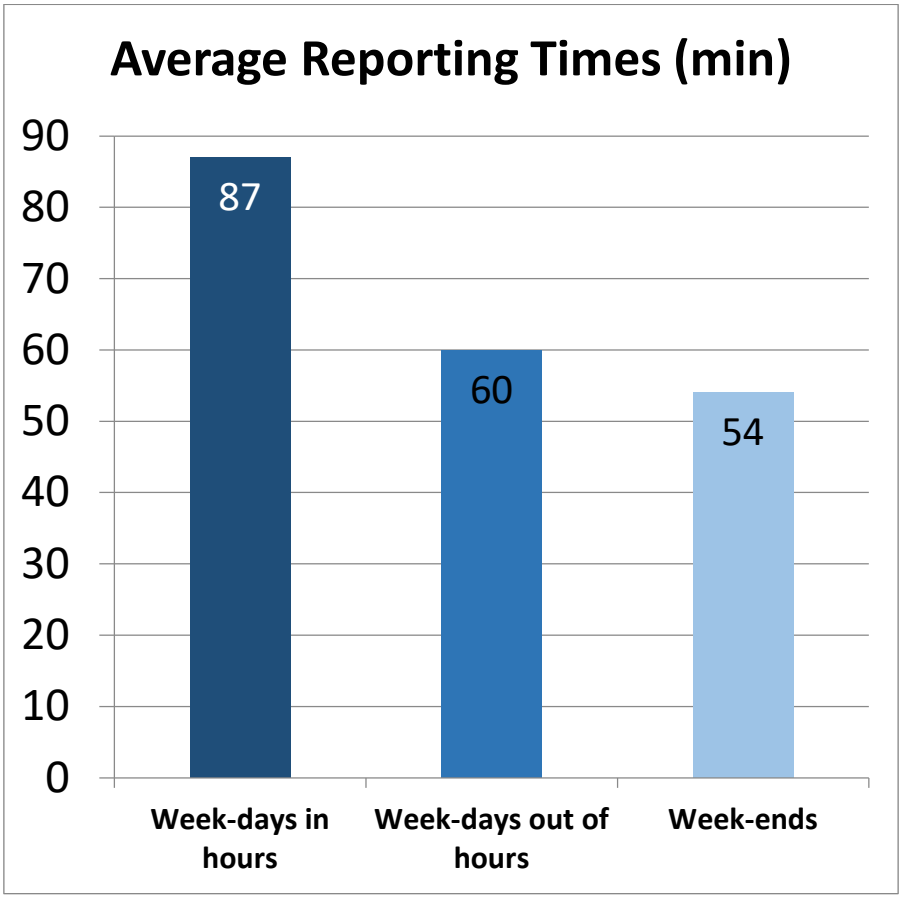


Figure 15 - Average reporting times

This is reported in minutes from the initial time of the CT/CTA scan to when the report was finalised on PACS.

In terms of clinical patient management, 11% (40/364) received intravenous thrombolysis and one patient was offered but refused this treatment. A total of 37 out of these 40 patients had an acute CTA performed.

2% (6/364) of patients had a mechanical thrombectomy procedure performed and all of them had an acute CT/CTA scan performed.

2% (7/364) had either a carotid endarterectomy or a carotid stenting performed during the same admission. Another 3 patients were considered for treatment but were found to be unsuitable, 2 patients had already a previous endarterectomy while 1 patient had a previous stent in place.

Upon review of discharge letters, all 364 patients had their secondary prevention medications reviewed and amended as needed before hospital discharge.

4.1.5 Discussion

The local imaging guidelines introduced at the Royal Victoria Infirmary in 2013 have been largely successful with 95% of patients presenting with symptoms of acute ischaemic stroke being adequately assessed with CT and CTA. Although the majority (80%) of CTA scans were of adequate quality, in 20% the aortic arch was not visualised, and this is an area that needs further improvement.

Most (58%) scans were performed out of hours, either in the evenings/nights or at the weekends. Because of this, most (57%) scans were reported initially by a radiology registrar, before being reviewed by a consultant. 25% of all the scans reviewed by a neuroradiology consultant had amendments, with 12% having a major amendment documented which if identified earlier could have potentially changed the initial patient management.

The patient management was affected by these imaging examinations, with 11% receiving intravenous thrombolysis, 2% having an acute thrombectomy, 2% having carotid endarterectomy or carotid stenting and 100% having their long-term preventive medications reviewed and adjusted.

The findings of this audit were presented locally at the Royal Victoria Infirmary and also regionally, at the northern radiologists annual scientific meeting in the summer of 2015. This has helped to bring awareness about the importance of performing acute CT/CTA imaging in patients that are likely to have a large vessel occlusive acute ischaemic stroke, including discussing the scan technicalities and important review areas.

This project has raised the issue of CTA training within the region, as there were both minor and major discrepancies recorded and the possibility of further improvement of reporting skills needed to be further explored.

4.2 Development of Validated CTA Teaching Archive

Next, I worked on developing a validated case archive of CTA scans. The studies selected were from patients that presented with clinical signs and symptoms of acute stroke to a tertiary hospital, Royal Victoria Infirmary, where their initial CTA scans were reported by radiology trainees.

Reviewing the scan data from the CTA audit performed, a validated case archive comprising 50 CTA scans was developed by having each scan reviewed by 3 neuroradiologists, two consultants and one fellow, and noting all the findings. There was a mixture of normal scans, scans with significant acute findings and others with significant incidental findings. All of these were specifically chosen to cover normal anatomy and most pathologies that could be encountered when reporting these types of studies. A total of 6 normal scans were included, specifically selected to demonstrate how to methodically assess a scan and include commonly encountered normal variants. The abnormal scans included such pathologies as intracranial occlusions, carotid stenoses and dissections, previous endarterectomies and other important incidental findings such as aneurysms, mass lesions, etc.

Reviewing the patients case notes and electronic records was used to obtain the presenting clinical details, the subsequent management and clinical outcomes up to the usual neurological follow-up, between 3 to 6 months. This data, together with the findings from the CTA scan was used to make a report type document for each patient that included 3 sections: a) Clinical Details, b) Brain CT / CTA Imaging, see Figure 16 and Figure 17 (with online videos), and c) Clinical Course.

Sample CTA case from validated case archive:

a) Clinical Details

- 75 years old lady
- Presents with 2 ½ hours of dysphasia
- PMHx: right sided endarterectomy one year ago for right amaurosis fugax, hypertension and hypercholesterolemia
- Normally lives on her own and she is independent (mRS1)

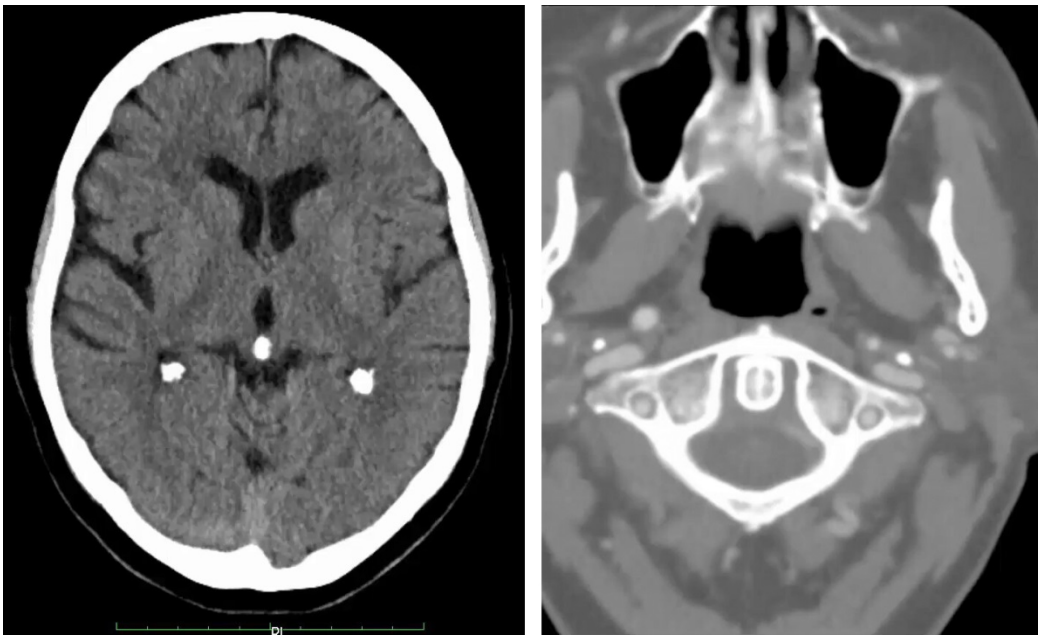


Figure 16 – Axial CT and CTA brain

Videos: https://bit.ly/2vmh2P8 (left) and https://bit.ly/2UUCtpE (right)

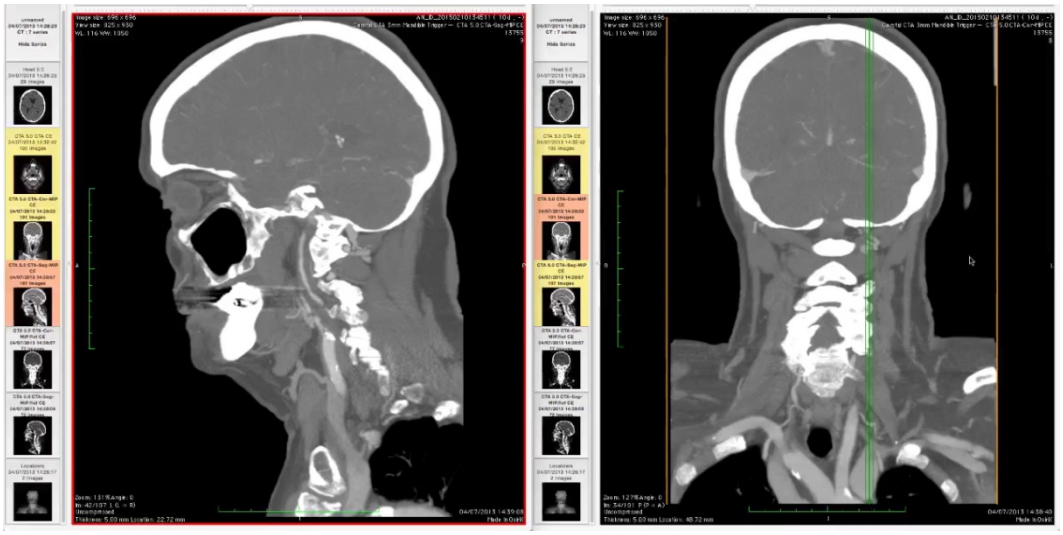


Figure 17 – CTA sagittal and coronal reconstructions

Video: https://bit.ly/2URoQaC

b) Brain CT/CTA Imaging

NECT

- No acute infarct
- Mild to moderate periventricular small vessel disease and lacunes

CTA

- Calcified atheroma at the left CCA bifurcation with significant stenosis of the left ICA at its origin. There is a small calibre left ICA distal to this stenosis.
- There is a kink affecting the proximal right ICA (SRS 9, IM68) which is indicative of the previous endarterectomy.
- Also make note of the right foetal posterior communicating artery (occurs in up to 30% of the population) and an absent right P1 PCA.

c) Clinical Course

- A left carotid endarterectomy was performed 5 days later.
- Within hours the patient developed two focal areas of haemorrhage within the left MCA territory thought to be secondary to reperfusion injury.
- She was managed conservatively and was discharged 12 days after initial admission to the local stroke and rehabilitation unit.
- The patient spent another 2 months and 2 weeks in rehabilitation before being discharged home (mRS 3).
- At her last clinic follow up 4 months after initial presentation, she has residual moderate dysphasia but otherwise is able to look after herself (mRS 2).

4.3 CTA Course Development and Validation

As a follow-up to the audit and the validated CTA case archive, I developed a simulated radiology training course for reviewing CTAs of patients presenting with hyperacute ischaemic stroke.

In summary, this project was developed with the aim of assessing if an intensive one-day course training radiology registrars how to read CTA studies improves their reporting skills. This project was very successful, and I wrote and published a paper about it (Cora *et al.*, 2017), see Appendix O – CTA Training Paper.

Training days were organised at the MacLab, a specific, purpose-built radiology centre where the Osirix 64-bit software is running as a teaching PACS system on 12 Apple 27 retina iMacs. Each full day course consisted of a few didactic lectures:

- Evidence for performing CT / CTA Imaging
- How to read CTAs including applied neurovascular anatomy and implications on decision making
- Radiographic considerations
- Osirix software review (if necessary)

This was followed by hands-on training, where each attendee could review between 15 to 20 scans, and they each had access to an iMac station, Figure 18.

Figure 18 - CTA course in the MacLab facilty

This led to the creation of a full day training course, see Appendix N – CTA Training Day Agenda.

Course days were organised in such a way as to ensure that all the radiology trainees were able to attend one of the sessions, which were spread over several months. I then reviewed the reports of the radiology trainees pre and post CTA training day, blinded as to whether reports were pre or post course, including neuroradiologists' amendments to their reports, to assess whether it had impacted on

their reporting performance and confidence. CTA reports, indicated for an acute stroke, reported by the trainees were reviewed and the rates of both minor and major errors were documented.

A total of 252 CTA reports done by 48 radiology trainees were assessed. Pre-training, the total discrepancy rate was 37%, 12% major and 25% minor errors. After the CTA training course day, the total discrepancy rate was 34%, 4% major and 30% minor errors. The reduction in the rate of major discrepancies was significantly reduced, p=0.037.

A survey done after the course showed that 73% of trainees reported being more confident with these types of CTA studies after attending the training. Importantly, this one-day intensive course based on a validated case archive of CTA scans in acute stroke significantly reduced major discrepancies in the interpretation skills for radiology trainees.

Parallel to this project, the developed course (Appendix N – CTA Training Day Agenda) was approved by the Royal College of Radiologists for 6 CPD points and it was delivered to general radiologists working in district general hospitals and to stroke physicians. The cases were also made available via a website I designed and linked to an online PACS type platform, hosted at the MacLab and running a web Osirix version.Course attendees could continue reviewing cases from home via a secure connection, Figure 19 and Figure 20 (with video link).

Figure 19 - CTA Website

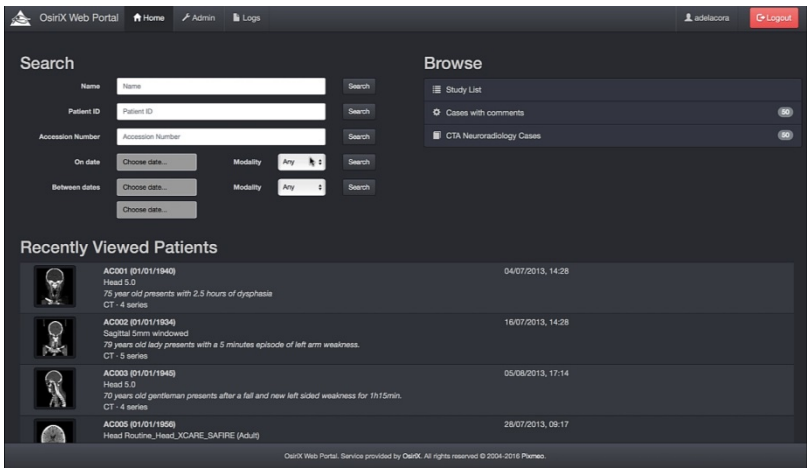


Figure 20 - Online CTA course interface

Video: https://bit.ly/2vmXD0d

The feedback from both these groups was very good, leading to a very successful course in the North East of England and the Royal College of Radiologists is currently working on making this available as part of their online courses.

Chapter 5. Development of a New Thrombectomy Technical Index

One of the objectives from the STABILISE trial was to attempt the development of a tortuosity scoring tool. Unfortunately, the trial results are not finalised, and I was not able to make an assessment linking arterial tortuosity and collateral brain circulation to clinical outcome post thrombectomy after LVO stroke. However, as I found this concept very interesting, I decided to work on a project to determine whether a technical score predicting the difficulty of a thrombectomy procedure would be clinically useful.

As discussed in previous chapters, mechanical thrombectomy can be performed in patients with contraindications to IVT and in those presenting later than 4.5 hours' time frame for which IVT is licensed (Department of Health, 2008). Thrombectomy can be technically very challenging especially in the older population patients with tortuous atherosclerotic vasculature.

One of the challenges when performing an acute thrombectomy procedure is navigating the arterial tree with different guidewires, catheters and any other required devices. Once the arterial (usually femoral) puncture has been performed, the next step is to navigate from the aortic arch, via the great vessels, into the intracranial circulation and then into the occluded target artery. Obtaining an angiogram of the arterial vasculature is essential for planning and performing the procedure. Tortuous vessels with atherosclerotic disease can pose a great challenge, especially when there are time constraints present, such as in acute stroke patients, where timely cerebral perfusion restoration is required.

In this chapter, I will discuss a newly developed technical scoring index that allows neurointerventionists to reliably predict the difficulty of a thrombectomy procedure. This could usefully inform: (a) decisions on the techniques to be used (route of arterial access, equipment, general anaesthetic versus sedation, first pass thrombectomy technique: e.g. aspiration, stent retriever or a combination) and (b) structure information provided to patients/relatives during assent conversations. However, due to the time critical nature of thrombectomy any such assessment tool needs to be evidence-based, intuitive and capable of being rapidly completed and interpreted.

5.1 Methods

Five domains were included in the Thrombectomy Technical Difficulty Index (TTDI) based on relevant literature of factors affecting the difficulty when performing a mechanical thrombectomy: aortic arch; vascular tortuosity; stenotic disease; clot burden score; and any other extra anatomical or pathological problems.

Before deciding which components to include, I reviewed the available literature on all these factors. Although not many papers were available with regards to performing thrombectomies, there were papers on technical aspects for performing carotid stenting, angiography and body interventional procedures, as discussed in the following paragraphs. Vascular tortuosity, for example, was described as being an anatomical factor that affects ease of navigation when performing endovascular procedures (Schwaiger *et al.*, 2015). For the development of this score, the aortic arch and the target vessel tortuosity were factors that are important. In addition, stenotic disease can increase the complexity of a procedure and can potentially lead to complications, another factor which was important to include when assessing CTAs for mechanical thrombectomy. More specific to removing the thrombus intracranially, there is evidence showing that clot location and length has an impact on the recanalization rate (Kaschka *et al.*, 2016). In addition, there is the potential for other potential complications resulting in a more challenging mechanical thrombectomy procedure, such as patients having previously had grafts or bypasses. These other types of miscellaneous potential issues were also considered when this score was designed. Before proceeding with the testing of this new score, all these factors, as well as their weighting, were reviewed by 5 consultants neurointerventionists for both face and content validation. All these different factors that need to be assessed when performing the scoring are discussed next in more detail.

5.1.1 Aortic Arch

The configuration of the aortic arch can lead to significant delays if it is difficult to navigate. More complex arch anatomy may require more fluoroscopy time, different technique and equipment. If there is significant atherosclerotic disease and calcifications, this may release scrapping debris during catheterisation (Keeley and

Grines, 1998). The aortic arch elongation classification has been previously described and is divided into different grades according to perceived increased navigational difficulty (Lin *et al.*, 2005):

- Grade I: great vessels are all arising normally from the top of the aortic arch
- Grade II: great vessels origins are between the perpendicular lines from the inner and outer curve of the aortic arch
- Grade III: innominate artery origin is proximal to a perpendicular line from the inner curvature of the aortic arch or is arising from the ascending aorta

5.1.2 Vascular Tortuosity

Internal carotid artery tortuosity has been reported in 35% of 1438 patients who underwent conventional angiography in a study done by Weibel and Fields (Weibel and Fields, 1965). More severe vessel tortuosity has been observed in the ageing population and linked to factors including hypertension, diabetes and atherosclerotic disease (Han, 2012) – risk factors which are commonly observed in stroke patients. A recent study by Schwaiger et al. demonstrated that mechanical thrombectomy in the anterior circulation was significantly less often successful in patients with larger vessel angles (Schwaiger *et al.*, 2015).

5.1.3 Stenotic Disease

Asymptomatic moderate carotid stenotic disease, defined as ≥50% but <70% stenosis, has been shown to be present in up to 7.5% of the population, while asymptomatic severe carotid stenotic disease, defined as ≥70% stenosis, has been shown to be present in up to 3.1% of the general population in a meta-analysis including 23706 participants (de Weerd *et al.*, 2010). Arterial stenoses due to atheroma can lead to significant procedural complications. The possibility of unsuccessful thrombectomy, embolus dislodgement or increased procedural time due to difficulty in passing the stenotic segment should be foreseen.

5.1.4 Clot Burden Score

The Calgary CTA Study Group developed a classification score to assess the thrombus load within the anterior circulation - Clot Burden Score (CBS), and demonstrated that it could be used to predict outcome at 3 months (Puetz *et al.*, 2008). A recent study performed on 34 patients with acute occlusion of the distal ICA and/or M1 MCA segment who were treated with mechanical thrombectomy, showed that the clot location and extent as assessed via the CBS had a significant impact on the recanalization rate and overall clinical outcome (Kaschka *et al.*, 2016).

5.1.5 Extra anatomical or pathological problems

Any other additional anatomical or pathological problems which may be encountered in rare instances, but which could significantly affect the outcome of the procedure should also be considered. It is known that anatomical variations of the aortic arch could be present in approximately 11% of the population and this may increase procedural time due to difficulties with vessel cannulation and are associated with possible neurological complications (Faggioli *et al.*, 2007).

5.2 Development of the Thrombectomy Technical Difficulty Index

The TTDI was designed to be used in conjunction with CTA examinations prior to performing a thrombectomy procedure. It underwent clinical face and content validity assessment by 5 consultant neurointerventionists who suggested minimal refinements to the new proposed score.

The total TTDI score represents a technical difficulty index (scores of ≤ 4 representing minimal difficulty, > 4 and < 8 representing mild to moderate difficulty, and ≥ 8 representing severe difficulty) by summing the scores assigned to each of the five domains, see Appendix P – Thrombectomy Technical Difficulty Index (TTDI). There was no further specific weighting of the score as this was done with a limited

number of patients. I plan to perform a larger prospective study, where this score can be used and then refined to see whether certain factors should have a different weighting.

5.2.1 Aortic arch elongation

Examples of the three-standard different aortic arch elongation grades were used as an aide memoire, Figure 21.

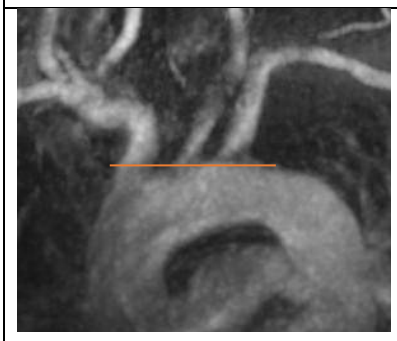
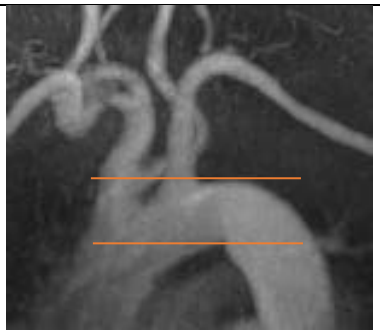
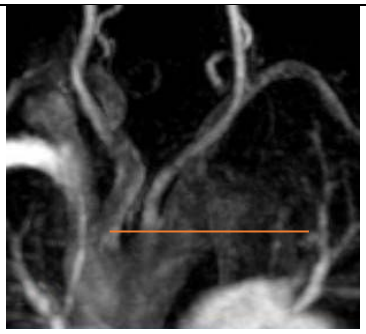
Grade I	Grade II	Grade III
		
Score = 1	Score = 2, or 3 if there is extra appreciable atheroma	Score = 3, or 4 if there is extra appreciable atheroma

Figure 21 - Aortic Arch Elongation Classification

5.2.2 Head and neck target artery tortuosity

A three-point qualitative scale was utilised. The descriptions with illustrative examples of the scale used are shown in Figure 22.

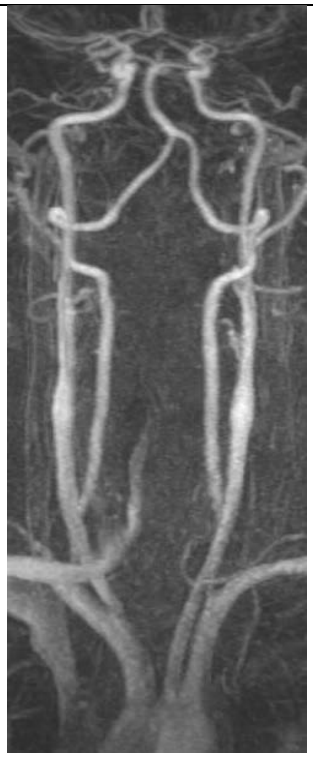
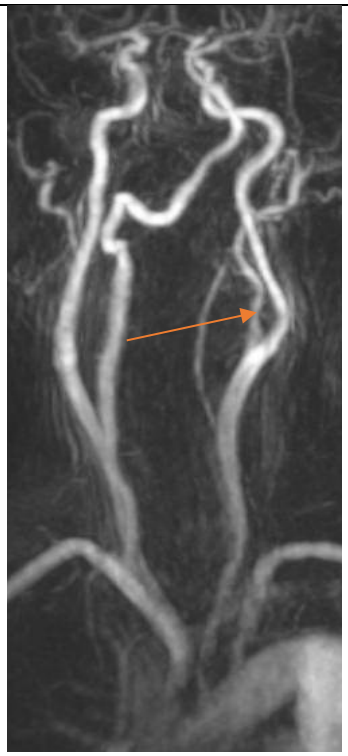
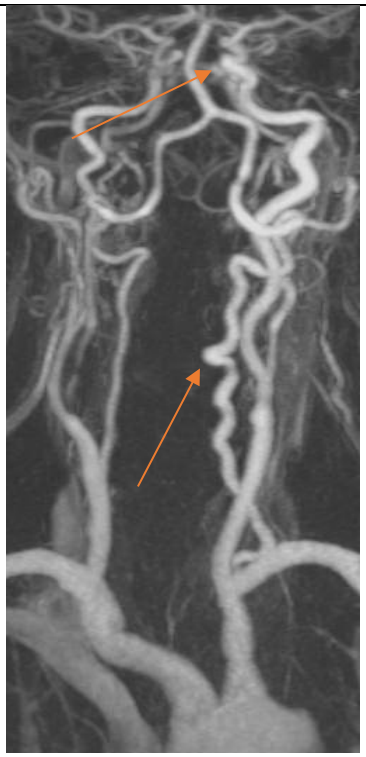
None/Mild	Moderate	Severe
		
Less than 30° deviation from the normal expected centre of blood flow	Approximately between 30° to 60° angle deviation from the normal expected centre of blood flow affecting the target vessel	More than 60° angle deviation from the normal expected centre of blood flow, including any tight kinks, loops or spiral twists
Score = 0	Score = 1	Score = 2

Figure 22 - Tortuosity qualitative scoring

5.2.3 Target artery stenosis

Any target artery stenosis was classified as follows: <50%, 50 – 69%, 70 – 95% and acute occlusion / critical stenosis and assigned scores of 0, 1, 2 and 3 respectively, see Appendix P – Thrombectomy Technical Difficulty Index (TTDI)Appendix P – Thrombectomy Technical Difficulty Index (TTDI).

5.2.4 Clot burden score

For this domain, a previously described clot burden score (Puetz *et al.*, 2008) was used for patients with anterior circulation strokes, Figure 23 . A score of 10 is normal and points are subtracted depending on the thrombus location. For posterior circulations strokes, there is no accepted clot burden scoring. Therefore, a simple thrombus scoring tool was utilised:

- Minimal to mild thrombus: PCA or another single branch beyond basilar tip, or Isolated basilar clot (<1/3 occluded) – score 0
- Moderate thrombus: <2/3 Basilar trunk + another vessel with clot occlusion, or >2/3, but not entire basilar trunk occluded – score 1
- Severe thrombus: Vertebral + >1/3 basilar vessel clot, or 3/3 basilar affected, or >2/3 basilar + another major vessel (PCA/SCA/PICA) – score 2

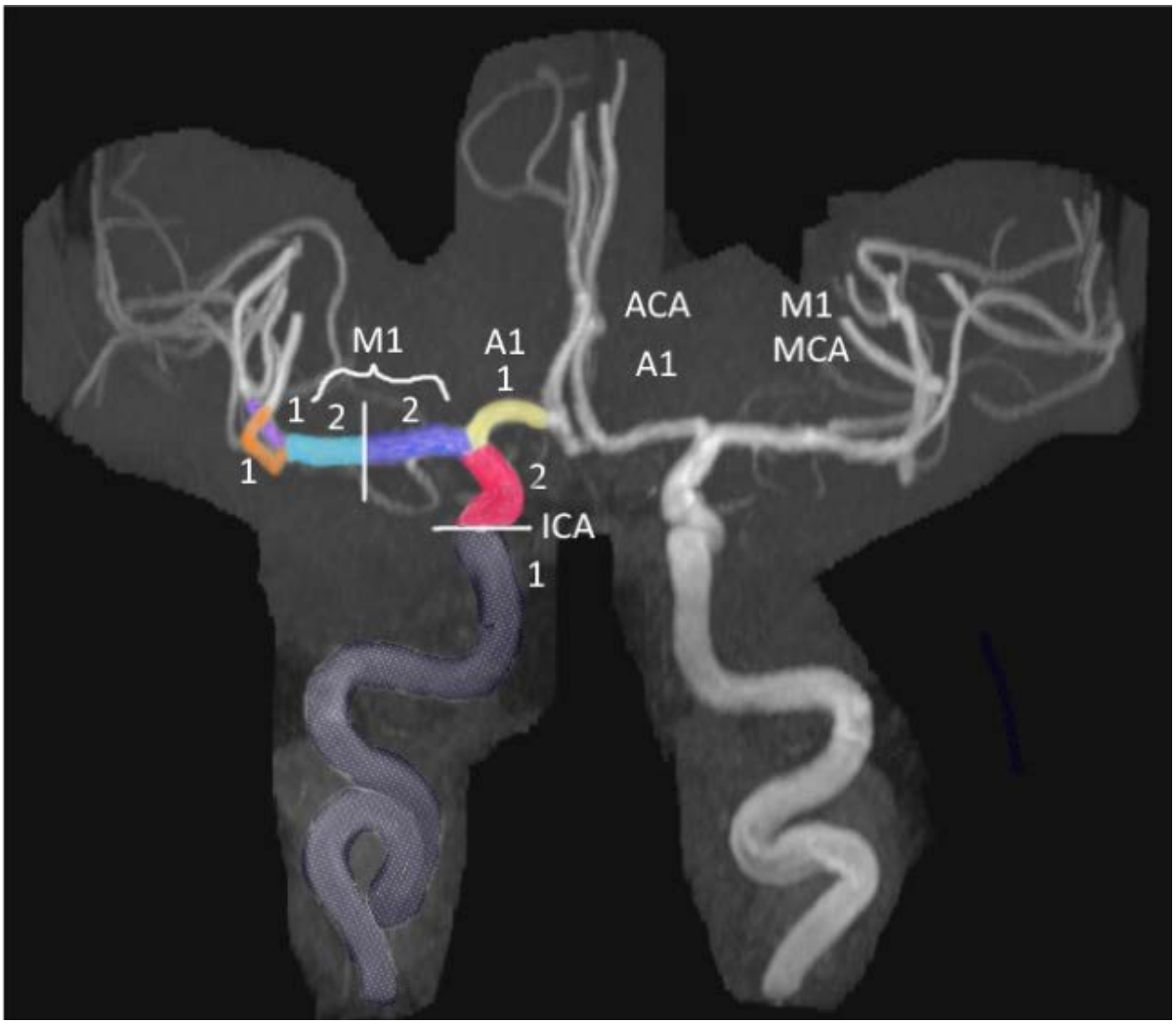


Figure 23 - Clot burden score in the anterior circulation

There is a total of 10 points and the score is calculated by subtracting points according to clot location: 2 points are subtracted for thrombus in the supraclinoid ICA and each of the proximal and distal halves of the MCA trunk. 1 point is subtracted for thrombus in the infraclinoid ICA, in the A1 ACA segment and for each affected M2 MCA branch. For example a carotid T occlusion with thrombus in the distal ICA, the proximal A1 ACA and the proximal M1 MCA would have a clot burden score of 10–(2 +1+2)=5.

5.2.5 Additional problems (e.g. variant anatomy)

A further single point can be added (at the discretion of the neurointerventionist) if any other problem that could potentially lead to procedural difficulty is identified: tandem occlusion, aortic coarctation, common brachiocephalic trunk (bovine arch), variant origin of the vertebral artery, right aortic arch, double aortic arch and any other variant anatomy / pathology - including known severe PVD, International Normalized Ratio/Prothrombin Time is significantly prolonged or other arterial access problem. A maximum of 1 point can be added irrespective of the number of issues.

5.3 Patient Selection and Data Collection

A consecutive sample of 30 patients who underwent mechanical thrombectomy at the Royal Victoria Infirmary from October 2013 to May 2016 with a comprehensive CT angiogram (CTA) as part of their initial assessment were used to assess the reliability and validity of the TTDI.

CTA scans were imported from our local PACS system and fully anonymised. One senior consultant INR (interventional neuroradiologist), Phil White, with more than 10 years' experience reviewed each case and assigned an expected procedural thrombectomy difficulty rating for each case: minimal, mild to moderate or severe difficulty. These ratings were used as the reference standard for assessing the extent of agreement (intra-class correlation coefficient, ICC) between the TTDI scores assigned to each patient by the 7 INRs. The ICC was also used to assess the extent of agreement of the 7 INRs with the expert opinion. Landis and Koch provided guidelines for interpreting ICC values and, specifically, values between 0.61 to 0.80 indicate substantial agreement, with values of 0.81 to 1.0 indicating almost perfect to perfect agreement (25).

A total of 7 INRs (4 senior, 3 junior) used the TTDI to assess each case. No clinical details were provided, except what was present on the scans and whether the thrombus was on the right/left side or in the anterior/posterior circulation. The total time that each INR took to assess all cases with the TTDI was recorded.

The TTDI category for each case assessed by the 7 INRs was subsequently analysed with reference to data on actual procedure duration, number of devices

used, recanalization using the mTICI grading of angiographic reperfusion and 90 day mRS (obtained from interrogation of thrombectomy procedure notes, patients' notes and clinical letters). For this analysis, each patient was attributed a consensus thrombectomy difficulty score by using the average TTDI score as assessed by the 4 senior INRs. Appropriate tests of differences (independent t tests and Mann-Whitney U tests) were used to establish whether actual data on procedures differed as a function of TTDI categories (due to the small number of severe cases, analyses were conducted using cases assigned as minimal and mild to moderate difficulty).

5.4 Results

Thirty patients, 19 males and 11 females, of median age 72 (range 33 – 87) were assessed. They had a median NIHSS of 18.5 (IQR = 13.5 – 22.5). Occlusion location was present in the M1 MCA in 18/30 (60%), ICA in 5/30 (17%), M2 MCA in 3/30 (10%), basilar artery in 3/30 (10%) and vertebral artery in 1/30 (3%). Treatment with IV tPA was administered in 16/30 (53%) of patients. Symptom onset to groin puncture was achieved in a median of 216 min (IQR 188 – 285). Symptom onset to reperfusion was achieved in a median time of 276 min (IQR 228 – 333).

Neurointerventionists recoded the total time to look at all cases and this resulted in a range of between 2 to 4 minutes to assess a single case with the TTDI.

5.4.1 Reliability Analysis

Intra-class correlation coefficient (ICC) between ratings from the 7 INRs was 0.89 (95% CI = 0.81 to 0.94), indicating almost perfect agreement. Once the TTDI score was categorised into a difficulty grading (minimal, mild to moderate, severe), the ICC was 0.85 (95% CI = 0.75 to 0.92).

The ICC for the TTDI scores between the reference expert opinion and the other 7 INRs was 0.86 (95% CI = 0.77 to 0.93).

5.4.2 Validity Analyses

Out of the 30 patients, 15 patients (50%) were assigned a minimal level of difficulty (TTDI ≤ 4), 13 patients (43%) were assigned as mild to moderate difficult (TTDI >4 to <8) and 2 patients (7%) as severe difficulty (TTDI ≥8).

Mean procedure duration was 46 (SD=20), 73 (SD=36) and 59 minutes for the patients in the minimal, mild to moderate and severe categories respectively. Further analysis showed that there was a trend towards increase in fluoroscopy times from the minimal to the mild to moderate category. The mean difference for procedure duration between minimal difficulty cases compared to mild to moderate [-27.61 mins, 95% CI = -50.02 to -5.19 mins) was statistically significant (t = -2.437 [df=26], p < 0.05).

The mean number of thrombectomy devices used was 1.1, 1.3. and 2 for the patients in the minimal, mild to moderate and severe categories respectively. The mean number of devices between cases assigned as minimal and mild to moderate difficulty was not statistically significant (p > 0.05).

Good recanalization rates (mTICI 2b/3) were achieved in the majority of patients within the minimal and mild to moderate category, and in half of the patients within the severe category, Table 9. mTICI between cases assigned as minimal and mild to moderate difficulty was not statistically significant (p > 0.05).

mTICI	**Minimal Difficulty** **N = 15**	**Mild to Moderate Difficulty** **N= 13**	**Severe Difficulty** **N = 2**
0	3 (20%)	1 (8%)	1 (50%)
1	1 (7%)	2 (15%)	0
2A	0	0	0
2B	4 (27%)	3 (23%)	1 (50%)
3	7 (47%)	7 (54%)	0

Table 9 - mTICI recanalization and predicted difficulty on TTDI

The mRS at 90 days post thrombectomy as a function of TTDI category is shown in Figure 24. 53% (8/15) of the patients assigned a minimal difficulty category TTDI (score ≤ 4), had a good outcome (mRS 0-2). For patients within the mild to moderate category, only 8% (1/13) had a good outcome, with approximately half with mRS = 3. For patients in the severe difficulty category, neither of the 2 patients had good functional outcome; despite good recanalization being achieved in one of these patients. mRS between cases assigned as minimal and mild to moderate difficulty was not statistically significant ($p > 0.05$).

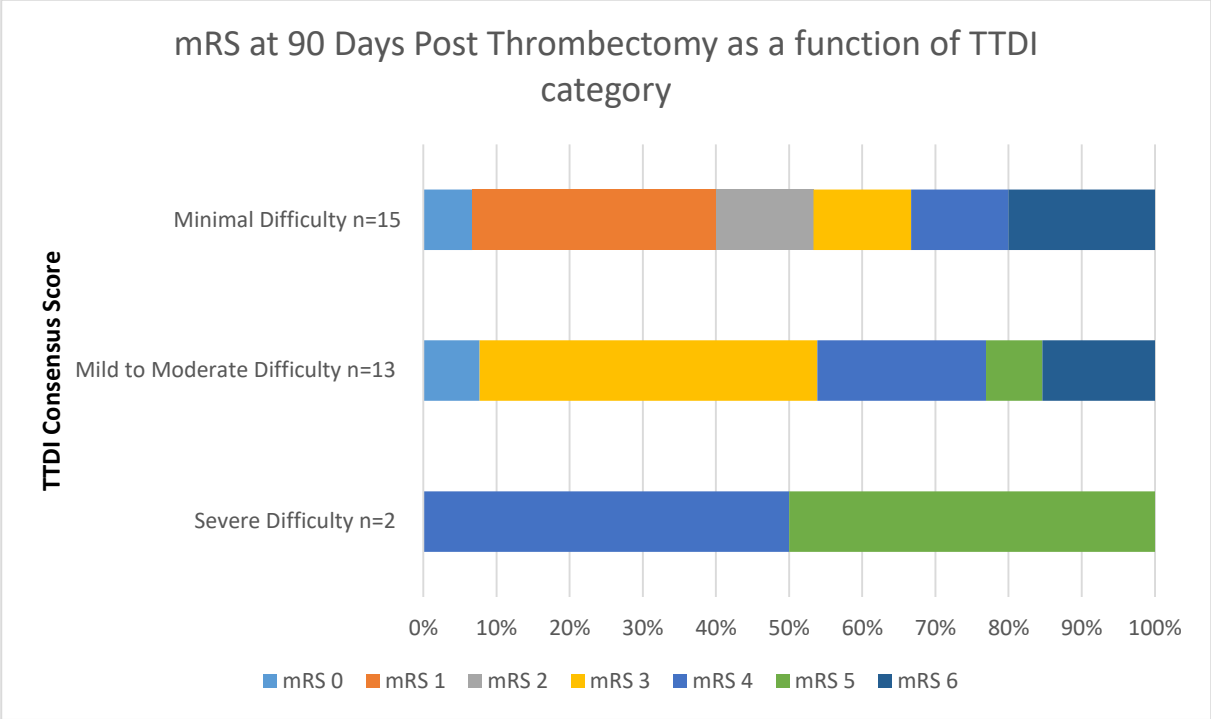


Figure 24 - mRS outcomes

This is presented at 3 months post thrombectomy as a function of TTDI category.

5.5 Discussion

Previous studies based on carotid artery stenting analysed multiple factors associated with a higher procedural complexity including: femoral arterial access, the arch anatomy, carotid artery tortuosity, stenotic grade and calcification (Choi *et al.*, 2004). Similarly, for mechanical thrombectomies different anatomical and pathological factors, including thrombus location and length have the potential to impact significantly on the procedure and its final outcome.

A clinical tool to assess technical difficulty of undertaking thrombectomy for acute stroke was developed. The TTDI demonstrated excellent inter-rater agreement between the raters, including difficulty ratings assessed by expert opinion. This demonstrates the TTDI is reliable for use in clinical practice.

The fluoroscopy time was not longer for the patients in the severe category, presumably because only 2 patients were in this sub-group and one of the cases was abandoned as ICA access was not possible. A trend towards using more devices with increasing difficulty grade was demonstrated. Good recanalization with a mTICI score of 2b/3 was achieved in 3/4 of patients within the minimal and mild to moderate categories and within 1/2 of the severe category, again showing a trend towards better procedural success for patients with lower scores.

Most importantly, there was a statistically significant difference in length of procedure between minimal and mild to moderate difficulty categories, with shorter times for patients with minimal technical index scores on the TTDI, which provides evidence of the predictive validity of the TTDI.

Interestingly, it appears that the score predicts mRS at 90 days better than it predicts procedural time to reperfusion. It suggests that procedural times increase together with the difficulty score, except for patients in the severe difficulty category. This could be because in one of the patients in the severe category, the procedure was abandoned due to access failure, essentially failure to reach the target vessel. This procedure was therefore significantly shorter as no thrombectomy passes were performed. Another potential confounding factor is that the score may also correlate with patients' frailty rather than just being an indicator of the procedural difficulty. We know that patients with more cardiovascular comorbidites such as hypertension, will have more challenging arteries, but also these patients may have health problems

that affect multiple other organ systems. It would be very useful in future studies, to assess the patients' frailty index and correlate that to this scoring tool.

There are however several limitations. This is a small study of only 30 consecutive patients in a single centre. The score was not developed with different weighting of each factor and further work is needed to validate and improve this score. A larger prospective multicentre study using this scoring tool and then performing binary logistic regression to test which components are associated with outcomes can potentially help with guidance as to which factors are more important. The score can then be refined with each factor being weighted accordingly.

There were also difficulties with assessing very long clots as the vessel of interest could not be adequately visualised. In these instances, the contralateral circulation was assessed for an approximation, although this does have its limits, for example in extensive ICA clots, there may be a very tight stenosis that is not fully appreciated. This approach cannot always be performed with clots in the posterior circulation. Another limitation is that there were patients which had thrombectomy in 2013 and early 2014 using older intra-arterial thrombectomy techniques. Subsequently distal access catheters have been developed.

To my knowledge, the TTDI is unique and there is no other technical difficulty assessment tool currently being used for thrombectomy procedures. A previous small study of carotid stenting has shown that anatomical vascular assessment using contrast enhanced MR angiography prior to surgery, altered the operative technique in 38% of patients and the procedure was aborted in 5% due to unfavourable anatomy (Timaran *et al.*, 2007).

The newly developed TTDI is a promising tool that can be used before performing a thrombectomy. It allows the neurointerventionists to take a few focused minutes to fully consider all the factors which may influence the procedure. In addition, it can lead to good discussions with the referring neurology team and help with developing a tailored treatment plan for each patient, considering both the risks and potential benefits of the procedure. It can help with decisions regarding anaesthesia (local sedation versus a general anaesthetic), whether there are any possible access issues (possibility of needing a prepared ultrasound machine nearby or whether a different access site should be considered), if for example the aortic arch is of higher grade and/or the great vessels are tortuous, it may prompt the interventionist to start

the procedure directly with a different catheter better suited for those situations. Depending on the clot burden, it may also help with deciding how to perform the initial pass: stent retriever, direct aspiration or a combination of both. The TTDI score together with the clinical picture may also be used for consenting purposes, possibly predicting the chances of success and relating this information to the patient and/or relatives. This may be very useful in the older patient population (≥80) where outcomes are poorer overall, and it is useful to look at all the available tools for decision making.

5.6 Conclusion

This study may affect thrombectomy planning and delivery, however further work is needed to assess the TTDI using prospective cases in different centres and in a larger number of patients, to better evaluate its usefulness for decision making prior to thrombectomy and consent purposes.

Chapter 6. Thrombectomy in the Older Population

The Stroke Research Group where I was based at during my postgraduate studies was part of the Institute of Neuroscience and Institute for Ageing. As I was learning more about stroke and mechanical thrombectomy during my studies, it became evident that there is a relative lack of evidence regarding the efficacy, safety and the clinical outcomes post mechanical thrombectomy in the older population. I set out to perform a collaborative research project on this topic which I found very interesting.

Stroke types, clinical signs and symptoms and the evidence for thrombectomy have already been discussed in the first two chapters of my thesis. The HERMES meta-analysis confirmed that there is clinical benefit in performing mechanical thrombectomy in patients that are of 80 years of age and older, but only a small number of patients were in this age group (Goyal *et al.*, 2016). Even though the benefit of thrombectomy remains, increasing age is a negative predictor of clinical outcome (Goyal *et al.*, 2016). The incidence of ischaemic stroke is higher in the older population and post stroke mortality triples for patients 85 years or older (Mozaffarian *et al.*, 2015). With increasing life expectancy worldwide, the older population who will present with clinical signs and symptoms of acute ischaemic stroke and who may potentially be considered for acute mechanical thrombectomy will increase. It is expected that from 2010 to 2050, the number of strokes will more than double and the majority of this increase will be among older patients of age 75 and older (Mozaffarian *et al.*, 2015). Older patients presenting with stroke have higher morbidity and mortality, receive less evidence-based care, have prolonged stays in hospital and are more likely to be discharged to an institution/rehabilitation centre (Mozaffarian *et al.*, 2015).

This was designed as a retrospective study aiming to provide further data from contemporary routine clinical practice to assess endovascular thrombectomies performed with modern devices and techniques in patients that are 80 years and older.

6.1 Materials and Methods

6.1.1 Study Population

The project was performed in three high volume international neurointerventional centres that perform acute thrombectomies: Newcastle, UK; Ottawa, Canada and Boston, USA. Data was collected on all consecutive thrombectomies performed from January 1, 2015 to June 31, 2018 on patients who were 80 years or older at time of their procedure. Institutional review board approval was obtained at each institution and the ethics board waived the need for patient consent.

All patients who had an attempted thrombectomy procedure with stent-retrievers, aspiration devices or a combination of both were reviewed in a retrospective fashion.

6.1.2 Inclusion criteria

All patients were assessed clinically in accordance with the local institutional guidelines. They needed to have a baseline mRS of 0-2 as assessed by the neurology stroke physician at the time of presentation and a clinical deficit resulting in an NIHSS score of 6 or higher to be suitable for the intervention. The brain parenchyma was assessed with a NCCT brain first to exclude intracranial haemorrhage. The ASPECTS score on NCCT had to be ≥6 or a significant mismatch as assessed by the local team had to be demonstrated on CTP. CTA was utilized to document a LVO, either as a single, multiphase or dynamic time resolved angiogram depending on the neurointerventional centre. Patients with an occlusion of the ICA, M1 MCA, proximal M2 MCA, P1 PCA or basilar artery were eligible for interventional treatment.

After the publication of the DAWN and DEFUSE 3 trials (Nogueira *et al.*, 2017; Albers *et al.*, 2018), patients who presented between 6 to 24 hours from symptom onset, including wake-up strokes, meeting either the DAWN or DEFUSE 3 trials imaging eligibility criteria in addition to the usual local clinical criteria, were also included.

6.1.3 Endovascular procedure

Patients who met the inclusion criteria underwent mechanical thrombectomy. If the patients were eligible, IV thrombolysis was also administered.

Procedures were performed with modern devices in use since 2015 with the choice of the technique left to the individual operator. Techniques included the use of stent retrievers with or without a balloon guiding catheter, aspiration performed via large bore distal access catheters or a combination (Deshaies, 2013; Kang and Park, 2017).

All patients had imaging within 24 hours post thrombectomy, mostly in the form of a CT scan, with some patients having MRI with GRE (gradient echo) or SWI sequences.

6.1.4 Data Collection and Clinical Follow-up

Data collected for each patient included basic demographics, risk factors for stroke, acute clinical and radiological findings and treatment details. Primary outcomes were the recanalization rates using the mTICI score and the 90 days clinical outcome as assessed by the mRS. Secondary outcomes included: stroke onset to treatment time; stroke onset to IV tPA administration; stroke onset to reperfusion; procedural and peri-procedural complications; and outcomes at 24 hours post-thrombectomy using the NIHSS.

Different sources were used to accumulate this data including clinical patient's notes, local PACS, electronic healthcare records including discharge letters and follow-up clinical visits. All regular follow-up visits were performed according to local clinical protocols. Some patients did not have a clinical 3 months follow-up visit, mostly due to transfers from other hospitals, and for this ethical approval was obtained and the patients were interviewed by phone to obtain the 3 months mRS.

6.1.5 Statistical methodology

All statistical analyses were performed using SPSS statistics software v25 (IBM Corporation, New York, USA). Descriptive statistics for all data are presented as medians and ranges for continuous variables and as numbers and percentages for categorical variables. Univariate analyses were performed using the Fisher's exact test for categorical data and the Student t test for continuous data. A $p < 0.05$ was considered statistically significant. Statistically significant variables were then used for the construction of a binary logistic regression model. OR with 95% CI were calculated.

6.1.6 Patient Population

A total of 168 patients aged 80 or greater were treated with mechanical thrombectomy. Twelve patients were excluded: 10 due to site of arterial occlusion being not proximal anterior circulation and another 2 patients due to incomplete data. One hundred and fifty-six patients were left for the analysis.

6.2 Results

6.2.1 Demographics and Baseline Imaging Data

There were 108/156 (69%) females and 48/156 (31%) males with a median age of 85 (range 80 to 103) with baseline clinical characteristics shown in Table 10. There was a high prevalence of atrial fibrillation 98/156 (63%) and hypertension 120/156 (77%).

Basic Demographics	**Population (n=156)**
Median Age (years)	85 (81 - 90)
Men	48 (31%)
Women	108 (69%)
Past Medical History	
Hypertension	120 (77%)
Diabetes Mellitus	33 (21%)
Atrial Fibrillation	98 (63%)
Smoking (recent or current)	26 (17%)
Clinical Characteristics	
Baseline NIHSS	20 (15 - 23)
Baseline glucose (mmol/L)	6.4 (5.5 - 8.3)
Imaging Characteristics	
ASPECTS at baseline	9 (8-10)
Intracranial Occlusion Location	
M1 MCA	84 (54%)
ICA T	30 (19%)
Tandem	21 (14%)
M2 MCA	21 (14%)
Collateral Status	
Good	83 (53%)
Moderate	45 (29%)
Poor	28 (18%)
Data are median (IQR), n(%), or mean (SD).	

Table 10 – Patient clinical and imaging characteristics

The median NIHSS score was 20 (IQR 15–23). On NCCT, the median ASPECTS score at baseline was 9 (IQR 8–10). The most common location of the target occlusion was the M1 MCA segment in 54% (84/156) of patients. ICA-T and other tandem occlusions were present in 33% (51/156) of patients. There was a minority of M2 MCA occlusions 14% (21/156). Collaterals were good in 53% (83/156) of patients treated as assessed on a previously described qualitative scale of poor, moderate and good (Miteff *et al.*, 2009).

Treatment Details and Process Times	
Treatment with intravenous alteplase	97 (62%)
Process times (min)	
Onset to IV tPA (min)	103 (75 - 137)
Onset to Reperfusion (min)	240 (175 - 305)
Anaesthesia details	
CS (conscious sedation)	132 (85%)
GA (general anaesthetic)	17 (11%)
CS transformed to GA during case	7 (5%)
Reperfusion (mTICI)	
0	27 (17%)
1/2a	23 (15%)
2b/3	106 (68%)
Data are median (IQR) or n(%).	

Table 11 - Thrombectomy Treatment Details and Timelines

6.2.2 Treatment Details

Intravenous thrombolysis was administered in 62% (97/156) of patients at a median time of 103 minutes from symptom onset. Thrombectomy procedures were performed under local anaesthesia/conscious sedation in 85% (132/156) of patients. General anaesthesia was used in 11% (17/156) of patients and in 5% (7/156) conscious sedation had to be converted to general anaesthesia, Table 11.

6.2.3 Radiological Outcomes

Good grade reperfusion as assessed by mTICI 2b or 3 score, was achieved in 68% (106/156) of patients with a median time of 240 minutes (IQR 175 - 305) from symptom onset, Table 11.

6.2.4 Clinical Outcomes

The median NIHSS at 24 hours improved to 12 from 20 at presentation. A good functional outcome at 3 months as assessed by an mRS of 0 - 2 was achieved in 26% (40/156) of patients, Table 12.

Outcomes	
NIHSS at 24 hours	12 (6-12)
mRS 0-2 at 90 days	40 (26%)
mRS 3-6 at 90 days	116 (74%)
Safety outcomes at 90 days	
Asymptomatic intracranial haemorrhage	18 (12%)
Symptomatic intracranial haemorrhage	9 (6%)
Mortality	64 (41%)
Data are n(%). NIHSS=National Institutes of Health Stroke Scale.	

Table 12 - Clinical and Safety Outcomes

6.2.5 Safety and Mortality

Symptomatic intracranial haemorrhage was present in 6% (9/156) of patients. Asymptomatic intracranial haemorrhage was detected in 12% (18/156). The 90-day mortality rate was 41% (64/156), Table 12.

6.2.6 Outcome Predictors

The association between individual variables and a good clinical outcome on univariate analysis is shown in Table 13. After seeking advice and with help from a statistician about how to best analyse this data; the factors shown to be significant on univariate analysis: age, NIHSS at presentation and good recanalization grade (mTICI 2b – 3), were taken and a binomial logistic regression was performed to ascertain the effects of the likelihood that patients will have a good clinical outcome (mRS 0-2). The logistic regression model was statistically significant, $\chi 2(3)=27.27$,

p<.001. The model explained 23.8% of the variance (Nagelkerke R^2) in good clinical outcome and correctly classified 79.2% of cases. Of the three predictor variables, only two were statistically significant, Table 14.

A patient with a good recanalization grade (mTICI 2b – 3) had 5.31 times higher odds (95%CI=1,84-15,29) of a good clinical outcome (mRS 0-2). Increasing NIHSS at presentation (OR 0,88, 95%CI=0,82-0,94) was associated with a decreased likelihood of good clinical outcome.

After thrombectomy, a lower 24h NIHSS was strongly predictive of good clinical outcome (mRS 0 – 2) at 3 months (OR 0,67, 95%CI=0,58-0,77, p<.001).

Factors Considered	mRS 90 days (0-2)	mRS 90 days (3-6)	P value
Demographics			
Female	25 (62.5%)	83 (71.6%)	0.32
Age	84 (81-87%)	85 (81-90)	0.005*
Baseline Blood Glucose	6.45 (5.5 - 8)	6.4 (5.5 - 8.6)	0.46
Diabetes	7 (17.5%)	26 (22.4%)	0.34
Hypertension	30 (75%)	90 (77.6%)	0.44
Atrial Fibrillation	29 (72.5%)	69 (59.%)	0.09
Smoking	4 (10%)	22 (19%)	0.23
Presentation/Intervention			
NIHSS at presentation	13 (10 - 22)	20 (16 - 23)	0.001*
ASPECTS	9 (8 - 10)	9 (8 - 9)	0.36
Time symptoms to r-tPA (min)	99 (70 - 145)	105 (79 - 135)	1
Occlusion site (ICA/Tandem)	13 (32.5%)	38 (32.8%)	0.24
Good Collaterals	25 (62.5%)	58 (50%)	0.13
General Anesthesia	3 (7.5%)	21 (18,1%)	0.13
Symptoms to reperfusion (min)	185 (131 - 253)	251 (215 - 346)	0.44
TICI2b-3	35 (87.5%)	71 (61.2%)	0.002*
Post Intervention			
NIHSS at 24h	4 (3 - 8)	15 (11 - 21)	0.001
** p < 0.05 was considered significant* *Categorical Variables are presented as number of cases and percentages* *Continuous Variables are presented as median values and interquartile ranges*			

Table 13 - Results of the univariate analysis for predictors of clinical outcome at 90 days

Variables	OR	95% CI	P
NIHSS at presentation	0.88	0.82 – .94	0.001
TICI 2b – 3	5.31	1.84 – 15.29	0.002

Table 14 - Results of the binary logistic regression for independent predictors of good clinical outcome

6.3 Discussion

Thrombectomy in patients of aged 80 years and older represents a real challenge – these patients have high rates of comorbidities (Piccirillo *et al.*, 2008) and pose procedural technical difficulties to arterial and clot access more frequently (Lin *et al.*, 2005). For instance, in the present series 14% (21/156) had tandem lesions, 19% (30/156) carotid T occlusion, 63% (98/156) atrial fibrillation and 77% (120/156) were hypertensive; all appreciably higher compared with other studies (Kastrup *et al.*, 2018). A greater proportion of patients had contra-indications to IV tPA as they were anticoagulated, only 62% (97/156) of them received IV tPA compared to 83% as reported in the general mechanical thrombectomy population (Goyal *et al.*, 2016). The present study demonstrates that in this patient population thrombectomy performed with contemporary devices and techniques is efficient (mTICI 2b/3 rate) and can be achieved in the expected timeframe, Table 11.

Because this study was performed in three different international centres, there was some variability in how patients were managed clinically. Although, a breakdown of each center was not performed, differences in practice are important to acknowledge. For example, in one particular centre, if at 24 hours post thrombectomy there was no significant improvement in terms of NIHSS, patients would be managed with palliative care. Potentially, some of these patients could have improved in the longer term and this practice may have contributed to the larger percentage of death in this patient population as compared to other studies.

Another additional potential factor to consider is patient's frailty. Although none of these patients were assessed pre procedure in terms of their frailty index, this data may be very relevant to their clinical outcomes. It is possible that patients recruited in international trials were healthier patients at baseline, with less comorbidities, therefore leading to improved outcomes and a smaller death percentage. Further

prospective studies, especially in this age group, would benefit from collecting frailty data at baseline to more accurately describe the population being studied.

An mTICI 2b - 3 reperfusion was achieved in 68% (106/156) of patients in a median time of 240 minutes (IQR 175 - 305). This compares favourably with results published by other studies, Table 15.

Due to the extended times after the publication of the DAWN and DEFUSE-3 trials, 14% (22/156) patients were reperfused later than 6 hours from symptom onset, including 5% (8/156) that were reperfused more than 10 hours from symptom onset.

In the HERMES meta-analysis, the percentage of good reperfusion was similar, 71% across all age groups, but this was achieved within a longer median timeframe of 285 minutes (IQR 210 - 362) (Goyal *et al.*, 2016). The good reperfusion time and technical success rate in this study is attributed to the use of modern devices in experienced high-volume centres.

This cohort presented a higher rate of intracranial haemorrhage (18%) as compared with the general population (10%) from the HERMES data. A recently published series showed even higher rates (42%) of intracranial haemorrhage in the older population (Alawieh *et al.*, 2018). The reason for the increased incidence of intracranial bleeding has not been elucidated. Although leukoaraiosis was not specifically assessed, worsening severity has been shown in a recent meta-analysis to be associated with increased risk of sICH as well as poor outcomes after IV tPA administration in the context of acute ischaemic stroke (Kongbunkiat *et al.*, 2017). However, other mechanisms, like increased vessel fragility may be involved and may have implications for the thrombectomy technique.

A good functional outcome of mRS 0-2 was achieved in approximately 1 in 4 patients, which is similar to previous studies in this age group, Table 15. This is somewhat lower compared with the HERMES data for patients of age ≥80 which showed that 30% achieved mRS of 0-2. In addition, the 90-day mortality rate of 41% is higher than the HERMES meta-analysis for this subgroup of patients (28%).

Some of the differences in mortality and mRS 0-2 outcome are probably accounted for by the use of “advanced brain imaging” in patient selection employed in 2/3 of the HERMES trials recruiting subjects over 80 years of age, notably the ESCAPE and REVASCAT trials (Goyal *et al.*, 2015, 2016; Dávalos *et al.*, 2017). Supporting this, ESCAPE demonstrated both appreciably greater mRS 0-2 and lower mortality rates

in patients aged 80 and older than results of the non-selective MR CLEAN trial (Berkhemer *et al.*, 2015; Goyal *et al.*, 2015). The REVASCAT trial used CTP routinely in the triaging patients over 80 years of age (Dávalos *et al.*, 2017), but a cut off of 70 not 80 years for its' published age analyses; the mortality in the older mechanical thrombectomy group was also 41% compared with 23% in their younger cohort and mRS 0-2 was 31% versus 53%. This study also included late presenters, and this is slightly different to the HERMES meta-analysis which very largely comprised early presenters (Goyal *et al.*, 2016).

Previous studies have identified low NIHSS at presentation, small infarct core, male gender and the use of IV tPA as predictors of good functional outcome at 3 months following mechanical thrombectomy (Alawieh *et al.*, 2018; Jayaraman *et al.*, 2018; Kastrup *et al.*, 2018). In the present patient population, a lower presenting NIHSS score was, similar to previous studies, an independent predictor of good outcome in the older population (Sallustio *et al.*, 2017; Alawieh *et al.*, 2018; Barral *et al.*, 2018; Kastrup *et al.*, 2018). An mTICI score of 2b – 3 was also an independent predictor of good outcome, but previous published studies have shown conflicting data regarding this (Cohen, Gomori and Leker, 2016; Barral *et al.*, 2018; Jayaraman *et al.*, 2018; Tonetti *et al.*, 2018), Table 15. This could be attributed to the short times from symptom onset to reperfusion of 240 min (IQR 175 – 305) which may have contributed to lower rates of futile reperfusion.

Younger age was not statistically related to good outcome in univariate analysis, but the result was borderline, consistent with other studies. A recently published series showed significantly worse outcomes with increasing age, but it included thrombectomies performed in 2013 with older devices and reported longer median times from symptom onset to reperfusion of 414 minutes (Alawieh *et al.*, 2018). Another study found that for patients who had complete or almost complete recanalization, with an mTICI score of 2c – 3, increasing age was not a poor prognostic factor (Jayaraman *et al.*, 2018).

After thrombectomy a lower NIHSS was highly correlated to a good clinical outcome at 3 months (OR 0,67, 95%CI=0,58-0,77, p<0,001). Another study comparing outcomes in patients aged 80 and older versus the general population similarly showed that a lower 24h NIHSS is a predictor of independent functional outcome at 3 months (Sallustio *et al.*, 2017).

The limitations of this study include its retrospective nature, multicentre and selection bias, a relatively limited patient population and the subjective grading of reperfusion results. Further work using prospective data in a larger study may help elucidate clinical and imaging predictors of outcome after thrombectomy in patients aged 80 and over to further improve patient selection and management.

Study	Number of Patients that had Thrombectomy	Age of study group	Median Time to Recanalization (min)*	mTICI 2b – 3*	ICH*	Mortality*	mRS o – 2 at 90 days*	Predictive Outcome Factors
Hilditch. et al., 2018. (Hilditch *et al.*, 2018)	860	≥ 80	350	78%	24%	34%	27%	N/A
Alawieh et al., 2018. (Alawieh *et al.*, 2018)	1346	346 patients ≥ 80, 1000 patients <80	414	88%	42%	35%	21%	Baseline mRS Baseline NIHSS Number of recanalization attempts Posterior circulation strokes
Kastrup et al., 2018. (Kastrup *et al.*, 2018)	209	≥ 80	N/A	61%	1%	14%	25%	Baseline ASPECTS Baseline NIHSS Age
Barral. et al., 2018. (Barral *et al.*, 2018)	169	≥ 80	304	82%	63%	33%	25%	Baseline NIHSS Baseline ASPECTS Male gender IV tPA administration
Sallustio et al., 2017. (Sallustio *et al.*, 2017)	62	≥ 80	318	69%	37%	40%	31%	Baseline NIHSS 24h NIHSS
Jayaraman et al., 2018. (Jayaraman *et al.*, 2018)	157 total, unclear how many 80+	≥ 18	N/A	N/A	3%	N/A	N/A	mTICI recanalization Age
Tonetti et al., 2018. (Tonetti *et al.*, 2018)	30	≥ 90	N/A	90%	7%	70%	14%	Final infarct volume <10cm3
Cohen, J.E., 2016. (Cohen, Gomori and Leker, 2016)	71	16 patients ≥ 80, 55 patients <80	280	88%	38%	40%	21%	Age mTICI recanalization
Son et al., 2017. (Son *et al.*, 2017)	207	34 patients ≥ 80, 173 patients <80	286	82%	6%	3%	44%	Baseline NIHSS Age Recanalization time mTICI recanalization (only in younger patients)
Kurre, W., Ludwig, A. & Fischer, S., 2013. (Kurre *et al.*, 2013)	109	≥ 80	N/A	88%	26.4 %	48%	17%	Baseline ASPECTS Baseline NIHSS

Table 15 - Thrombectomy studies in older patients with acute ischaemic stroke

6.4 Conclusion

In patients aged 80 or older, mechanical thrombectomy may be performed within accepted timelines with good reperfusion rates. This patient population is challenging with an increased proportion of tandem lesions, carotid T occlusions and an increased rate of death and poor functional outcomes at 3 months. A lower presenting NIHSS and mTICI 2b – 3 reperfusion grades are independent predictors of good outcomes. After thrombectomy, a lower 24h NIHSS is a predictor of good long-term outcome. Further work is needed to ensure optimum patient selection for endovascular thrombectomy in the older population.

Chapter 7. Thesis Conclusion

I started my postgraduate studies with the aim of evaluating the new ERIC and SOFIA mechanical thrombectomy devices. This was part of the STABILISE trial and I had the opportunity to work extensively on this project from the initial ethical submission to developing all the paperwork and online platform for collecting the required patient data, enrolling different sites for patient recruitment, developing the monitoring systems to ensure adequate running of the trial, reviewing reported adverse events and taking action as required and responding to the different queries of the enrolling sites.

Local guidelines for performing initial imaging in patients presenting with acute stroke symptoms were developed at the Royal Victoria Infirmary in Newcastle, which is a tertiary hospital having a neuroradiology department and neurointerventionists who can perform mechanical thrombectomy. After these were developed, I set out a local project to assess whether these guidelines were being followed. The results from my CTA audit project were presented locally and this helped to improve adherence to these guidelines and improve overall patient care.

The start-up of the STABILISE trial was slow and there was a lack of patients being referred for mechanical thrombectomy from the neighbouring district general hospitals. One of the problems was that their local radiology departments were not comfortable with performing and interpreting acute CTA scans to assess for signs of acute stroke and / or LVO.

The initial lack of recruitment in the STABILISE trial highlighted the fact that there was room for improvement in the imaging diagnosis of acute ischaemic stroke within the North East of England. Continuing from the CTA audit, which had allowed me to review a large number of scans, I decided to develop a validated case archive of CTA scans from patients who presented with acute stroke symptoms, to be used for teaching purposes. Together with help from my neuroradiology colleagues, all the selected scans were reviewed and their findings, including initial patient presentation and patient outcomes, collated in a report type document. This data was anonymised and with permission from the Newcastle Upon Tyne NHS Trust and with help from the HENE (Health Education North East) Radiology MacLab Training Centre, these

cases were uploaded onto their servers to be used for teaching. I developed a one-day course where attendees received lectures and then practiced reviewing scans at their own stations and in their own time. This was very successful with radiology trainees, general radiology consultants and stroke physicians. It was approved for 6 RCR (Royal College of Radiologists) CPD (continuing professional development) points by the Royal College of Radiology. Its online version that I helped create is currently being developed as an online course on the RCR website to be made available across the UK. This project was presented orally at the BSNR (British Society of Neuroradiologists) annual meeting in 2016 and was awarded the 1st prize for a trainee research project, see Appendix Q – Awards, Publications, Presentations, Teaching, Conferences and Courses Attended Throughout my Ph.D. Studies.

This project had helped with recruitment into the STABILISE trial which eventually had picked up, although still at a slower rate than initially predicted. Because of this and due to the fact that techniques in endovascular therapies were rapidly changing, a trial amendment was put in, allowing for more operator flexibility when performing these procedures. Together with the team working on the STABILISE trial, we were successful in recruiting more sites for enrolment and boosting the number of enrolled patients. The trial was extended from its original planned end date and will finish at the end of April 2019. This being the date when my thesis is due, I unfortunately cannot report on the finalised results and I only have access to preliminary blinded data. The preliminary results have been described in the chapter on the STABILISE trial, but no definite conclusions can be drawn at this time. After the collection and statistical analysis of the final data, I will be involved with writing up the paper to be published in a journal for world-wide dissemination.

Another point to discuss is whether a randomized control trial is the best way to evaluate this type of new technology. When the STABILISE trial was developed, mechanical thrombectomy was not yet proven and it was not part of normal clinical care. At the time, setting up a randomized control trial was considered the best way to investigate these new thrombectomy devices. There are other study designs that can be considered and another type of study design that may have been efficacious to perform is an umbrella or platform trial. In these types of trials, a master protocol is used to investigate multiple hypotheses in concurrent studies. The benefit of this is being able to add or remove arms throughout the study and this type of trial design may have helped with the rate of recruitment. If the study would have been

developed later on, once mechanical thrombectomy was already a validated treatment, then a stepped wedge trial methodology to study these new devices could have potentially been done with better recruitment rates. In this type of trial, initially participants could have received the control treatment after which the rest of the participants could all receive the new intervention in a wave, and this would have been a good way to perform this trial. Conducting this trial with registry data or as a type of clinical audit where the data was routinely collected from all patients undergoing mechanical thrombectomy could have potentially been done, if the study was set-up after mechanical thrombectomy was approved as a treatment nation-wide. Using either one of these two strategies I believe would have significantly increased uptake while at the same time reducing the burden on the research staff with following-up on patients and data collection, as most of the data would have been readily available in the patient's clinical charts.

The initial part of my thesis included an extensive review of literature relating to stroke and mechanical thrombectomy. The first chapter discussed stroke and its classification, imaging tests and acute treatments, including a short history of devices for mechanical thrombectomy. The second chapter focussed on the up to date evidence for mechanical thrombectomy and all the major trials were presented. This evidence has been rapidly evolving throughout the running of the STABILISE trial and this chapter presents the latest evidence up to January 2019. Significant developments have been made to the way thrombectomy is performed with new tools and techniques as well as how patients are chosen with advanced imaging being shown to allow selection of patients up to 24 hours post initial stroke symptoms onset.

Chapter 5 concerns the development of a new scoring tool to predict mechanical thrombectomy case difficulty in LVO by assessing the initial CTA scan. This project demonstrated great potential as it can help operators decide on the best method and devices for a case and this may lead to a more personalised and patient oriented approach in delivering mechanical thrombectomy. The aim of this is to attain a faster and safer recanalization to ensure improved patient outcomes. The scores' simplicity and robustness have the potential to make it a performant tool for the neurointerventional team. This project represents an innovative and original contribution and I am looking forward to publishing this study in a prestigious journal.

I plan to undertake further research to assess this scoring tool in a prospective manner in a multicentric study.

Endovascular therapies for stroke being relatively new had limited data regarding older patients presenting with acute LVO. I worked on a multicentric study to assess the safety and efficacy of mechanical thrombectomy in patients that are 80 years of age and older. This is the content for Chapter 6 of my thesis and currently represents one of the largest cohorts of older patients. The results showed that although their types of strokes are more challenging to treat with endovascular therapies and their clinical results are poorer than in the younger population, the latest retrieval devices and techniques allow for good rates of recanalization. Further data is needed to ensure optimum patient selection in this age group, but this study showed that better outcomes are achieved in patients that have a lower baseline NIHSS, a good grade of reperfusion (mTICI 2b-3) and a lower 24 hours NIHSS. This multicentric study is highly relevant in our ageing population in the developed world and adds important information to the current literature on stroke and mechanical thrombectomy in the older population. This project was partially presented orally at the CAR (Canadian Association of Radiologists) annual meeting in 2018 and received the 1st prize for research undertaken by a trainee. It was also accepted as a poster presentation at the RSNA (Radiological Society of North America) annual meeting in 2018 where it was awarded the Student Travel Award.

From my thesis projects, there is grounds for further research to be undertaken. The data from the STABILISE trial will also be used to work on a study looking at MRI scans post thrombectomy and its value in predicting outcomes. There has been significant research work acute ischaemic stroke due to LVO including collaterals, patient selection and outcomes in endovascular therapy and the data will be assessed to see whether we can contribute to the current literature. The newly developed thrombectomy score needs to be further assessed in a prospective fashion and I plan to do this after this paper is published, ideally, I would like this to be a collaborative project with multiple sites. The CTA teaching course has been very successful in England and I have been asked to deliver and possibly launch another online version in Canada.

This thesis has focused on a variety of research topics related to mechanical thrombectomy: new retrieval devices, imaging assessment including the development of a course, a new CTA assessment tool and an analysis of outcomes in the older

patient population. This work has added significant and original contributions to the existing knowledge base related to endovascular treatment with mechanical thrombectomy. I plan to continue undertaking further research in this exciting field throughout my career.

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Appendix A - Modified Rankin Scale

mRS	Symptoms
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

Appendix B – STABILISE Ethics Application

Full Set of Project Data IRAS Version 4.0.0

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Stroke: an evaluation of Thrombectomy in the Ageing Brain Version 1

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product
( ) Clinical investigation or other study of a medical device
( ) Combined trial of an investigational medicinal product and an investigational medical device
(●) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
( ) Basic science study involving procedures with human participants
( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
( ) Study involving qualitative methods only
( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
( ) Study limited to working with data (specific project only)
( ) Research tissue bank
( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(●) No
b) Will you be taking new human tissue samples (or other human biological samples)?	( ) Yes	(●) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(●) No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (•) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which review bodies are you applying to?

- [x] NHS/HSC Research and Development offices
- [ ] Social Care Research Ethics Committee
- [x] Research Ethics Committee
- [ ] Confidentiality Advisory Group (CAG)
- [ ] National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

(•) Yes ( ) No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

6. Do you plan to include any participants who are children?

( ) Yes (•) No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

(•) Yes ( ) No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

( ) Yes (•) No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Stroke: an evaluation of Thrombectomy in the Ageing Brain Version 1

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

A3-1. Chief Investigator:

Title Forename/Initials Surname

Post
Qualifications
Employer
Work Address

Post Code
Work E-mail
* Personal E-mail
Work Telephone
* Personal Telephone/Mobile
Fax

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

Title Forename/Initials Surname

Address

Post Code
E-mail
Telephone
Fax

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):
Sponsor's/protocol number:
Protocol Version:
Protocol Date:
Funder's reference number:
Project website:

Registry reference number(s):
The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

Additional reference number(s):

A5-2. Is this application linked to a previous study or another current application?

◯ Yes ◯ No

Please give brief details and reference numbers.

A5-3. US DHHS grant application.

PHS grant application number:
Name of Program Director:

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, this summary will be published on the website of the National Research Ethics Service following the ethical review.*

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex

organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

A6-3. Proportionate review of REC application *The initial project filter has identified that your study may be suitable for proportionate review by a REC sub-committee. Please consult the current guidance notes from NRES and indicate whether you wish to apply through the proportionate review service or, taking into account your answer to A6-2, you consider there are ethical issues that require consideration at a full REC meeting.*

◯ Yes - proportionate review ◯ No - review by full REC meeting

Further comments (optional):

Note: This question only applies to the REC application.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply.*

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☐ Randomised controlled trial
- ☐ Other (please specify)

A9-2. Is there a sub-study?

◯ Yes ◯ No ◯ Not Answered

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- ☐ Design of the research
- ☐ Management of the research
- ☐ Undertaking the research
- ☐ Analysis of results
- ☐ Dissemination of findings
- ☐ None of the above

Give details of involvement, or if none please justify the absence of involvement.

A14-2. Have you tested the acceptability of using patient identifiable data in this study without consent?

Please give details.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- ☐ Blood
- ☐ Cancer
- ☐ Cardiovascular
- ☐ Congenital Disorders
- ☐ Dementias and Neurodegenerative Diseases
- ☐ Diabetes
- ☐ Ear
- ☐ Eye
- ☐ Generic Health Relevance
- ☐ Infection
- ☐ Inflammatory and Immune System
- ☐ Injuries and Accidents
- ☐ Mental Health
- ☐ Metabolic and Endocrine
- ☐ Musculoskeletal
- ☐ Neurological
- ☐ Oral and Gastrointestinal
- ☐ Paediatrics
- ☐ Renal and Urogenital
- ☐ Reproductive Health and Childbirth
- ☐ Respiratory
- ☐ Skin

☐ Stroke

Gender:	Male and female participants
Lower age limit:	Years
Upper age limit:	Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

◯ Yes ◯ No

A21. How long do you expect each participant to be in the study in total?

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

◯ Yes ◯ No

A24. What is the potential for benefit to research participants?

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

A26. What are the potential risks for the researchers themselves? *(if any)*

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of social care or GP records, or review of medical records. Indicate whether this will be done by the direct care team or by researchers acting under arrangements with the responsible care organisation(s).*

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

◯ Yes ◯ No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

◯ Yes ◯ No

A29. How and by whom will potential participants first be approached?

A30-1. Will you obtain informed consent from or on behalf of research participants?

◯ Yes ◯ No

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◯ Yes ◯ No

If No, how will it be recorded?

A30-3. Why is it not practicable for either the researcher's organisation, or the current holder of the information required by the researcher, to seek or obtain patient consent for proposed use of patient identifiable information?

A31. How long will you allow potential participants to decide whether or not to take part?

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

◯ Yes
◯ No
◯ Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

◯ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
◯ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
◯ The participant would continue to be included in the study.
◯ Not applicable – informed consent will not be sought from any participants in this research.
◯ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☐ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☐ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☐ Storage of personal data on any of the following:
  - ☐ Manual files (includes paper or film)
  - ☐ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☐ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

Further details:

A37. Please describe the physical security arrangements for storage of personal data during the study?

A38. How will you ensure the confidentiality of personal data? *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

A39. Please specify whether identifiers will be held in the same database as the clinical data, or in a separate database and linked through a unique study or case number. *If held separately, please specify how and at what point the separation will occur. If held in the same database, will the identifiers be encrypted? If so, specify what will be encrypted and who will continue to have access.*

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

A42. Who will have control of and act as the custodian for the data generated by the study?

Title Forename/Initials Surname

Post

Qualifications
Work Address

Post Code
Work Email
Work Telephone
Fax

A43. How long will personal data be stored or accessed after the study has ended?

- ◯ Less than 3 months
- ◯ 3 – 6 months
- ◯ 6 – 12 months
- ◯ 12 months – 3 years
- ◯ Over 3 years

A44. For how long will you store research data generated by the study?

Years:
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended. *Say where data will be stored, who will have access and the arrangements to ensure security.*

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

◯ Yes ◯ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

◯ Yes ◯ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

◯ Yes ◯ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◯ Yes ◯ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50-1. Will the research be registered on a public database?

The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◯ Yes ◯ No

Please give details, or justify if not registering the research.

Please ensure that you have entered registry reference number(s) in question A5-1.

A50-2. Will the research be registered on a public database such as the Research Register for Social Care?

◯ Yes ◯ No

Please give details, or justify if not registering the research.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

☐ Peer reviewed scientific journals
☐ Internal report
☐ Conference presentation
☐ Publication on website
☐ Other publication
☐ Submission to regulatory authorities
☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
☐ No plans to report or disseminate the results
☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

A53. Will you inform participants of the results?

◯ Yes ◯ No

Please give details of how you will inform participants or justify if not doing so.

5. Scientific and Statistical Review

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

☐ Review by independent statistician commissioned by funder or sponsor

- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☐ Review by a statistician within the Chief Investigator's institution
- ☐ Review by a statistician within the research team or multi−centre group
- ☐ Review by educational supervisor
- ☐ Other review by individual with relevant statistical expertise

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title Forename/Initials Surname

Department
Institution
Work Address

Post Code
Telephone
Fax
Mobile
E-mail

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

A58. What are the secondary outcome measures? *(if any)*

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:
Total international sample size (including UK):
Total in European Economic Area:

Further details:

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

A61-1. Will participants be allocated to groups at random?

○ Yes ○ No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

A64. Details of research sponsor(s)

A64-1. Sponsor

A64-2. Please explain how the responsibilities of sponsorship will be assigned between the co-sponsors listed in A64-1

A65. Has external funding for the research been secured?

- ☐ Funding secured from one or more funders
- ☐ External funding application to one or more funders in progress
- ☐ No application for external funding will be made

What type of research project is this?

- ○ Standalone project
- ○ Project that is part of a programme grant
- ○ Project that is part of a Centre grant
- ○ Project that is part of a fellowship/ personal award/ research training award
- ○ Other

Other – please state:

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

○ Yes ○ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ○ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Title Forename/Initials Surname

Organisation
Address

Post Code
Work Email
Telephone
Fax
Mobile

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Comprehensive Local Research Network for this NHS organisation:

To support communication between the REC and R&D contacts for this study, please select the Comprehensive Local Research Network (CLRN) for this NHS organisation. This CLRN will be the Lead CLRN for your study.

For information about support and advice available through the Lead CLRN and the CLRNs for participating sites see http://www.crncc.nihr.ac.uk/about_us/processes/csp. A map showing the CLRNs is available at http://www.crncc.nihr.ac.uk/about_us/ccrn.

A69-1. How long do you expect the study to last in the UK?

Planned start date:
Planned end date:
Total duration:
Years: Months: Days:

A69-2. How long do you expect the study to last in all countries?

Planned start date:
Planned end date:
Planned end date
(clinical interventions):
Planned end date
(all trial procedures):
Total duration:
Years: Months: Days:

A71-1. Is this study?

- ◯ Single centre
- ◯ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☐ England
- ☐ Scotland
- ☐ Wales

☐ Northern Ireland
☐ Other countries in European Economic Area

Does this trial involve countries outside the EU?
◯ Yes ◯ No

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☐ NHS organisations in England
☐ NHS organisations in Wales
☐ NHS organisations in Scotland
☐ HSC organisations in Northern Ireland
☐ GP practices in England
☐ GP practices in Wales
☐ GP practices in Scotland
☐ GP practices in Northern Ireland
☐ Joint health and social care agencies (eg community mental health teams)
☐ Local authorities
☐ Phase 1 trial units
☐ Prison establishments
☐ Probation areas
☐ Independent (private or voluntary sector) organisations
☐ Educational establishments
☐ Independent research units
☐ Other (give details)

Total UK sites in study:

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

◯ Yes ◯ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care*

(HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (NHS sponsors only)
☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
☐ Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☐ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ○ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ○ No ○ Not sure

B. All research other than CTIMPs

In this sub-section, an adult means a person aged 16 or over.

B1. What impairing condition(s) will the participants have?

The study must be connected to this condition or its treatment.

B2. Justify the inclusion of adults unable to consent for themselves. It should be clear why the research could not be carried out as effectively if confined to adults capable of giving consent.

B3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?

B4. Does the research have the potential to benefit participants who are unable to consent for themselves?

◯ Yes ◯ No

B5. Will the research contribute to knowledge of the causes or the treatment or care of persons with the same impairing condition (or a similar condition)?

◯ Yes ◯ No

B6. Will the research involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

◯ Yes ◯ No

Questions B7 and B8 apply to any participants recruited in England and Wales.

B7. What arrangements will be made to identify and consult persons able to advise on the presumed wishes and feelings of participants unable to consent for themselves and on their inclusion in the research?

Please enclose a copy of the written information to be provided to consultees. This should describe their role under section 32 of the Mental Capacity Act and provide information about the research similar to that which might be given to participants able to consent for themselves.

B8. Is it possible that a participant requiring urgent treatment might need to be recruited into research before it is possible to identify and consult a person under B7?

◯ Yes ◯ No

If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or advice from a consultee as soon as practicable thereafter.

B9. What arrangements will be made to continue to consult such persons during the course of the research where necessary?

B10. What steps will you take, if appropriate, to provide participants who are unable to consent for themselves with information about the research, and to consider their wishes and feelings?

B11. Is it possible that the capacity of participants could fluctuate during the research? How would this be handled?

B12-1. What will be the criteria for withdrawal of participants?

B13. Describe what steps will be taken to ensure that nothing is done to which participants appear to object (unless it is to protect them from harm or minimise pain or discomfort).

B14. Describe what steps will be taken to ensure that nothing is done which is contrary to any advance decision or statement by the participant?

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

12. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication *(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further

information. We would be grateful if you would indicate one of the contact points below.

- ◯ Chief Investigator
- ◯ Sponsor
- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature: .....

Print Name:

Date: *(dd/mm/yyyy)*

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

Signature: .....

Print Name:

Post:

Organisation:

Date: *(dd/mm/yyyy)*

Appendix C – STABILISE Ethics Approval Letter

NHS
Health Research Authority
NRES Committee North East - Newcastle & North Tyneside 1
Room 002
Rolling Mill Road
Jarrow
NE32 3DT

Telephone: 0191 4283548

04 July 2014

Professor Phil White
Professor of Interventional and Diagnostic Neuroradiology
Newcastle University
Institute for Ageing & Health
3-4 Claremont Terrace
Newcastle upon Tyne
NE2 4AE

Dear Professor White

Study title:	**Stroke: an evaluation of Thrombectomy in the Ageing Brain - [including] where IV thromboysis fails or is contraindicated.**
REC reference:	**14/NE/0113**
IRAS project ID:	**142197**

Thank you for your letter of 04 July 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair and the lead reviewer.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Ms Gillian Mayer, nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper		26 March 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		26 July 2013
GP/consultant information sheets or letters	1.1	06 June 2014
Letter from sponsor		22 August 2013
Letter from sponsor		06 March 2014
Letters of invitation to participant	v1.0	15 January 2014
Non-validated questionnaire [Patient Questionnaire 3 Month]	1	20 June 2014
Non-validated questionnaire [Patient Questionnaire 12 Month]	1	20 June 2014
Other [Instructions for ERIC device]		23 January 2014
Participant consent form [Patient Consent form (Continuing Participation)]	v1.0	09 January 2014
Participant consent form [Consent Form]	v1.0	09 January 2014
Participant consent form [Consultee Declaration Form]	v1.0	09 January 2014
Participant information sheet (PIS) [PIS (Continuing Participation)]	1.1	23 June 2014
Participant information sheet (PIS) [Clinical Information Sheet for Thrombectomy Treatment]	1.0	23 June 2014
Participant information sheet (PIS) [Consultee]	1.1	23 June 2014
Participant information sheet (PIS) [Relative PIS (Short)]	1.1	23 June 2014
Participant information sheet (PIS) [PIS (Pre-Scanning)]	1.1	23 June 2014
Participant information sheet (PIS) [PIS]	1.1	23 June 2014
Participant information sheet (PIS) [Consultee (Pre-Screening)]	1.1	13 June 2014
Participant information sheet (PIS) [PIS (Short)]	1.1	23 June 2014
Participant information sheet (PIS) [Consultee (Short)]	1.1	13 June 2014
Participant information sheet (PIS) [Relative PIS (Pre-Scanning)]	1.1	23 June 2014
REC Application Form		26 March 2014
Research protocol or project proposal	1.1	23 June 2014
Response to Request for Further Information	P. White	04 July 2014
Summary CV for Chief Investigator (CI)		23 January 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/NE/0113	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp

Dr Mike Bone
Vice Chair

Email:nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr Sean Scott, The Newcastle upon Tyne Hospitals NHS Foundation Trust*

Appendix D – STABILISE Inclusion and Exclusion Criteria

Inclusion Criteria

- Clinical diagnosis of acute ischaemic stroke
- Male or non-pregnant female ≥18 years of age
- Clinically significant neurological deficit and NIHSS score ³6
- Enrolment, randomisation and procedure commencement (groin puncture) possible within 90 minutes of the CT/CTA diagnosis of LVO (AND maximum 5.5h after stroke onset anterior circulation, 8.5h for posterior circulation)
- Occlusion of the MCA trunk, MCA bifurcation or intracranial internal carotid artery (including carotid-T), M1 or ≤2 proximal M2 branches; intracranial vertebral/basilar/P1 posterior cerebral artery (PCA) demonstrated on CTA, MRA, or DSA
- Interventional device delivery (guide catheter placed in target artery beyond aortic arch and angio obtained) can be achieved within 6 hours of onset of the stroke (9h for posterior circulation occlusions)
- Consent of patient or appropriate consultee
- Independent prior to the stroke (estimated mRS 0-2)
- Expected to be able to be followed up at 12 months

Exclusion Criteria

- CT evidence of ICH, or evidence of extensive (defined as >1/3 MCA territory **or** Alberta Stroke Program Early CT score (ASPECTS) score ≤6) established hypodensity on CT
- Clinical history suggestive of subarachnoid haemorrhage even if CT normal
- Eligible for a “treatment policy” (i.e. phase III trial) RCT of stroke thrombectomy in that institution & willing to be randomised into such
- Vascular access contraindications e.g. bilateral femoral bypass surgery, tight ipsilateral carotid or vertebral stenosis (if judged not readily amenable to acute intervention by Interventional Neuroradiologist [INR] who would carry out the procedure), unsuitable proximal vascular anatomy likely to render

endovascular catheterisation difficult, unsafe or impossible (as judged by INR who would carry out the procedure)

- Extracranial: chronic/atherosclerotic ipsilateral internal carotid artery (ICA) or dominant vertebral artery occlusion
- Alternative intracranial pathology potentially responsible for the new symptoms
- Medical co-morbidities which would preclude safe cerebral vessel catheterisation or which are expected to limit life expectancy to <3 months (e.g. severe cardiac, renal or hepatic failure, significant coagulopathy, metastatic malignancy)
- Known allergy to radiological contrast
- Absolute contraindication to MRI

Appendix E – STABILISE Study Workbook

Patient I.D. |___|___|___|___|___|___|

Newcastle University

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

STABILISE

Stroke: an **e**valuation of **T**hrombectomy in the **A**geing **B**rain - [including] where **I**V thrombo**L**ysis fails or **IS** contraindicated

Case Report Form

Version & Date: 1.1 21st Oct 2014

Visit 1: Pre-Randomisation / Randomisation Visit

Date and time of stroke team assessment:

Date: ☐☐/☐☐/☐☐☐☐ Time: ☐☐:☐☐

Informed Consent Obtained From:

Patient ☐ Consultee ☐

Date of consent: ☐☐/☐☐/☐☐☐☐

Time of consent: ☐☐:☐☐

Demographic Data

Gender ☐ Male ☐ Female

Patient initials ☐☐☐

Date of Birth: ☐☐/☐☐/☐☐☐☐

Weight ☐☐☐ kg

Smoking status

☐ Current ☐ Former ☐ Never ☐ Don't know

Normal Residence & Domestic Circumstances

☐ Home alone

☐ Home with family/friends

☐ Sheltered housing alone

☐ Other* (sheltered housing with family friends/ residential home/nursing home/long stay hospitalisation)

*** If these apply patient cannot be randomised**

Risk Factors

Heart Disease (e.g. other acute coronary syndrome, coronary revascularisation, angina pectoris)	☐ Yes ☐ No
Stroke (prior to current stroke) a) Date of most recent stroke b) Type of stroke	☐ Yes ☐ No ☐☐/☐☐/☐☐☐☐ ☐ Ischaemic ☐ Haemorrhagic ☐ Unknown
History of diabetes	☐ Yes ☐ No
History of high blood pressure	☐ Yes ☐ No
Atrial fibrillation a) type of atrial fibrillation	☐ Yes ☐ No ☐ Paroxysmal ☐ Permanent
Carotid endarterectomy/stent a) side of carotid endarterectomy/stent	☐ Yes ☐ No ☐ Left ☐ Right ☐ Both

Any other significant medical history Yes ☐ No ☐

If yes, please provide the following details: condition, start date, end date/ongoing, medication required:

_____

_____

_____

_____

Please record medical history information on the medical history page of the eCRF.

Concomitant medications Yes ☐ No ☐

If yes, please provide the following details: name, start date, end date/ongoing, dose, frequency, route, indication.

_____

_____

_____

_____

Please record concomitant medication information on the concomitant medication page of the eCRF.

Symptom Onset

Date of onset ☐☐/☐☐/☐☐☐☐ Time of onset: ☐☐:☐☐

Record time of onset as the last known time to be asymptomatic if present on waking

Symptoms present on awakening from sleep? Yes ☐ No ☐

Clinical Stroke Subtype

Side of brain? ☐ Right ☐ Left ☐ Both

Class? ☐ TACS ☐ PACS ☐ POCS ☐ LACS

Study Imaging

	Initial Investigation	Time	Date
☐	CT	☐☐:☐☐	☐☐/☐☐/☐☐☐☐
☐	CT-Angiogram	☐☐:☐☐	☐☐/☐☐/☐☐☐☐
CT Details:			
☐	MRI	☐☐:☐☐	☐☐/☐☐/☐☐☐☐
☐	MRA	☐☐:☐☐	☐☐/☐☐/☐☐☐☐
MR Details:			

If CT/CTA not performed please state why:_____

_____

_____

_____

Physical Measurements

Date and time measurements were taken:

Date: ☐☐/☐☐/☐☐☐☐ Time: ☐☐:☐☐

Blood Pressure		Heart Rate	Temperature
Systolic	Diastolic	Beats per minute	°C
☐☐☐/☐☐☐		☐☐	☐☐.☐

Please record physical measurements on the vitals log page of the eCRF.

Patient I.D. |__|__|__|__|__|

NIH Stroke Scale

Date of Assessment: ☐☐/☐☐/☐☐☐☐ Time of Assessment: ☐☐:☐☐

Assessment by: _____

Assessment	Description		
Level of consciousness	Alert	0	☐
	Not alert, but arousable with minimal stimulation	1	☐
	Not alert, required repeated stimulation to attend	2	☐
	Coma. Reflex movements only.	3	☐
Ask patient the month and their age	Answers both correctly	0	☐
	Answers one correctly	1	☐
	Both incorrect	2	☐
Ask patient to open and close eyes and nonparetic hand	Obeys both correctly	0	☐
	Obeys one correctly	1	☐
	Both incorrect	2	☐
Best gaze (only horizontal eye movement)	Normal	0	☐
	Partial gaze palsy	1	☐
	Forced deviation, not overcome by oculocephalic manoeuvre	2	☐
Visual field testing:	No visual field loss	0	☐
	Partial hemianopia	1	☐
	Complete hemianopia	2	☐
	Bilateral hemianopia (blind including cortical blindess)	3	☐
Facial paresis (ask patient to show teeth or raise eyebrows and close eyes tightly)	Normal symmetrical movement	0	☐
	Minor paralysis (flattened nasolabial fold, asymmetry on smiling)	1	☐
	Partial paralysis (total or near total paralysis of lower face	2	☐
	Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	3	☐
Motor function – arm (right and left): (test each arm separately, non-paretic side first. Extend arms 90 degrees (or 45 if recumbent) for 10 seconds)	Normal – no drift	0	☐ R ☐ L
	Drift to intermediate position but does not hit bed	1	☐ R ☐ L
	Some effort against gravity	2	☐ R ☐ L
	No effort against gravity	3	☐ R ☐ L
	No movement	4	☐ R ☐ L
	Untestable (joint fused or limb amputated)	-	☐ R ☐ L

Assessment	Description		
Motor function – leg (right and left)	Normal (hold leg 30 degrees position for 5 seconds)	0	☐ R ☐ L
	Drift but does not hit bed	1	☐ R ☐ L
	Some effort against gravity	2	☐ R ☐ L
	No effort against gravity	3	☐ R ☐ L
	No movement	4	☐ R ☐ L
	Untestable (joint fused or limb amputated)	-	☐ R ☐ L
Limb ataxia (finger-nose, heel-shin on each side. Ataxia disproportionate to weakness only)	No ataxia (or comatose)	0	☐
	Present in one limb	1	☐
	Present in two limbs	2	☐
Sensory (use pinprick to test arms, legs, trunk and face –compare both sides)	Normal	0	☐
	Mild to moderate decrease in sensation. Aware of touch.	1	☐
	Severe to total sensory loss	2	☐
Best language (describe picture, name items, read sentences, ask patient to write if intubated)	No aphasia	0	☐
	Mild to moderate aphasia. Loss of fluency or comprehension.	1	☐
	Severe aphasia. Fragmented communication.	2	☐
	Mute. No usable speech or comprehension.	3	☐
Dysarthria (read several words)	Normal articulation	0	☐
	Mild to moderate slurring of words	1	☐
	Near unintelligible or unable to speak	2	☐
	Intubated or other physical barrier	3	☐
Extinction and inattention	Normal	0	☐
	Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities	1	☐
	Severe hemi-inattention or hemi-inattention to more than one modality	2	☐
Sum Score			

Pre admission modified Rankin Scale

Date of Assessment: ☐☐/☐☐/☐☐☐☐ Time of Assessment: ☐☐:☐☐

Assessment by: _____

- ☐ **0** No symptoms
- ☐ **1** No significant disability despite symptoms
- ☐ **2** Slight disability but able to look after own affairs without assistance
- ☐ **3** Moderate disability: requires some help but able to walk without assistance
- ☐ **4** Moderately severe disability: unable to walk without assistance, unable to attend to own bodily needs without assistance
- ☐ **5** Severe disability: bedridden, incontinent, requiring constant nursing care and attention

Score:_____

Investigation Results

Optional unless there is relevant clinical history or suspicion of disease.

Date and time of first sample taken:

Date ☐☐/☐☐/☐☐☐☐ Time: ☐☐:☐☐

Analyte	Result	Analyte	Result
Blood Glucose	_____ mmol/l	**Or** Capillary Blood Glucose	_____ mmol/l
Creatinine *(if renal impairment known or suspected)*	_____ umol/l	Prothrombin Time Count *(if clotting or haematological disorder known or suspected)*	_____ sec
Urea *(if renal impairment known or suspected)*	_____ mg/dl	APTT Ratio Count *(if clotting or haematological disorder known or suspected)*	_____
INR *(if on Warfarin)*	_____	Platelet Count *(if clotting or haematological disorder known or suspected)*	_____ 10^9/l

Inclusion Criteria

	Yes	No
1. Clinical diagnosis of acute ischaemic stroke	☐	☐
2. Male or non-pregnant female ≥50 years of age	☐	☐
3. Clinically significant neurological deficit and NIHSS score ≥10	☐	☐
4. Enrolment, randomisation and procedure commencement (groin puncture) possible within 90 minutes of the CT/CTA diagnosis of LVO (AND maximum 5.5h after stroke onset anterior circulation, 8.5h for posterior circulation)	☐	☐
5. Occlusion of the MCA trunk, MCA bifurcation or intracranial internal carotid artery (including carotid-T), M1 or ≤2 proximal M2 branches; intracranial vertebral/basilar/P1 posterior cerebral artery (PCA) demonstrated on CTA, MRA, or DSA	☐	☐
6. Interventional device delivery (guide catheter placed in target artery beyond aortic arch and angio obtained) can be achieved within 6 hours of onset of the stroke (9h for posterior circulation occlusions)	☐	☐
7. Consent of patient or agreement from appropriate consultee	☐	☐
8. Independent prior to the stroke (estimated mRS 0-2)	☐	☐
9. Expected to be able to be followed up at 12 months	☐	☐

If any of the shaded boxes is ticked, subject is <u>not</u> eligible for the study.

Exclusion Criteria

	Yes	No
1. CT evidence of ICH, or evidence of extensive (defined as >1/3 MCA territory or Alberta Stroke Program Early CT score (ASPECTS) score ≤7) established hypodensity on CT or pcASPECTS score <8		
2. Clinical history suggestive of subarachnoid haemorrhage even if CT normal	☐	☐
3. Eligible for a "treatment policy" (i.e. phase III trial) RCT of stroke thrombectomy in that institution & willing to be randomised into such	☐	☐
4. Vascular access contraindications e.g. bilateral femoral bypass surgery, tight ipsilateral carotid or vertebral stenosis (if judged not readily amenable to acute intervention by Interventional Neuroradiologist [INR] who would carry out the procedure), unsuitable proximal vascular anatomy likely to render endovascular catheterisation difficult, unsafe or impossible (as judged by INR who would carry out the procedure)	☐	☐
5. Extracranial: **chronic/atherosclerotic** ipsilateral internal carotid artery (ICA) or dominant vertebral artery occlusion	☐	☐
6. Alternative intracranial pathology potentially responsible for the new symptoms	☐	☐
7. Medical co-morbidities which would preclude safe cerebral vessel catheterisation or which are expected to limit life expectancy to <3 months (e.g. severe cardiac, renal or hepatic failure, significant coagulopathy, metastatic malignancy)	☐	☐
8. Known allergy to radiological contrast	☐	☐
9. Absolute contraindication to MRI	☐	☐

If any of the shaded boxes is ticked, subject is <u>not</u> eligible for the study

Eligibility

If the subject is eligible to participate in the study, are they to be included? ☐ Yes ☐ No

If no, please comment:

_____

_____

_____

If the patient is eligible for the study, please randomise using your site specific PIN for randomisation.

Patient was not included. Did this patient have a thrombectomy procedure outside of this trial?

☐ Yes ☐ No

Please comment:

_____

_____

_____

Visit 2: Procedure (Part 1 of 2)

If the patient is eligible for the study, please randomise

Date of randomisation: ☐☐/☐☐/☐☐☐☐

Time of randomisation: ☐☐:☐☐

Treatment arm patient randomised to:

☐ IAT with standard "thrombectomy" device and continue standard best medical care

☐ IAT with novel ERIC™ "thrombectomy" device & continue standard best medical care

Randomisation Number: _____

IV rtPA details

IV rtPA administered ☐Yes ☐No

If No, please go to page 14
If Yes, please complete below

Date IV rtPA treatment commenced ☐☐/☐☐/☐☐☐☐

Time IV rtPA treatment commenced ☐☐:☐☐

Dose of IV rtPA treatment _____

Date IV rtPA treatment completed ☐☐/☐☐/☐☐☐☐

Time IV rtPA treatment completed ☐☐:☐☐

Physical measurements at start of IV rtPA infusion

Date and time measurements were taken:

Date: ☐☐/☐☐/☐☐☐☐ Time: ☐☐:☐☐

Blood Pressure		Heart Rate	Temperature
Systolic	Diastolic	Beats per minute	°C
☐☐☐/☐☐☐		☐☐	☐☐ ☐

Adverse Events

Are there any adverse events reported? ☐ Yes ☐ No

If yes, please report in full on adverse events page.

Timepoint **NB. Complete only those timepoints routinely collected in your institution**	**Date** dd/mm/yyyy	**Time** hh:mm (24 hr clock)	**Blood Pressure**		**Heart Rate** Beats per minute	**Temp.** °C
			Systolic	**Diastolic**		
1hr after starting infusion						
2 hrs after starting infusion						
3 hrs after starting infusion						
2 hrs after starting infusion						
4 hrs after starting infusion						
5 hrs after starting infusion						
6 hrs after starting infusion						
7 hrs after starting infusion						
8 hrs after starting infusion						
9 hrs after starting infusion						
10 hrs after starting infusion						
11 hrs after starting infusion						
12 hrs after starting infusion						
13 hrs after starting infusion						
14 hrs after starting infusion						
15 hrs after starting infusion						
16 hrs after starting infusion						

Timepoint **NB. Complete only those timepoints routinely collected in your institution**	**Date** dd/mm/yyyy	**Time** hh:mm (24 hr clock)	**Blood Pressure**		**Heart Rate** Beats per minute	**Temp.** °C
			Systolic	**Diastolic**		
17 hrs after starting infusion						
18 hrs after starting infusion						
19 hrs after starting infusion						
20 hrs after starting infusion						
21 hrs after starting infusion						
22 hrs after starting infusion						
23 hrs after starting infusion						
24 hrs after starting infusion						
28 hrs after starting infusion						
32 hrs after starting infusion						
36 hrs after starting infusion						
40 hrs after starting infusion						
44 hrs after starting infusion						
48 hrs after starting infusion						

Visit 2: Procedure (Part 2 of 2)

Has NIHSS been reviewed immediately pre-procedure? ☐ Yes ☐ No
Please note that this needs to be performed if the patient is transferred from another centre.

Patient must have a NIHSS of ≥10 to undergo the procedure within the trial.

Physical measurements at start of procedure

Date and time measurements were taken:

Date: ☐☐/☐☐/☐☐☐☐ Time: ☐☐:☐☐

Blood Pressure		Heart Rate	Temperature
Systolic	Diastolic	Beats per minute	°C
☐☐☐/☐☐☐		☐☐	☐☐.☐

Thrombectomy procedure details

Patient anaesthesia or sedation:

☐ General anaesthesia ☐ Sedation & LA ☐ Local anaesthesia only

Date of groin puncture ☐☐/☐☐/☐☐☐☐

Time of groin puncture ☐☐:☐☐

Date of catheter placement (distal to aortic arch) ☐☐/☐☐/☐☐☐☐

Time of catheter placement (distal to aortic arch) ☐☐:☐☐

Date of 1st angiographic run on TARGET occluded artery segment ☐☐/☐☐/☐☐☐☐

Time of 1st angiographic run on TARGET occluded artery segment ☐☐:☐☐

Vessel status at initial angiographic run:

☐ 0 = No reperfusion

☐ 1 = Flow beyond occlusion without distal branch perfusion

☐ 2a = Reperfusion of less than half of the downstream target arterial territory

☐ 2b = Reperfusion of more than half, yet incomplete, in the downstream target arterial territory

☐ 3 = Complete perfusion of the downstream target arterial territory, including distal branches with slow flow

Total duration of procedure (groin puncture to end of thrombectomy) ☐☐☐min

Post procedure care details

☐ NeuroITU or equivalent ☐ Hyperacute Stroke Unit

☐ HDU ☐ Normal neuro/stroke ward

☐ Other details: _____

Adverse Events

Are there any adverse events reported? ☐ Yes ☐ No

If yes, please report in full on adverse events page.

Device details

Device name	Details	
☐ 1. ERIC system ☐ 2. Covidien ev3 Solitaire & derivatives ☐ 3. Penumbra retriever/thrombectomy aspiration system & derivatives ☐ 4. Concentric Trevo/Trevo2 & derivatives ☐ 5. Acandis Aperio ☐ 6. MindFrame Capture device & derivatives ☐ 7. Codman ReVive & derivatives ☐ 8. Phenox BONNET & derivatives ☐ 9. Phenox pRESET & derivatives ☐ 10. Other approved device – specify:	Number of deployments (0-3)	_____
	Start time that device is in situ in occluded vessel	☐☐:☐☐
	Time last removed/deployed	☐☐:☐☐
	Vessel status at end of deployment	☐ 0 = No reperfusion ☐ 1 = Flow beyond occlusion without distal branch perfusion ☐ 2a = Reperfusion of less than half of the downstream target arterial territory ☐ 2b = Reperfusion of more than half, yet incomplete, in the downstream target arterial territory ☐ 3 = Complete perfusion of the downstream target arterial territory, including distal branches with slow flow

Device name	Details	
☐ 1. ERIC system ☐ 2. Covidien ev3 Solitaire & derivatives ☐ 3. Penumbra retriever/thrombectomy aspiration system & derivatives ☐ 4. Concentric Trevo/Trevo2 & derivatives ☐ 5. Acandis Aperio ☐ 6. MindFrame Capture device & derivatives ☐ 7. Codman ReVive & derivatives ☐ 8. Phenox BONNET & derivatives ☐ 9. Phenox pRESET & derivatives ☐ 10. Other approved device – specify:	Number of deployments (0-3)	_____
	Start time that device is in situ in occluded vessel	☐☐:☐☐
	Time last removed/deployed	☐☐:☐☐
	Vessel status at end of deployment	☐ 0 = No reperfusion ☐ 1 = Flow beyond occlusion without distal branch perfusion ☐ 2a = Reperfusion of less than half of the downstream target arterial territory ☐ 2b = Reperfusion of more than half, yet incomplete, in the downstream target arterial territory ☐ 3 = Complete perfusion of the downstream target arterial territory, including distal branches with slow flow

Did the patient receive any intra-arterial drug infusions?

☐ Yes ☐ No

If Yes,

Name(s) of intra-arterial drug given or other drugs given _____

Date IA drug treatment commenced ☐☐/☐☐/☐☐☐☐

Time IA drug treatment commended ☐☐:☐☐

Dose of IA drug treatment given: ☐☐.☐____ units

Date IA drug treatment completed ☐☐/☐☐/☐☐☐☐

Time IA drug treatment completed ☐☐:☐☐

Did the patient receive more than one intra-arterial infusion?

☐ Yes ☐ No

If yes,

Name of second intra-arterial drug given or other drugs given _____

Date second IA drug treatment commenced ☐☐/☐☐/☐☐☐☐

Time second IA drug treatment commended ☐☐:☐☐

Dose of second IA drug treatment given: ☐☐.☐____ units

Date second IA drug treatment completed ☐☐/☐☐/☐☐☐☐

Time second IA drug treatment completed ☐☐:☐☐

If the patient received more than two intra-arterial infusions, please provide details in the 'concomitant medications' section

Other concomitant medications, including anaesthesia or sedation (please include the following details: name, start date & time, end date & time/ ongoing, dose, frequency, route, indication)

Physical Measurements

Please record observations made clinically (as per institutional protocol) for 48 hours post-procedure table (BP, HR, T) to be filled in pages 21-22.

Timepoint **NB. Complete only those timepoints routinely collected in your institution**	**Date** dd/mm/yyyy	**Time** hh:mm (24 hr clock)	**Blood Pressure**		**Heart Rate** Beats per minute	**Temp** °C
			Systolic	**Diastolic**		
1hr post procedure						
2hrs post procedure						
3 hrs post procedure						
4 hrs post procedure						
5 hrs post procedure						
6 hrs post procedure						
7 hrs post procedure						
8 hrs post procedure						
9 hrs post procedure						
10 hrs post procedure						
11 hrs post procedure						
12 hrs post procedure						
13 hrs post procedure						
14 hrs post procedure						
15 hrs post procedure						

Timepoint **NB. Complete only those timepoints routinely collected in your institution**	**Date** dd/mm/yyyy	**Time** hh:mm (24 hr clock)	**Blood Pressure**		**Heart Rate** Beats per minute	**Temp** . °C
			Systolic	**Diastolic**		
16 hrs post procedure						
17 hrs post procedure						
18 hrs post procedure						
19 hrs post procedure						
20 hrs post procedure						
21 hrs post procedure						
22 hrs post procedure						
23 hrs post procedure						
24 hrs post procedure						
28 hrs post procedure						
32 hrs post procedure						
36 hrs post procedure						
40 hrs post procedure						
48 hrs post procedure						
48 hrs post procedure						

Adverse Events

Are there any adverse events reported? ☐ Yes ☐ No

If yes, please report in full on adverse events page.

Visit 3: 24 hours (22-36 hours) post treatment

Physical measurements

Date and time measurements were taken:

Date: ☐☐/☐☐/☐☐☐☐ Time: ☐☐:☐☐

Blood Pressure		Heart Rate	Temperature
Systolic	Diastolic	Beats per minute	°C
☐☐☐/☐☐☐		☐☐	☐☐.☐

Adverse Events

Are there any adverse events reported? ☐ Yes ☐ No

If yes, please report in full on adverse events page.

Post Treatment Imaging

	Brain imaging	Time	Date
☐	**MRI**	☐☐:☐☐ ☐☐:☐☐ ☐☐:☐☐	☐☐/☐☐/☐☐☐☐ ☐☐/☐☐/☐☐☐☐ ☐☐/☐☐/☐☐☐☐
☐	**MRA**	☐☐:☐☐ ☐☐:☐☐ ☐☐:☐☐	☐☐/☐☐/☐☐☐☐ ☐☐/☐☐/☐☐☐☐ ☐☐/☐☐/☐☐☐☐
If MRI/MRA not performed please state the reason:			
☐	**CT**	☐☐:☐☐ ☐☐:☐☐ ☐☐:☐☐	☐☐/☐☐/☐☐☐☐ ☐☐/☐☐/☐☐☐☐ ☐☐/☐☐/☐☐☐☐
☐	**CTA**	☐☐:☐☐ ☐☐:☐☐ ☐☐:☐☐	☐☐/☐☐/☐☐☐☐ ☐☐/☐☐/☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Physical measurements

Date and time measurements were taken:

Date: ☐☐/☐☐/☐☐☐☐ Time: ☐☐:☐☐

Blood Pressure		Heart Rate	Temperature
Systolic	Diastolic	Beats per minute	°C
☐☐☐/☐☐☐		☐☐	☐☐.☐

NIH Stroke Scale

Date of Assessment: ☐☐/☐☐/☐☐☐☐ Time of Assessment: ☐☐:☐☐

Assessment by: _____

Assessment	Description		
Level of consciousness	Alert	0	☐
	Not alert, but arousable with minimal stimulation	1	☐
	Not alert, required repeated stimulation to attend	2	☐
	Coma. Reflex movements only.	3	☐
Ask patient the month and their age	Answers both correctly	0	☐
	Answers one correctly	1	☐
	Both incorrect	2	☐
Ask patient to open and close eyes and nonparetic hand	Obeys both correctly	0	☐
	Obeys one correctly	1	☐
	Both incorrect	2	☐
Best gaze (only horizontal eye movement)	Normal	0	☐
	Partial gaze palsy	1	☐
	Forced deviation, not overcome by oculocephalic manoeuvre	2	☐
Visual field testing:	No visual field loss	0	☐
	Partial hemianopia	1	☐
	Complete hemianopia	2	☐
	Bilateral hemianopia (blind including cortical blindness)	3	☐
Facial paresis (ask patient to show teeth or raise eyebrows and close eyes tightly)	Normal symmetrical movement	0	☐
	Minor paralysis (flattened nasolabial fold, asymmetry on smiling)	1	☐
	Partial paralysis (total or near total paralysis of lower face	2	☐
	Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	3	☐
Motor function – arm (right and left): (test each arm separately, non-paretic side first. Extend arms 90 degrees (or 45 if recumbent) for 10 seconds)	Normal – no drift	0	☐ R ☐ L
	Drift to intermediate position but does not hit bed	1	☐ R ☐ L
	Some effort against gravity	2	☐ R ☐ L
	No effort against gravity	3	☐ R ☐ L
	No movement	4	☐ R ☐ L
	Untestable (joint fused or limb amputated)	-	☐ R ☐ L

Assessment	Description		
Motor function – leg (right and left)	Normal (hold leg 30 degrees position for 5 seconds)	0	☐ R ☐ L
	Drift but does not hit bed	1	☐ R ☐ L
	Some effort against gravity	2	☐ R ☐ L
	No effort against gravity	3	☐ R ☐ L
	No movement	4	☐ R ☐ L
	Untestable (joint fused or limb amputated)	-	☐ R ☐ L
Limb ataxia (finger-nose, heel-shin on each side. Ataxia disproportionate to weakness only)	No ataxia (or comatose)	0	☐
	Present in one limb	1	☐
	Present in two limbs	2	☐
Sensory (use pinprick to test arms, legs, trunk and face –compare both sides)	Normal	0	☐
	Mild to moderate decrease in sensation. Aware of touch.	1	☐
	Severe to total sensory loss	2	☐
Best language (describe picture, name items, read sentences, ask patient to write if intubated)	No aphasia	0	☐
	Mild to moderate aphasia. Loss of fluency or comprehension.	1	☐
	Severe aphasia. Fragmented communication.	2	☐
	Mute. No usable speech or comprehension.	3	☐
Dysarthria (read several words)	Normal articulation	0	☐
	Mild to moderate slurring of words	1	☐
	Near unintelligible or unable to speak	2	☐
	Intubated or other physical barrier	3	☐
Extinction and inattention	Normal	0	☐
	Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities	1	☐
Sum			

Investigation Results

Optional unless there is relevant clinical history or suspicion of disease.

Date and time of sample taken:

Date ☐☐/☐☐/☐☐☐☐ Time: ☐☐:☐☐

Analyte	**Result**	**Analyte**	**Result**
Blood Glucose	_____ mmol/l	**Or** Capillary Blood Glucose	_____ mmol/l
Creatinine *(if renal impairment known or suspected)*	_____ umol/l	Prothrombin Time Count *(if clotting or haematological disorder known or suspected)*	_____ sec
Urea *(if renal impairment known or suspected)*	_____ mg/dl	APTT Ratio Count *(if clotting or haematological disorder known or suspected)*	_____
INR *(if on Warfarin)*	_____	Platelet Count *(if clotting or haematological disorder known or suspected)*	_____ 10^9/l

Visit 4: 72 ± 8 hours post treatment (or hospital discharge if earlier)

Date and time of visit:

Date: ☐☐/☐☐/☐☐☐☐ Time: ☐☐:☐☐

Is this a hospital discharge visit?

Yes ☐ No ☐

Physical measurements

Blood Pressure		Heart Rate	Temperature
Systolic	Diastolic	Beats per minute	°C
☐☐☐/☐☐☐		☐☐	☐☐.☐

NIH Stroke Scale

Assessment by: _____

Assessment	Description		
Level of consciousness	Alert	0	☐
	Not alert, but arousable with minimal stimulation	1	☐
	Not alert, required repeated stimulation to attend	2	☐
	Coma. Reflex movements only.	3	☐
Ask patient the month and their age	Answers both correctly	0	☐
	Answers one correctly	1	☐
	Both incorrect	2	☐
Ask patient to open and close eyes and nonparetic hand	Obeys both correctly	0	☐
	Obeys one correctly	1	☐
	Both incorrect	2	☐
Best gaze (only horizontal eye movement)	Normal	0	☐
	Partial gaze palsy	1	☐
	Forced deviation, not overcome by oculocephalic manoeuvre	2	☐
Visual field testing:	No visual field loss	0	☐
	Partial hemianopia	1	☐
	Complete hemianopia	2	☐
	Bilateral hemianopia (blind including cortical blindness)	3	☐
Facial paresis (ask patient to show teeth or raise eyebrows and close eyes tightly)	Normal symmetrical movement	0	☐
	Minor paralysis (flattened nasolabial fold, asymmetry on smiling)	1	☐
	Partial paralysis (total or near total paralysis of lower face	2	☐
	Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	3	☐
Motor function – arm (right and left): (test each arm separately, non-paretic side first. Extend arms 90 degrees (or 45 if recumbent) for 10 seconds)	Normal – no drift	0	☐ R ☐ L
	Drift to intermediate position but does not hit bed	1	☐ R ☐ L
	Some effort against gravity	2	☐ R ☐ L
	No effort against gravity	3	☐ R ☐ L
	No movement	4	☐ R ☐ L
	Untestable (joint fused or limb amputated)	-	☐ R ☐ L

Assessment	Description		
Motor function – leg (right and left)	Normal (hold leg 30 degrees position for 5 seconds)	0	☐ R ☐ L
	Drift but does not hit bed	1	☐ R ☐ L
	Some effort against gravity	2	☐ R ☐ L
	No effort against gravity	3	☐ R ☐ L
	No movement	4	☐ R ☐ L
	Untestable (joint fused or limb amputated)	-	☐ R ☐ L
Limb ataxia (finger-nose, heel-shin on each side. Ataxia disproportionate to weakness only)	No ataxia (or comatose)	0	☐
	Present in one limb	1	☐
	Present in two limbs	2	☐
Sensory (use pinprick to test arms, legs, trunk and face –compare both sides)	Normal	0	☐
	Mild to moderate decrease in sensation. Aware of touch.	1	☐
	Severe to total sensory loss	2	☐
Best language (describe picture, name items, read sentences, ask patient to write if intubated)	No aphasia	0	☐
	Mild to moderate aphasia. Loss of fluency or comprehension.	1	☐
	Severe aphasia. Fragmented communication.	2	☐
	Mute. No usable speech or comprehension.	3	☐
Dysarthria (read several words)	Normal articulation	0	☐
	Mild to moderate slurring of words	1	☐
	Near unintelligible or unable to speak	2	☐
	Intubated or other physical barrier	3	☐
Extinction and inattention	Normal	0	☐
	Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities	1	☐
Sum			

Adverse Events

Are there any adverse events reported? ☐ Yes ☐ No

If yes, please report in full on adverse events page.

Visit 5: Day 7 (±2) post treatment (or at discharge if sooner)

Date and time of visit:

Date: ☐☐/☐☐/☐☐☐☐ Time: ☐☐:☐☐

Is this a hospital discharge visit?

Yes ☐ No ☐

Physical measurements

Blood Pressure		Heart Rate	Temperature
Systolic	Diastolic	Beats per minute	°C
☐☐☐/☐☐☐		☐☐	☐☐.☐

Patient I.D. | | | | | |

NIH Stroke Scale

Assessment by: _____

Assessment	Description		
Level of consciousness	Alert	0	☐
	Not alert, but arousable with minimal stimulation	1	☐
	Not alert, required repeated stimulation to attend	2	☐
	Coma. Reflex movements only.	3	☐
Ask patient the month and their age	Answers both correctly	0	☐
	Answers one correctly	1	☐
	Both incorrect	2	☐
Ask patient to open and close eyes and nonparetic hand	Obeys both correctly	0	☐
	Obeys one correctly	1	☐
	Both incorrect	2	☐
Best gaze (only horizontal eye movement)	Normal	0	☐
	Partial gaze palsy	1	☐
	Forced deviation, not overcome by oculocephalic manoeuvre	2	☐
Visual field testing:	No visual field loss	0	☐
	Partial hemianopia	1	☐
	Complete hemianopia	2	☐
	Bilateral hemianopia (blind including cortical blindess)	3	☐
Facial paresis (ask patient to show teeth or raise eyebrows and close eyes tightly)	Normal symmetrical movement	0	☐
	Minor paralysis (flattened nasolabial fold, asymmetry on smiling)	1	☐
	Partial paralysis (total or near total paralysis of lower face	2	☐
	Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	3	☐
Motor function – arm (right and left): (test each arm separately, non-paretic side first. Extend arms 90 degrees (or 45 if recumbent) for 10 seconds)	Normal – no drift	0	☐ R ☐ L
	Drift to intermediate position but does not hit bed	1	☐ R ☐ L
	Some effort against gravity	2	☐ R ☐ L
	No effort against gravity	3	☐ R ☐ L
	No movement	4	☐ R ☐ L
	Untestable (joint fused or limb amputated)	-	☐ R ☐ L

Assessment	Description		
Motor function – leg (right and left)	Normal (hold leg 30 degrees position for 5 seconds)	0	☐ R ☐ L
	Drift but does not hit bed	1	☐ R ☐ L
	Some effort against gravity	2	☐ R ☐ L
	No effort against gravity	3	☐ R ☐ L
	No movement	4	☐ R ☐ L
	Untestable (joint fused or limb amputated)	-	☐ R ☐ L
Limb ataxia (finger-nose, heel-shin on each side. Ataxia disproportionate to weakness only)	No ataxia (or comatose)	0	☐
	Present in one limb	1	☐
	Present in two limbs	2	☐
Sensory (use pinprick to test arms, legs, trunk and face –compare both sides)	Normal	0	☐
	Mild to moderate decrease in sensation. Aware of touch.	1	☐
	Severe to total sensory loss	2	☐
Best language (describe picture, name items, read sentences, ask patient to write if intubated)	No aphasia	0	☐
	Mild to moderate aphasia. Loss of fluency or comprehension.	1	☐
	Severe aphasia. Fragmented communication.	2	☐
	Mute. No usable speech or comprehension.	3	☐
Dysarthria (read several words)	Normal articulation	0	☐
	Mild to moderate slurring of words	1	☐
	Near unintelligible or unable to speak	2	☐
	Intubated or other physical barrier	3	☐
Extinction and inattention	Normal	0	☐
	Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities	1	☐
Sum			

Adverse Events

Are there any adverse events reported? ☐ Yes ☐ No

If yes, please report in full on adverse events page

Visit 6: 30 days

Adverse Events

Are there any adverse events reported? ☐ Yes ☐ No

If yes, please report in full on adverse events page

Patient I.D. |_|_|_|_|_|

Visit 7: 90 (±7) days

Date of questionnaire completion:

Date: ☐☐/☐☐/☐☐☐☐

modified Rankin Scale

Date of Assessment: ☐☐/☐☐/☐☐☐☐ Time of Assessment: ☐☐:☐☐

Assessment by: _____

- ☐ **0** No symptoms
- ☐ **1** No significant disability despite symptoms
- ☐ **2** Slight disability but able to look after own affairs without assistance
- ☐ **3** Moderate disability: requires some help but able to walk without assistance
- ☐ **4** Moderately severe disability: unable to walk without assistance, unable to attend to own bodily needs without assistance
- ☐ **5** Severe disability: bedridden, incontinent, requiring constant nursing care and attention

Score:_____

Home time evaluation

Has the patient returned home between admission and day 90? ☐ Yes ☐ No

Number of nights spent in own home/with relatives since stroke onset to day 90 ☐☐

Adverse Events

Are there any adverse events reported? ☐ Yes ☐ No

If yes, please report in full on adverse events page

Visit 8: Day 365 (±10)

Date of questionnaire completion:

Date: ☐☐/☐☐/☐☐☐☐

modified Rankin Scale

Date of Assessment: ☐☐/☐☐/☐☐☐☐ Time of Assessment: ☐☐:☐☐

Assessment by: _____

- ☐ **0** No symptoms
- ☐ **1** No significant disability despite symptoms
- ☐ **2** Slight disability but able to look after own affairs without assistance
- ☐ **3** Moderate disability: requires some help but able to walk without assistance
- ☐ **4** Moderately severe disability: unable to walk without assistance, unable to attend to own bodily needs without assistance
- ☐ **5** Severe disability: bedridden, incontinent, requiring constant nursing care and attention

Score:_____

Adverse Events

Are there any adverse events reported? ☐ Yes ☐ No

If yes, please report in full on adverse events page

Concomitant medication during the study period (additional pages can be added to the end of workbook as necessary)

Please report all medication administered following consent to study, up until study completion at day 90. Report trade name where possible rather than drug name.

No.	Drug	Dose	Onset Date	End Date	Ongoing Day 90?		
1.					Y	N	U
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							
12.							

Study completion/withdrawal

Please refer to the 'patient completion/withdrawal guidance notes' provided in the study site file.

Did the patient die? ☐ Yes Date of death ☐☐/☐☐/☐☐☐☐

☐ No

Did the patient complete the study?

☐ Yes Date of completion: ☐☐/☐☐/☐☐☐☐

☐ No (a) date of withdrawal ☐☐/☐☐/☐☐☐☐

(b) reasons for not completing the study:

- ☐ Patient withdrawal of consent
- ☐ Relative/consultee withdrawal of consent
- ☐ Termination of the clinical trial
- ☐ Other details:

Investigator Statement

I hereby certify that all information entered by myself or my team is, to the best of my knowledge, correct.

Signature: _____ Date: ☐☐/☐☐/☐☐☐☐

Appendix F – STABILISE Thrombectomy Treatment Details

Newcastle University *Print on local headed paper* The Newcastle upon Tyne Hospitals NHS NHS Foundation Trust

Thrombectomy Treatment

Has NIHSS been reviewed immediately pre-procedure? ☐ Yes ☐ No
Please note that this needs to be performed if the patient is transferred from another centre.

Patient must have a NIHSS of ≥10 to undergo the procedure within the trial.
For patients which failed to respond to IVT, their NIHSS must not have improved by ≥4 points, 30 minutes post infusion bolus to a NIHSS of <8.

Thrombectomy procedure details

Patient anaesthesia or sedation:

☐ General anaesthesia ☐ Sedation & LA ☐ Local anaesthesia only

Date of groin puncture ☐☐/☐☐/☐☐☐☐

Time of groin puncture ☐☐:☐☐

Date of catheter placement (distal to aortic arch) ☐☐/☐☐/☐☐☐☐

Time of catheter placement (distal to aortic arch) ☐☐:☐☐

Date of 1st angiographic run on TARGET occluded artery segment ☐☐/☐☐/☐☐☐☐

Time of 1st angiographic run on TARGET occluded artery segment ☐☐:☐☐

Vessel status at initial angiographic run:

☐ 0 = No reperfusion

☐ 1 = Flow beyond occlusion without distal branch perfusion

☐ 2a = Reperfusion of less than half of the downstream target arterial territory

☐ 2b = Reperfusion of more than half, yet incomplete, in the downstream target arterial territory

☐ 3 = Complete perfusion of the downstream target arterial territory, including distal branches with slow flow

Device details

Device name	Details	
☐ 1. ERIC system ☐ 2. Covidien ev3 Solitaire & derivatives ☐ 3. Penumbra retriever/thrombectomy aspiration system & derivatives ☐ 4. Concentric Trevo/Trevo2 & derivatives ☐ 5. Acandis Aperio ☐ 6. MindFrame Capture device & derivatives ☐ 7. Codman ReVive & derivatives ☐ 8. Phenox BONNET & derivatives ☐ 9. Phenox pRESET & derivatives ☐ 10. Other approved device – specify:	Number of deployments (0-3)	_____
	Start time that device is in situ in occluded vessel	☐☐:☐☐
	Time last removed/deployed	☐☐:☐☐
	Vessel status at end of deployment	☐ 0 = No reperfusion ☐ 1 = Flow beyond occlusion without distal branch perfusion ☐ 2a = Reperfusion of less than half of the downstream target arterial territory ☐ 2b = Reperfusion of more than half, yet incomplete, in the downstream target arterial territory ☐ 3 = Complete perfusion of the downstream target arterial territory, including distal branches with slow flow

Device details

Device name	Details	
☐ 1. ERIC system ☐ 2. Covidien ev3 Solitaire & derivatives ☐ 3. Penumbra retriever/thrombectomy aspiration system & derivatives ☐ 4. Concentric Trevo/Trevo2 & derivatives ☐ 5. Acandis Aperio ☐ 6. MindFrame Capture device & derivatives ☐ 7. Codman ReVive & derivatives ☐ 8. Phenox BONNET & derivatives ☐ 9. Phenox pRESET & derivatives ☐ 10. Other approved device – specify:	Number of deployments (0-3)	_____
	Start time that device is in situ in occluded vessel	☐☐:☐☐
	Time last removed/deployed	☐☐:☐☐
	Vessel status at end of deployment	☐ 0 = No reperfusion ☐ 1 = Flow beyond occlusion without distal branch perfusion ☐ 2a = Reperfusion of less than half of the downstream target arterial territory ☐ 2b = Reperfusion of more than half, yet incomplete, in the downstream target arterial territory ☐ 3 = Complete perfusion of the downstream target arterial territory, including distal branches with slow flow

Did the patient receive any intra-arterial drug infusions?

☐ Yes ☐ No

If Yes,

Name(s) of intra-arterial drug given or other drugs given _____

Date IA drug treatment commenced ☐☐/☐☐/☐☐☐☐

Time IA drug treatment commended ☐☐:☐☐

Dose of IA drug treatment given: ☐☐.☐____ units

Date IA drug treatment completed ☐☐/☐☐/☐☐☐☐

Time IA drug treatment completed ☐☐:☐☐

Did the patient receive more than one intra-arterial infusion?

☐ Yes ☐ No

If yes,

Name of second intra-arterial drug given or other drugs given _____

Date second IA drug treatment commenced ☐☐/☐☐/☐☐☐☐

Time second IA drug treatment commended ☐☐:☐☐

Dose of second IA drug treatment given: ☐☐.☐____ units

Date second IA drug treatment completed ☐☐/☐☐/☐☐☐☐

Time second IA drug treatment completed ☐☐:☐☐

Other concomitant medications, including anaesthesia or sedation (please include the following details: name, start date & time, end date & time/ ongoing, dose, frequency, route, indication)

_____

_____

_____

_____

Total duration of procedure ☐☐☐ min
(groin puncture to end of thrombectomy)

Post procedure care details:

☐ NeuroITU or equivalent ☐ Hyperacute Stroke Unit

☐ HDU ☐ Normal neuro/stroke ward

☐ Other details: _____

Appendix G – STABILISE Patient Information Sheet

Newcastle University *Print on local headed paper* The Newcastle upon Tyne Hospitals NHS NHS Foundation Trust

Stroke: an evaluation of Thrombectomy in the Ageing Brain (STABILISE) Trial

Patient Information Sheet

Invitation to take part in this clinical trial

We are approaching people who have suffered a stroke to invite them to participate in a clinical trial. Before you decide whether you would like to participate, we would like you to understand why the research is being done and what it would involve for you. One of the research team will go through the information sheet with you and answer any questions you have.

Our trial is testing whether strokes caused by a blockage in a large artery might be more effectively treated with a new clot removal device (SOFIA™- Soft Torqueable Catheter Optimized For Intracranial Access and/or ERIC™ - Embolus Retriever with Interlinked Cage) compared with current standard devices. Part 1 tells you the purpose of the trial and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the trial.

Part 1

What is the purpose of this trial?

Most strokes are caused by a clot blocking an artery in the brain (called "ischaemic strokes"). Some patients with strokes of this type can be treated with a "clot-busting" (thrombolytic) drug.

However, the larger the artery blocked, the less likely it is that drug treatment will open it. Since the large blockages are likely to cause more severe strokes, there is a need for more effective treatment.

Recently, medical devices ("thrombectomy devices") have been developed that allow specialist doctors to remove blood clots from large arteries in the brain by feeding the device through the circulation. These are able to open blockages more often than drug treatment alone, in up to 80% of cases (4 out of 5 people). Current devices for thrombectomy were generally not purpose designed but adapted from other existing devices. They may not work as well as they could. In particular they can be difficult to use in older people and most previous studies of clot removal have excluded older patients. In this trial we will compare the results in people treated with new clot

removal devices (SOFIA™ and/or ERIC™) compared with standard existing thrombectomy devices. We are undertaking this trial to test whether the use these new purpose designed stroke clot removal devices is as safe and at least as effective as existing devices. For those taking part in the trial, treatment will be allocated at random by computer software designed to allocate patients to treatment in such a way that the results of the trial will be meaningful. There is quite a lot of information already available on existing devices, but not on the new SOFIA™ and ERIC™ devices. So to enable this study to provide the most useful data possible on the new SOFIA™ and ERIC™ devices there is a 2:1 chance of having the new device treatment.

Why have I been invited?

You have been invited to participate in this clinical trial because you have just suffered a stroke, caused by a clot blocking a large artery in the brain and the doctors looking after you have advised that clot removal (thrombectomy) should be performed. We are planning to recruit 120 people who have just suffered a stroke to this trial.

Do I have to take part?

It is up to you to decide whether to join the clinical trial. We will describe the trial and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

All the people taking part will be given the current best medical treatment for them (with a clot-busting drug if safe to do so) as well as clot removal. After making sure that a blockage is present in a blood vessel that can be treated with a device, we will use a computer system to assign at random whether people will go to treatment with the new thrombectomy device. Two thirds of the people in the trial will go on to have new device treatment, and the other third will have clot removal using a standard device(s). This randomisation will enable us to compare the results to see whether the new device is comparable with the existing standard devices.

A number of tests are part of routine care for people treated for acute stroke. All of these will be done as normal, although we wish to record many of the results for the trial.

Extra procedures for the trial include the following in all people, whether or not they undergo new device treatment:

- MRI scan will be done around 24 hours after treatment to see if the blockage has been cleared successfully and to enable us to gather more information on who responds best to clot removal treatment. This is instead of the usual

follow-up CT scan. So it is a replacement rather than an additional test and results in reduced exposure to X-ray radiation.

- Some extra physical examinations (neurological assessments) are done at 72 hours, 7 days (or at hospital discharge if sooner). These take around 15 minutes.
- Some extra checks on the effects of the stroke on day-to-day function using questionnaires on two occasions at 3 and 12 months after the stroke. These take around 5 minutes and involve questions about activities such as washing, dressing, eating and walking, and whether there are any restrictions on your activities. These will either be undertaken at standard clinic appointments, by mail or telephone.

Expenses and payments

No expenses are available for taking part in this clinical trial.

What will I have to do?

Following device treatment, you will be required to attend all scheduled clinic visits and/or complete telephone/postal interviews up until 365 days post treatment.

What are the alternatives for diagnosis or treatment?

If you do not take part in this clinical trial you will continue to receive all treatment or tests that your doctors think is required in line with current best medical practice.

What are the possible disadvantages and risks of taking part in the trial?

It should be noted that the risks of the new device are not entirely known, but it is approved (CE marked) for this use based on a small study indicating it can be used safely for thrombectomy. It is not expected that the SOFIA™ and ERIC™ devices will be associated with a different risk from standard thrombectomy devices but the STABILISE trial will confirm that. Thrombectomy devices have to be fed up to blood vessels in the head. There is a risk of damage to the wall of blood vessels that have tubes and devices fed through them. This may cause bleeding in the brain. The extra risk of bleeding that causes worsening of someone's condition is around 1-2% (1in 100 to 1 in 50) with conventional devices. Bruising and bleeding at the groin where the tube is placed into an artery may also occur.

Overall, the risks of participating in the trial are considered small.

What are the side effects of any treatment received when taking part?

The side effects of taking part in this trial are, as far as we know, no different to the side effects of standard device treatment.

What are the possible benefits of taking part in the trial?

You may not benefit personally from taking part in the trial. The main benefit will be to provide information that may help with treatment of future patients with stroke.

What if there is a problem?
Any complaint about the way you have been dealt with during the trial or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the trial be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are in Part 2.

If the information Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2

What will happen if I don't want to carry on with the trial?
You are completely free to withdraw from the trial at any time. You do not have to give a reason for this decision. We will use only information that has been collected up to the point that you withdraw.

What if there is a problem?
Complaints:
If you have a concern about any aspect of this trial, you should ask to speak to the researchers who will do their best to answer your questions (using numbers below). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from local Patient Advice and Liaison Services (PALS) [insert details].

Harm:
In the event that something does go wrong and you are harmed during the trial and this is due to someone's negligence then you may have grounds for a legal action for compensation against the responsible NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). There are no special compensation arrangements for non-negligent harm.

Will my taking part in the trial be kept confidential?
We wish to record details of relevant medical conditions, information about the stroke itself (for example the time symptoms first appeared, the problems that it caused, any treatment given, and the results of other tests) and your progress over the first 365 days.

All scan/angio pictures will be saved on computer files and transferred to Newcastle University for analysis. Your personal details will be removed from scans and coded before copies are sent. The analysis will be done on NHS and University computers, and will be examined by experts from other parts of the UK. A list that links your details, including contact details such as address and telephone numbers, with the code number will be kept securely at the local research site (i.e. the local hospital), separate from trial information.

Your involvement in the trial will be documented in your medical records and we will write to your GP to inform them that you are taking part.

You will not be identified personally in any reports or publications in medical journals arising from the trial.

It is usually important to pull together all available information about new treatments, so we wish to share information about the trial with other researchers who are working on stroke, including scan pictures and individual data. All information that is shared will be anonymous. Your individual anonymized data will not be shared outside the EU and we will comply with the data protection act.

Your medical records may be examined by relevant authorities (for example government bodies, NHS Research & Development staff) to ensure that the trial has been conducted to proper standards.

You will be given a copy of the information sheet and consent forms to keep.

Involvement of General Practitioner (GP)

Your GP will be notified of your participation in this clinical trial and you will need to give your consent for this. Your GP will be provided with a brief summary of what the trial entails. They will also be notified of who the consent was obtained from (patient/relative/legal representative/independent clinician).

What will happen to the results of the clinical trial?

The results of the trial will be submitted for publication to scientific journals and a lay summary will be provided to participants who would like to see one.

Who is organising and funding the research?

This trial is being funded jointly by the National Institute for Health Research (NIHR) Newcastle Biomedical Research Centre based at Newcastle upon Tyne Hospitals NHS Foundation Trust/Newcastle University and MicroVention Terumo Inc. who make the ERIC™ device.

Who has reviewed this clinical trial?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This trial has been reviewed and given a favourable opinion by the North East Research Ethics Committee.

The trial is sponsored by Newcastle upon Tyne Hospitals NHS Foundation Trust.

Further information and contact details
If you wish to discuss any other aspect of the trial, you can do so with [insert local researcher] via the following number [insert local contact number].

Independent advice on this specific trial is available from [insert local clinician details].

Appendix H – STABILISE Consent Form

Print on local headed paper

STABILISE Trial CI: Prof Phil White	Centre Number: ☐☐	Patient ID Number: ☐☐☐

Stroke: an evaluation of Thrombectomy in the Ageing Brain (STABILISE) Trial

Consent Form

	Please initial box
I confirm that I have read and understand the patient information sheet dated ..... (version .....) for the above trial and have had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that sections of any of my medical notes may be looked at by responsible individuals from the NHS Trust or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
I understand that anonymous data from the trial, including scans, may be shared with other researchers. I give permission for data to be used in this way.	☐
I agree to my GP being informed of my participation in this trial.	☐
I agree to take part in the above trial.	☐

Name of Patient (Print name)	Date	Signature
Name of Person taking consent	Date	Signature

When completed: original for site file, 1 copy to be kept in medical notes, 1 copy for patient

Appendix I –STABILISE Consultee Information Sheet

Newcastle University *Print on local headed paper* The Newcastle upon Tyne Hospitals NHS NHS Foundation Trust

Stroke: an evaluation of Thrombectomy in the Ageing Brain (STABILISE) Trial

Consultee Information Sheet

We are approaching people who have suffered a stroke to invite them to participate in a clinical trial. We are undertaking a trial to test whether strokes caused by a blockage in a large artery can be more effectively treated with a new clot removal device (SOFIA™- Soft Torqueable Catheter Optimized For Intracranial Access and/or ERIC™ – Embolus Retriever with Interlinked Cage) compared with current standard devices.

We feel the patient you are representing is unable to decide for themselves whether to participate in this trial. To help decide if he or she should join the trial, we'd like to ask your opinion on whether or not they would want to be involved. Please consider what you know of their wishes and feelings, and consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence.

If you decide the patient would have no objection to taking part in this trial we will ask you to read and sign the "Consultee Declaration Form". You will be given a copy to keep. We will keep you fully informed during the trial so you can let us know if you have any concerns or you think the patient should be withdrawn.

If you decide that the patient would not wish to take part it will not affect the standard of care they receive in any way.

If you are unsure about taking the role of consultee you may seek independent advice.

We will understand if you do not want to take on this responsibility.

The following information is the same as would have been provided to the patient on whose behalf you are being asked to advice. Part 1 tells you the purpose of the trial and what will happen to the patient if they take part. Part 2 gives you more detailed information about the conduct of the trial.

Part 1

What is the purpose of this trial?

Most strokes are caused by a clot blocking an artery in the brain (called "ischaemic strokes"). Some patients with strokes of this type can be treated with a "clot-busting" (thrombolytic) drug.

However, the larger the artery blocked, the less likely it is that drug treatment will open it up. Since the large blockages are likely to cause more severe strokes, there is a need for more effective treatment. Recently, medical devices ("thrombectomy devices") have been developed that allow specialist doctors to remove blood clots from large arteries in the brain by feeding the device through the circulation. These are able to open blockages more often than drug treatment alone, in up to 80% of cases (4 out of 5 people). Current devices for thrombectomy were generally not purpose designed but adapted from other existing devices. They may not work as well as they could. In particular they can be difficult to use in older people and most previous studies of clot removal have excluded older patients. In this trial we will compare the results in people treated with new clot removal devices (SOFIA™ and/or ERIC™) compared with standard existing thrombectomy devices. We are undertaking this trial to test whether the use of these new purpose designed stroke clot removal devices are as safe and at least as effective as existing devices. For those taking part in the trial, treatment will be allocated at random by computer software designed to allocate patients to treatment in such a way that the results of the trial will be meaningful. There is quite a lot of information already available on existing devices but not on the new SOFIA™ and ERIC™ devices. So to enable this study to provide the most useful data possible on the new Sofia™ and ERIC™ devices there is a 2:1 chance of having the new device treatment.

Why has the patient been invited?

The patient you are representing has been invited to participate in this clinical trial because they have just suffered a stroke, caused by a clot blocking a large artery in the brain and the doctors looking after them have decided that clot removal (thrombectomy) should be performed. We are planning to recruit 120 people who have just suffered a stroke to this trial.

Does the patient have to take part?

It is up to you to decide on behalf of the patient who is unable to make a decision themselves whether they would wish to take part in the trial. We will describe the trial and go through this information sheet. If you decide that the patient would wish to take part, you will be asked to sign the "Consultee Declaration Form". You are free to withdraw the patient at any time without giving a reason. This would not affect the standard of care they will receive.

If the patient regains the ability to make decisions about themselves, they will be provided with a Patient Information Sheet (Continuing Participation) and asked for their permission to continue being involved in the trial.

What will happen to the patient if they take part?

All the people taking part will be given the current best medical treatment for them (with a clot-busting drug if safe to do so) as well as clot removal. After making sure that a blockage is present in a blood vessel that can be treated with a device, we will use a computer system to assign at random whether people will go on to have treatment with the new thrombectomy device. Two thirds of the people in the trial will go on to have new device treatment, and the other third will have clot removal using a standard device(s). This randomisation will enable us to compare the results to see whether the new device is comparable with the existing standard devices.

A number of tests are part of routine care for people treated for acute stroke. All of these will be done as normal, although we wish to record many of the results for the trial.

Extra procedures for the trial include the following in all people, whether or not they undergo new device treatment:

- MRI scan will be done around 24 hours after treatment to see if the blockage has been cleared successfully and to enable us to gather more information on who responds best to clot removal treatment. This is instead of the usual follow-up CT scan. So it is a replacement rather than an additional test and results in reduced exposure to X-ray radiation.
- Some extra physical examinations (neurological assessments) are done at 72 hours, 7 days (or at hospital discharge if sooner). These take around 15 minutes.
- Some extra checks on the effects of the stroke on day-to-day function (using questionnaires) on two occasions at 90 and 365 days after the stroke. These take about 5 minutes and involve questions about activities such as washing, dressing, eating and walking, and whether there are any restrictions on the patient's daily activities. These will either be undertaken at standard clinic appointments but can also be done by post or by telephone.

Expenses and payments

No expenses are available for taking part in this trial.

What will the patient have to do?

Following device treatment, the patient will be required to attend all scheduled clinic visits and/or complete telephone/postal interviews up until 365 days post treatment.

What are the alternatives for diagnosis or treatment?
If the patient does not take part in the clinical trial they will continue to receive all treatment or tests that their doctor thinks is required in line with current best practice.

What are the possible advantages and risks of taking part in the trial?

It should be noted that the risks of the new devices are not entirely known but they are CE marked for this use based on a small study indicating they can be used safely for thrombectomy. It is not expected that the SOFIA™ and ERIC™ devices will be associated with a different risk from standard thrombectomy devices but the STABILISE trial will confirm that. Thrombectomy devices have to be fed up to blood vessels in the head. There is a risk of damage to the wall of blood vessels that have tubes and devices fed through them. This may cause bleeding in the brain. The extra risk of bleeding that causes worsening of someone's condition is around 1-2% (1 in 100 to 1 in 50) with conventional devices. Bruising and bleeding at the groin where the tube is placed into an artery may occur.

Overall, the risks of participating in the trial are considered small.
What are the side effects of any treatment received when taking part?
The side effects of taking part in this trial are, as far as we know, no different to the side effects of standard device treatment.

What are the possible benefits of taking part in the trial?
An individual may not benefit personally from taking part in the trial. The main benefit will be to provide information that may help with treatment of future patients with stroke.

What if there is a problem?
Any complaint about the way the patient has been dealt with during the trial or any possible harm they may suffer will be addressed. The detailed information on this is given in Part 2.

Will the patient's taking part in the trial be kept confidential?
Yes. We will follow ethical and legal practice and all information about the patient will be handled in confidence. The details are in Part 2.

If the information Part 1 has interested you and you are considering that the patient would wish to participate, please read the additional information in Part 2 before making any decision.

Part 2

What will happen if the patient doesn't want to carry on with the trial?

You are completely free to withdraw the patient from the trial at any time. You do not have to give a reason for this decision. We will use only information that has been collected up to the point that you withdraw the patient.

What if there is a problem?

Complaints:

If you have a concern about any aspect of this trial, you should ask to speak to the researchers who will do their best to answer your questions (using numbers below). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from local Patient Advice and Liaison Services (PALS) [insert details].

Harm:

In the event that something does go wrong and the patient is harmed during the trial and this is due to someone's negligence then the patient may have grounds for a legal action for compensation against the responsible NHS Trust but they may have to pay their own legal costs. The normal National Health Service complaints mechanisms will still be available to the patient (if appropriate). There are no special compensation arrangements for non-negligent harm.

Will the patient's taking part in the trial be kept confidential?

We wish to record details of relevant medical conditions, information about the stroke itself (for example the time symptoms first appeared, the problems that it caused, any treatment given, and the results of other tests) and the patient's progress over the first 365 days.

All scan/angio pictures will be saved on computer files and transferred to Newcastle University for analysis. The patient's personal details will be removed from scans and coded before copies are sent. The analysis will be done on NHS and University computers and will be examined by experts from other parts of the UK. A list that links the patient's details, including contact details such as address and telephone numbers, with the code number will be kept securely at the local research site (i.e the local hospital), separate from trial information.

The patient's involvement in the trial will be documented in their medical records and we will write to their GP to inform them that they are taking part.

The patient will not be identified personally in any reports or publications in medical journals arising from the trial.

It is usually important to pull together all available information about new treatments, so we wish to share information about the trial with other researchers who are working on stroke, including scan pictures and individual data. All information that is shared will be anonymous. The patient's individual anonymized data will not be shared outside the EU and we will comply with the data protection act,

The patient's medical records may be examined by relevant authorities (for example government bodies, NHS Trust staff) to ensure that the trial has been conducted to proper standards.

You will be given a copy of this information sheet and the consultee declaration form to keep.

Involvement of General Practitioner (GP)
The patient's GP will be notified of their participation in this clinical trial and you will need to give your permission for this. The patient's GP will be provided with a brief summary of what the trial entails. They will also be notified of who has given consent (patient/relative/legal representative/independent clinician).

What will happen to the results of the clinical trial?
The results of the trial will be submitted for publication to scientific journals and a lay summary will be provided to participants who would like to see one.

Who is organising and funding the research?
This trial is being funded jointly by the National Institute for Health Research (NIHR) Newcastle Biomedical Research Centre based at Newcastle upon Tyne Hospitals NHS Foundation Trust/Newcastle University and MicroVention Terumo Inc. who make the ERIC™ device.

Who has reviewed this clinical trial?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect the patient's interests. This trial has been reviewed and given a favourable opinion by the North East Research Ethics Committee.

The trial is sponsored by Newcastle upon Tyne Hospitals NHS Foundation Trust.

Further information and contact details
If you wish to discuss any other aspect of the trial, you can do so with [insert local researcher] via the following number [insert local contact number].

Independent advice on this specific trial is available from [insert local clinician details].

Appendix J – STABILISE Consultee Declaration

Print on local headed paper

STABILISE Trial CI: Prof Phil White	Centre Number: ☐☐	Patient ID Number: ☐☐☐

Stroke: an evaluation of Thrombectomy in the Ageing Brain (STABILISE) Trial

Consultee Declaration Form

	Please initial box
I confirm that I have been consulted about the patient's participation in this research. I have read and understood the consultee or relatives information sheet dated …… (version .....) and have had the opportunity to ask questions.	☐
In my opinion he or she would have no objection to taking part in the trial.	☐
I understand that I can request that he or she is withdrawn from the trial at any time, without giving any reason, without their medical care or legal rights being affected.	☐
I understand that relevant sections of any of the patient's medical notes and data collected during the trial may be looked at by responsible individuals from the NHS Trust or from the regulatory authorities where it is relevant to their taking part in this research.	☐
I understand that anonymous data from the trial, including scans, will be transferred for analysis, and may be shared with the other researchers in the future.	☐
I agree to the patient's GP being informed of their participation in this trial.	☐

_____
Name of Patient (print name)

_____	_____	_____
Name of Consultee (print name)	Date	Signature

_____
Relationship to Patient

_____	_____	_____
Name of Person undertaking consultation (print name)	Date	Signature

When completed: original for site file, 1 copy to be kept in medical notes, 1 copy for consultee

Appendix K – STABILISE Protocol

Newcastle University

The Newcastle Tyne Hospitals
NHS Foundation Trust

STABILISE

Stroke: an **e**valuation of **T**hrombectomy in the **A**geing **B**rain – [including] where **I**V thrombo**L**ysis **IS** contraindicated

Protocol

Short Title/Acronym:	STABILISE
ISRCTN Number:	15698516
REC Reference:	14/NE/0113
Sponsor Reference:	R&D number: 6893
Protocol Version & Date:	2.1, 31 July 2015
Funded by:	NIHR Newcastle Biomedical Research Centre /MicroVention Terumo Inc
Sponsored by:	Newcastle upon Tyne Hospitals NHS Foundation Trust

1. Protocol Contacts

Co-Chief Investigators (CIs):

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Consultant Stroke Physician
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Lead Biostatistician:

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Emergency Contact (out of office hours emergency contact):

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Professor of Diagnostic and
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Newcastle University Institute for Ageing
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3-4 Claremont Terrace
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NE2 4AE
UK
Tel: +44 (0) 191 208 6238
Fax: +44 (0) 191 208 5540
Email: phil.white@ncl.ac.uk

Independent Data Monitoring Committee (IDMC):

Dr Rustam Al-Shahi Salman (chair)
MRC Senior Fellow
University of Edinburgh
UK

Dr Andy Vail (biostatistican) (member)
Manchester University

Dr Andy Molyneux (member)
Oxford University Neurosurgery and Neuroradiology Research Unit
UK

Trial Steering Committee (TSC):

Prof Malcolm Macleod (independent chair)
University of Edinburgh Department of Neurology
UK

Dr Anand Dixit (member)
Stroke Physician
Royal Victoria Infirmary
Newcastle

Prof Alain Bonafe (member)
Neuroradiology
Montpellier
France

+ Trial CIs (White & Ford)

Sponsor:

Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH) will act as the sponsor for this trial.

NUTH Research & Development (R&D) Representative**:**
Sean Scott
Newcastle Joint Research Office
Tel: +44(0)191 282 5490
Email: Sean Scott@nuth.nhs.uk

Funder:

National Institute for Health (NIHR) Newcastle University Biomedicine Research Centre based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University and MicroVention Terumo Inc. are jointly funding this trial.

2. Protocol Signature Page

2.1 Protocol Authorisation Signatories

Signature …… Date …….

Professor Phil White, Co-Chief Investigator

2.2 Principal/Chief Investigator Signature

I confirm that I have read and understood protocol version …… dated ……..... I agree to comply with the trial protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature …… Date …….

Print Name ……

Site Name/ID ……

3. Contents Page

4. Glossary of Abbreviations

Abbreviation	Definition
AE	Adverse event
ASPECTS	Alberta Stroke Program Early CT score
CI	Chief Investigator
eCRF	Electronic Case Report Form
CRN	Clinical Research Network
CSP	NIHR Coordinated System for gaining NHS Permission
CT	Computed tomography
CTA	Computed tomography angiogram
CTP	Computed tomography perfusion
DSA	Digital subtraction angiography
DWI	Diffusion weighted imaging
ECASS	European Cooperative Acute Stroke Study
eGFR	Estimated glomerular filtration rate
FLAIR	Fluid-attenuated inversion recovery
GP	General Practitioner
IA	Intra-arterial
ICA	Internal carotid artery
IAT	Intra-arterial thrombectomy
ICH	Intracerebral haemorrhage
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IFU	Instructions for Use
IMS	Interventional Management of Stroke
IV	Intravenous
IVT	Intravenous thrombolysis
MCA	Middle cerebral artery
LVO	Large vessel occlusion
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale

NCTU	Newcastle Clinical Trials Unit
NIHR	National Institute for Health Research
NIHSS	National Institute of Health Stroke Scale
NUTH	Newcastle upon Tyne Hospitals NHS Foundation Trust
PCA	Posterior cerebral artery
PH	Parenchymal haemorrhage
PHr	Parenchymal haemorrhage remote
PI	Principal Investigator
PIS	Patient Information Sheet
PV	Pharmacovigilence
rtTPA	Recombinant tissue plasminogen activator
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
RFA	Rankin Focused Assessment
SAE	Serious adverse event
SITS-MOST	Safe Implementation of Thrombolysis in Stroke-Monitoring Study
SICH	Symptomatic intracranial haemorrhage
SOP	Standard operating procedure
SRN	Stroke Research Network
STIR	Stroke Imaging Repository
TICI	Thrombolysis in cerebral infarction
TMG	Trial Management Group
TSC	Trial Steering Committee

5. Responsibilities

Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH) will act as the sponsor for this trial.

Funder: NIHR Newcastle University Biomedicine Research Centre and MicroVention Terumo Inc. are jointly funding this trial.

Trial Management: A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated by Newcastle Clinical Trial Unit (NCTU).

Principal Investigator: The Principal Investigator (PI) will have overall responsibility for the conduct of the trial at a particular trial site.

Trial Management:

The following functions falling under the responsibility of the sponsor will be delegated to Prof Phil White and Prof Gary Ford (co-Chief Investigators):

- Ethics Committee Opinion (including application for research ethics committee favourable opinion, notification of protocol amendments and end of trial, site specific assessment & local approval)
- R&D Approval (including application for global checks, via NIHR Coordinated System for gaining NHS Permission (CSP))
- Good Clinical Practice and Trial Conduct (including GCP arrangements, data monitoring, emergency & safety procedures)
- Administration of funding for the trial

Trial Conduct at Site:

Investigator Responsibilities:

- Trial conduct and the welfare of trial subjects
- Familiarity with the trial intervention(s)
- Compliance with the protocol, documentation of any protocol deviations and reporting of all serious adverse events
- Screening and recruitment of subjects
- Ensuring all trial-related medical decisions are made by a qualified physician, who is an investigator or co-investigator for the trial.
- Provision of adequate medical care in the event of an adverse event
- Obtaining local approval and abiding by the policies of Research Governance

- Compliance with the Principles of GCP, the Research Governance Framework for Health and Social Care, the Data Protection Act and any other relevant legislation and regulatory guidance
- Ensuring that no participant is recruited into the trial until all relevant regulatory permissions and approvals have been obtained
- Obtaining written informed consent from participants prior to any trial specific procedures
- The Principal Investigator (PI) shall be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. S/he shall provide a current signed & dated curriculum vitae as evidence for the Trial Master File
- Ensuring Trial Site team members are appropriately qualified by education, training and experience to undertake the conduct of the trial
- Availability for Investigator meetings, monitoring visits and in the case of an audit.
- Maintaining trial documentation and compliance with reporting requests
- Maintaining a site file, including copies of trial approval, list of subjects and their signed informed consent forms
- Documenting appropriate delegation of tasks to other trial personnel e.g. Research Nurse, Co-Investigator(s), Trial Manager, Database Manager
- Ensuring data collected is accurate, timely & complete
- Providing updates on the progress of the trial
- Ensuring subject confidentiality is maintained during the project and archival period
- Ensuring archival of trial documentation for a minimum of 5 years following the end of the trial, unless local arrangements require a longer period

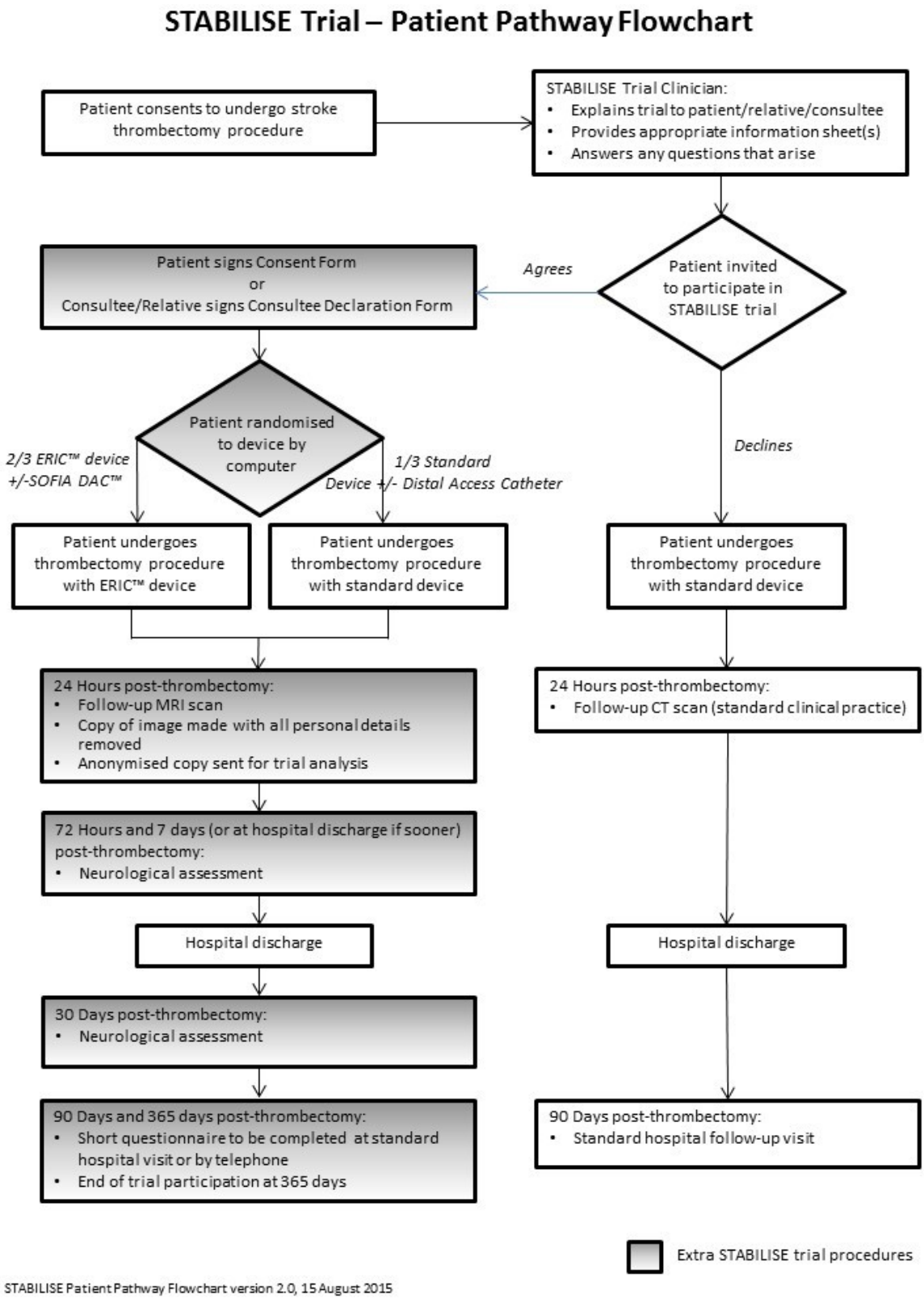
6. Protocol Summary

Title of Trial:	**S**troke: an **e**valuation of **T**hrombectomy in the **A**geing **B**rain - [including] where **I**V thrombo**L**ysis **IS** contraindicat**E**d
Short Title:	STABILISE
Protocol Version:	2.1
Protocol Date:	31 July 2015
Co-Chief Investigators:	Professor Phil White & Professor Gary Ford
Sponsor:	Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH)
Funders:	NIHR Newcastle Biomedicine Research Centre / MicroVention Terumo Inc.
Trial Design	Multicentre prospective phase 2 single-blinded randomised controlled trial of novel device (ERIC) versus standard thrombectomy device(s)
Trial Duration:	3 years
Number of Trial Sites:	6-10 UK 2-3 EU outside UK
Trial Population:	Patients with an acute ischaemic stroke due to large vessel occlusion who on clinical grounds have been referred for thrombectomy (and are not suitable for enrolment into a treatment policy trial)
Trial Size:	120 in total
Rationale:	No randomised controlled trial has yet evaluated whether thrombectomy is associated with improved clinical outcome in a truly heterogeneous stroke population. However it is clear that use of mechanical thrombectomy devices in acute ischaemic stroke is associated with higher rates of recanalisation in large artery occlusions. But thrombectomy studies mostly exclude the elderly (>75 years) or those with a contraindication to IV thrombolysis. Outcomes and safety in such populations are unclear. Most current thrombectomy devices were adapted (crudely) from devices originally designed for a different purpose and as such have major limitations in distal or tortuous vessels. STABILISE will investigate a novel purpose designed thrombectomy device (MV “ERIC”™

	device) together with the (MV “SOFIA”) distal access catheter. Both of these devices have design features making them favourable to accessing distal/tortuous vessels.
Trial Intervention:	Randomisation to type of device to be used in clinical neurointerventional procedure will be undertaken, commencing a maximum of 5-8.5h after stroke onset. Participation in the trial will entail follow-up (clinical and radiological) for up to 365 days.
Primary Objective:	To determine if a novel thrombectomy device can be utilized safely and successfully in the heterogeneous population presenting with large vessel occlusion (LVO) acute ischaemic stroke
Secondary Objectives:	• To determine the preliminary efficacy (recanalization rate) and safety of the thrombectomy device and inform design of a phase III clinical trial • To determine the procedural safety of thrombectomy in a wider stroke population • To investigate the use of early MRI post thrombectomy as a biomarker of clinical outcome
Primary Outcome Measure:	The proportion of patients with favourable angiographic outcome based on independent core lab assessment measured by STIR II modification of TICI scale.
Registration/Randomisation:	Web randomisation through Newcastle Clinical Trials Unit. Patients randomised on a 2:1 basis in favour of the investigational device.
Inclusion Criteria:	• Clinical diagnosis of acute ischaemic stroke • Male or non-pregnant female ≥18 years of age • Clinically significant neurological deficit and NIHSS score ≥6 • Enrolment and procedure commencement (groin puncture) possible within 90 minutes of the imaging confirmation of LVO stroke (and within a maximum 5.5-8.5h after stroke onset- >5.5h ONLY for posterior circulation) • Occlusion of the main middle cerebral artery (MCA) trunk, MCA bifurcation or intracranial internal carotid artery (carotid-T, M1 or ≤2 proximal M2 branches), or intracranial vertebral or basilar artery or P1 PCA demonstrated on CTA, MRA, or DSA • Interventional device delivery (guide catheter placed in target artery beyond aortic arch and angio obtained) can be achieved within 6h hours

	of onset of the stroke (9h for vertebrobasilar occlusions) • Consent of patient or “appropriate consultee” • Independent prior to the stroke (mRS 0-2) • Expected to be able to be followed up at 12 months
Exclusion Criteria:	• CT evidence of intracranial haemorrhage, or evidence of extensive (>1/3 MCA or ASPECTS <6) established hypodensity on CT. In posterior circulation strokes pc-ASPECTS <6 or >1/3 of territory • Clinical history suggestive of subarachnoid haemorrhage even if CT normal • **Eligible & willing** to be randomised into a treatment policy trial of stroke thrombectomy • Known major vascular access contraindications e.g. femoral bypass surgery • Unsuitable proximal vascular anatomy likely to render endovascular catheterisation difficult, unsafe or impossible in the view of the interventional neuroradiologist. • Alternative intracranial pathology potentially responsible for the new symptoms • Medical co-morbidities which would preclude safe cerebral vessel catheterisation or which are expected to limit life expectancy to <3 months (e.g. severe cardiac, renal or hepatic failure, significant coagulopathy, metastatic malignancy) • Known allergy to radiological contrast
Statistical Analysis:	All statistical analyses will be conducted according to Statistical Analysis Plan, which will be authored by the Trial Statistician and agreed by the Trial Steering Committee. This is a phase II trial to investigate feasibility, safety and surrogate measures of efficacy to inform the design of a subsequent multicentre definitive trial. This early phase trial will investigate angiographic success rate and will consider moving to a definitive trial with a rate >75% in this unrestricted group of patients and a clinical outcome not worse than standard device thrombectomy in an unbiased comparator group.

6.1 Trial Flow Chart



7. Background

7.1 Background

After arterial occlusion, brain tissue undergoes infarction over a period of minutes to hours depending upon the severity of the reduction in cerebral perfusion.[1] Restoration of blood flow by recanalisation of the occluded artery limits the extent of damage. Reperfusion may occur spontaneously due to endogenous clot breakdown, but therapeutic intervention using thrombolytic drugs increases the chances of reperfusion[2] and is therefore associated with increased probability of favourable outcome if delivered promptly after symptom onset. Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rtPA) significantly increases the proportion of patients achieving independence 3 months after ischaemic stroke when delivered within a maximum of 4.5h after onset of symptoms.[3-5] Since stroke has not been regarded as a medical emergency in the past, large-scale reconfiguration of health care systems has been necessary to deliver rtPA to patients, and although the proportion of patients undergoing intravenous (IV) thrombolysis is small globally, there has been a rapid expansion in the numbers treated in the UK and elsewhere in recent years. However, IV thrombolysis results in recanalisation of the occluded artery in only just over 50% of patients,[6] and the probability of successful recanalisation is least with occlusions in large arteries, reflecting the larger volume of clot.[7,8] Patients with large artery occlusion also have the most severe clinical presentations and poorest outcomes.[9,10] Recanalisation rates for occlusions of the terminal internal carotid artery (ICA) or main middle cerebral artery (MCA M1) are reported to be only 9% and 33% respectively, compared to 66% in smaller MCA branches (M2 or distal).[7] The speed of recanalisation is also important, with more rapid recanalisation being associated with higher probability of early neurological improvement and independence at 90 days.[6]

The intra-arterial (IA) delivery of thrombolytic agents directly into the occluded vessel via microcatheter injection offers hypothetical advantages in terms of thrombolytic dose titration, but only three randomised controlled trials (RCTs) have evaluated IA thrombolytic drug delivery,[11,12] and in addition to inconsistent clinical efficacy and control groups that did not receive what would now be regarded as best medical care, the specific agents employed in these trials (urokinase and pro-urokinase) are no longer available. A combined IV+IA thrombolytic drug approach was evaluated in the first open label Interventional Management of Stroke (IMS) trial,[13] compared with IV rtPA alone. In the more recent Synthesis trial IA therapy alone (overwhelmingly IA lysis) was compared with IV thrombolysis and no advantage was demonstrated for IA.[14]

The use of IA thrombolytic drugs has been superseded by the development in recent years of a wide range of mechanical devices which can directly revascularise occluded cerebral vessels. However, evidence of efficacy for devices has been limited to case series and prospective observational studies, mostly designed simply to establish the mechanical characteristics and performance of a device with respect to the limited end-point of recanalisation of intracranial vessels, which is all that is currently required for licensing by regulatory authorities. Recanalisation rates are higher than expected for IV thrombolysis compared with historical controls, in some instances very considerably so.[15-19] However, despite these high rates of recanalisation, clinical outcomes have in some cases been poorer than would be expected based on historical controls given IV thrombolytic treatment. Relevant factors that may increase risk of IA thrombectomy include higher reported risks of SICH (around 9% compared to 2-4% for IV thrombolysis), and longer procedure duration, leading to more prolonged onset-to-treatment time; a marked reduction in the probability of favourable outcome with IV thrombolytic therapy over the first 4.5h after onset is well documented[3] and reflects a combination of reducing volumes of salvageable tissue over time as well as increased bleeding risk. The additional time incurred in IA delivery – often up to 6h after symptom onset before microcatheter deployment even in experienced centres[19,20] - may offset any benefit from improved recanalisation rates, since reperfusion of non-viable brain tissue carries no clinical benefit and may increase bleeding risks. On the other hand, patients selected for IA treatment usually have more severe strokes, successful recanalisation is uncommon with IV treatment alone, and favourable outcomes in registry studies are more frequent than expected for IV treatment in groups of equivalent clinical severity with definite arterial occlusion.

In order to define the overall role for mechanical thrombectomy, evaluation in RCTs is ongoing. In five recently completed IA trials, thrombectomy was demonstrated to be significantly superior to IVT alone.[21-25]

Those RCTs that recently concluded mostly excluded the very elderly population and also included relatively few patients with a contraindication to IVT – ~90% of patients overall in these 5 recently published trials receiving IVT, yet patients with contraindications to IVT account for >50% of patients with large vessel occlusion (LVO) stroke in routine practice series/registries. Further studies are required in a more truly representative patient population. The non-randomised literature in the real world patient population is also very limited – studies have mainly reported average ages far younger than seen in routine clinical practice.

Current thrombectomy devices are mostly based on stents designed as an adjunct to intracranial aneurysm endovascular coiling and fortuitously found to be useful in stroke.

However as a result they are not purpose designed for thrombectomy and can fail to access/work in distal and/or tortuous vessels or those with long clot occlusions. Tortuous vessels are certainly far more common in the elderly and long clots are more prevalent in those who fail to respond to IVT. By contrast the **MV "ERIC"™ STROKE DEVICE (Embolus retriever with interlinked cage)** is specifically designed for thrombectomy and has potential advantages in older patients with tortuous vessels and long clots. It has design features that lend itself to:

1) tortuous access – low profile and interlinked but flexible clot retrieval baskets along its length
2) distal access – ability to select a device with fewer baskets and of very low profile so enabling smaller diameter microcatheter to be used for better & safer distal access
3) long segment clot – ability to select a long device with more & larger clot retrieval baskets

Preliminary work in animals and then in humans *in vivo* (for CE mark approval) look promising and indicate that the **MV "ERIC"™ STROKE DEVICE** design features do seem to work. In addition the **MV "SOFIA"™ distal access catheter (Soft torqueable catheter Optimized For Intracranial Access)** provides easier navigation in tortuous vessels and has steerable control around bifurcations.

As a result there is a clear rationale to investigate these devices in a truly heterogeneous stroke population presenting with LVO. This is required to confirm safety and technical efficacy and to inform the design of a definitive phase III clinical trial of the devices.

We know that there is still a paucity of information with regard to the role of advanced brain imaging in large vessel occlusive stroke. In particular the use of thrombectomy correlated to patient age and the use of advanced brain imaging as a predictor of thrombectomy outcome specific to LVO stroke has not been systematically evaluated to date – including arterial tortuosity and rigorous assessment of the brain's collateral circulation. We will perform such an evaluation as part of the STABILISE trial.

If aortic arch/carotid/vertebrobasilar vessel tortuosity is shown to be linked to procedural outcome (any one of technical success, complication rates and clinical outcome) then development of a clinically applicable "tortuosity scoring tool" would be a very valuable output from this trial. Tortuosity by age cohort in LVO stroke has not been evaluated previously, and not at all in relation to its role in IAT. Only one small preliminary non-randomised study

(n=39) has attempted to link age to collateral status[26] but that study wasn't restricted to LVO stroke (the most relevant group) nor was any comparative age cohort analysis performed.

But the study did suggest a distinct age related tissue process is occurring as collateral score was the only factor found to correlate positively with age. This certainly merits further systematic investigation in larger studies and specifically in the most clinically relevant population – LVO stroke.

We already know that outcome for IAT is probably independently linked to time to treatment and severity of initial stroke[27] but we actually have very limited data on any independent link to patient age so far. STABILISE will contribute additional important data on this topic. There is early evidence that collateral flow may be a key determinant of response to IA thrombectomy[28] as well as IV thrombolysis.[29,30] However in the only study looking specifically at collateral scoring related to IAT outcome to date, collateral scoring did predict eventual outcome.[30] However there are some major limitations in this study that limit its generalizability - a) IAT was not performed with modern stentriever technology, which significantly speeds up recanalisation time and has significantly greater recanalisation rates over equipment used in the 2011 study;[29,30] b) patients did not have proven LVO before going to attempt thrombectomy (hence 24% of those included in this IAT study did not actually receive thrombectomy!); c) patients were considerably younger (mean age <65years) than typically reported in European IAT studies; d) nor did the study specifically examine patient age as related to predictive value of collateral score. STABILISE will be able to address most of these limitations.

We do not know currently whether there is any defined link between age and collateral scoring in LVO stroke.[29,31] STABILISE will be able to investigate such a correlation.

Additionally the use of magnetic resonance imaging (MRI) early post LVO stroke has only been prospectively investigated in one study (n=104) to date.[32] However this study almost exclusively concentrated on other issues – largely around penumbra size assessed by an automated software programme predicting outcome after IAT, rather than use of MRI post IAT as a marker of outcomes and age did not feature in the analyses reported. Only 13% of the DEFUSE 2 patients had thrombectomy using a stentriever device.

In particular the DEFUSE 2[32] study did not examine:

i. Role of MRI to evaluate IAT complications that cannot be demonstrated on computed tomography (CT) (very small strokes or microbleeds) but which may be relevant to immediate further management

ii. Any link between complications [identified on MRI] to patient age is unknown i.e. is there an age specific risk?

iii. The use of MRI (diffusion weighted imaging (DWI)/fluid-attenuated inversion recovery (FLAIR) match for defined infarct core) as a biomarker (predictor) for outcome in the subgroup of LVO stroke has not been evaluated nor whether there is any link between age and MRI findings. Again STABILISE will explore these potential uses of MRI and compare the findings in a middle aged cohort with an elderly cohort of patients.

7.2 Rationale - Hypothesis

We hypothesise that mechanical thrombectomy using the MV "SOFIA" and "ERIC"™ STROKE DEVICES will be associated with at least an equivalent rate of occluded vessel recanalisation without a better safety profile compared with standard modern thrombectomy devices. We will also examine functional recovery in this prospective and representative group of patients with significant LVO stroke treated by IAT compared with standard medical care assessed by shift analysis on the modified Rankin Scale (Rankin Focused Assessment) at day 90.

Regarding the advanced brain imaging components of STABILISE:

- We hypothesise that vessel tortuosity and/or brain collaterals in LVO stroke will be linked to "stentriever" IAT outcome. If linked, development of a clinically useful tortuosity assessment tool would be initiated
- Early MRI post LVO stroke will be an accurate determinant of IAT complications and be helpful to direct future patient management. It is hypothesised that early MRI will have utility as a predictive biomarker of long term clinical outcome in LVO stroke post thrombectomy
- We hypothesise that age will be independently linked to outcomes – technical, safety and clinical – of stroke thrombectomy and will undertake an exploratory analysis of influence of device used.

8. Objectives

The trial will investigate if a novel thrombectomy devise can be utilised safely and successfully in the heterogeneous population presenting with large vessel occlusion (LVO) acute ischaemic stroke. This investigation of feasibility, safety and surrogate measures of efficacy will be used to inform the design of a subsequent multicentre definitive trial if the angiographic success rate is >75% in the complete trial population (unrestricted group) of patients and the clinical outcome is not worse than standard device thrombectomy in the unbiased comparator group.

8.1 Primary Objective

To determine if a novel thrombectomy device (**"ERIC"™ DEVICE)** and a distal access catheter (**"SOFIA"™)** can be utilized successfully in the heterogeneous population presenting with large vessel occlusion (LVO) acute ischaemic stroke with recanalization rate by blinded core lab assessment as the primary efficacy assessment.

8.2 Secondary Objectives

- To determine safety of the thrombectomy device and inform design of a phase III clinical trial
- To determine the procedural safety of thrombectomy in a wider stroke population
- To investigate the use of early MRI post thrombectomy as a biomarker of clinical outcome

9. Trial Design

This is multi-centre prospective phase II single-blinded randomised controlled trial comparing a novel thrombectomy device with standard stent based thrombectomy in male and female patients aged ≥50 years with acute ischaemic stroke. Patients will be randomised to either the novel thrombectomy device or standard thrombectomy device in a 2:1 ratio.

A target of up to 120 subjects will be recruited from 8-12 centres in 3-4 European countries (6-8 in UK; 2-4 in Austria, Denmark and Sweden) over a period of 2 years. Potential participants will be identified on referral to participating acute stroke services and will be screened using the clinical inclusion and exclusion criteria listed in section 10. Data collected for routine clinical care will be used for clinical trial documentation (e.g. blood results, National Institutes of Health Stroke Scale (NIHSS) score, imaging findings) (further details are in Section 10). Consent will specifically include the use of clinically routine data for trial purposes, and for review of imaging studies by independent observers.

This early phase trial investigating feasibility, safety and surrogate measures of efficacy will be used to inform the design of a subsequent multi-centre definitive trial if the angiographic success rate is >75% in the unrestricted group of patients and the clinical outcome is not worse than standard device thrombectomy in the unbiased comparator group.

9.1 Primary Outcome Measure

Proportion of subjects with good recanalisation (grade 3/2b) based on the STIR (stroke imaging) II modified TICI scale as defined by an independent blinded core lab assessment of digital subtraction angiography (DSA).

9.2 Secondary Outcome Measures

- Safety Outcomes:
  - Symptomatic intracranial haemorrhage rates defined as local or remote parenchymal haemorrhage type 2 (PH2 or PHr2 intracerebral haemorrhage (ICH) by European Cooperative Acute Stroke Study (ECASS) 2 definition) on the 24h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24h, or leading to death (Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) definition). Defined by local PI
  - Any intracranial haemorrhage on periprocedural or 24h CT or MRI (defined by central imaging review)
  - Extracranial bleeding, groin haematoma requiring evacuation / surgery or transfusion or definitely prolonging hospital stay. Defined by local PI
  - Other extracranial haemorrhage. Defined by local PI
  - Other clinical complication assessed by operator as procedural – reported by local PI
- Feasibility Outcomes:
  - Proportion of identified patients consenting and randomised
  - Attrition at day 90 and day 180
  - Time to thrombectomy
  - Duration of thrombectomy procedure
- Neurological recovery - change in distribution of modified Rankin Scale (mRS) scores adjusted by baseline variables (shift analysis) at day 90 and day 365
- Early major neurological improvement of 8 or more points, or return to NIHSS total score of 0 or 1, at 72 hours (or at discharge if earlier)

- Functional recovery according to Rankin
- Sustained (i.e. 24h) recanalisation rates in subjects undergoing interventional procedures (magnetic resonance angiography (MRA) assessment); any recanalisation rates (TICI 0-1 versus 2-3 DSA and 24h MRA)
- Days spent at home in first 90 days after stroke
- Mortality rates
- Exploratory analysis of correlation between collateral scoring on computed tomography angiogram (CTA) and clinical outcome
- MRI markers of procedural risk – new acute DWI lesions (outside the clinical/CT stroke presentation) & haemorrhage

9.3 Trial Closure/Definition of End of Trial

The trial will end when the TSC agrees that one or more of the following situations applies:

i. The planned recruitment target and follow-up has been achieved
ii. The Independent Data Monitoring Committee (IDMC) has advised discontinuation, e.g. because of safety concerns about the trial
iii. There is insufficient funding to support further recruitment, and no reasonable prospect of additional support being obtained
iv. New information makes it inappropriate to continue to randomise patients to one or other arm of the trial
v. Recruitment is so poor that completion of the trial cannot reasonably be anticipated

The safety aspects of the trial will be overseen by an IDMC consisting of an independent stroke physician, medical statistician and neurointerventionist. The progress of the trial will be assessed at regular intervals determined by the IDMC. During the period of recruitment to the trial, interim analyses of mortality and of any other information that is available on major outcome measures (including SAEs believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the IDMC, along with any other analyses that the Committee may request.

The end of the trial is defined as the last participant who has completed the 365 day follow up visit.

10. Subject Population

It is anticipated that the trial will run at 8-12 sites in 3-4 European countries, including the UK, Austria, Denmark and Sweden. All the participating hospitals will have acute stroke services and neuroscience centre within the same Trust/institution (see Eligibility Criteria for Trial Centres section 10.3).

The trial will recruit male and female patients aged ≥18 years with acute ischaemic stroke. Eligible patients must have vascular imaging evidence of a relevant arterial occlusion (anticipated to be determined by CTA in the majority, although MRA or DSA are allowable). Vascular imaging is expected to be the standard of care at all participating centres for patients with clinically suspected LVO stroke and this should be acquired prior to consent.

Patients eligible for IV rtPA will have treatment initiated as per standard practice, up to 4.5h after symptom onset.

After ascertaining that IAT is feasible within the trial timescale (randomisation and procedure commencement (groin puncture) within 90 minutes of confirming *LVO diagnosis* and placement of a guide catheter beyond the aortic arch within 5.5 hours of stroke onset (8.5h for posterior circulation strokes)), consent for the STABILISE trial will be sought from patients or from their legal representatives (appropriate consultee) if deemed ineligible for any other ongoing phase III neurointerventional randomised controlled trial (RCT) at that centre.

10.1 Inclusion Criteria

- Clinical diagnosis of acute ischaemic stroke
- Male or non-pregnant female ≥18 years of age
- Clinically significant neurological deficit and NIHSS score ≥6
- Enrolment, randomisation and procedure commencement (groin puncture) possible within 90 minutes of the CT/CTA diagnosis of LVO (AND maximum 5.5h after stroke onset anterior circulation, 8.5h for posterior circulation)
- Occlusion of the MCA trunk, MCA bifurcation or intracranial internal carotid artery (including carotid-T), M1 or ≤2 proximal M2 branches; intracranial vertebral/basilar/P1 posterior cerebral artery (PCA) demonstrated on CTA, MRA, or DSA

- Interventional device delivery (guide catheter placed in target artery beyond aortic arch and angio obtained) can be achieved within 6 hours of onset of the stroke (9h for posterior circulation occlusions)
- Consent of patient or appropriate consultee
- Independent prior to the stroke (estimated mRS 0-2)
- Expected to be able to be followed up at 12 months

10.2 Exclusion Criteria

- CT evidence of ICH, or evidence of extensive (defined as >1/3 MCA territory **or** Alberta Stroke Program Early CT score (ASPECTS) score ≤6) established hypodensity on CT
- Clinical history suggestive of subarachnoid haemorrhage even if CT normal
- Eligible for a “treatment policy” (i.e. phase III trial) RCT of stroke thrombectomy in that institution & willing to be randomised into such
- Vascular access contraindications e.g. bilateral femoral bypass surgery, tight ipsilateral carotid or vertebral stenosis (if judged not readily amenable to acute intervention by Interventional Neuroradiologist [INR] who would carry out the procedure), unsuitable proximal vascular anatomy likely to render endovascular catheterisation difficult, unsafe or impossible (as judged by INR who would carry out the procedure)
- Extracranial: chronic/atherosclerotic ipsilateral internal carotid artery (ICA) or dominant vertebral artery occlusion
- Alternative intracranial pathology potentially responsible for the new symptoms
- Medical co-morbidities which would preclude safe cerebral vessel catheterisation or which are expected to limit life expectancy to <3 months (e.g. severe cardiac, renal or hepatic failure, significant coagulopathy, metastatic malignancy)
- Known allergy to radiological contrast
- Absolute contraindication to MRI

10.3 Eligibility Criteria for Trial Centres

An accreditation committee (consisting of Prof Phil White, Prof Gary Ford and another TSC member) will review data provided by centres to ensure adequate experience by the

interventional team and documentation of protocols for intra-arterial management of acute stroke.

Each centre must have a hyperacute stroke team including consultant stroke physicians or neurologist(s) with an on call system e.g. for delivery of IV thrombolysis for ischaemic stroke. They must also have a team of interventionists (2 or more) undertaking regular cerebral endovascular interventional procedures including thrombectomy for stroke.

Local protocols for advanced stroke imaging techniques (including CTA and/or CT Perfusion (CTP) and MRI techniques including DWI/MRP/MRA) must be in place.

Intra-arterial thrombectomy procedures will be carried out by designated consultant interventionists with substantial expertise in cerebral interventional endovascular procedures and the techniques required for stroke thrombectomy. Good collaboration between the hyperacute stroke team and interventionists is essential and centres should have regular neurovascular meetings.

Centres will be required to submit documentation of detailed local protocols for the treatment of acute stroke. Prospective centres will need to provide documentation that evidence is being kept of angiographic and clinical outcomes for their acute ischaemic stroke interventions (e.g. audits of recent results for both IVT and their IA experience).

As a guide, centres will have treated ≥20 patients with hyperacute ischaemic stroke using intra-arterial thrombectomy within the preceding 24 months. In addition a much larger experience in cerebral endovascular interventional procedures will need to be documented.

Centres where there is no routine use of advanced imaging in stroke and limited experience of thrombectomy for ischaemic stroke will not be able to join STABILISE.

11. Screening, Recruitment and Consent

11.1 Identification & Screening

Potential participants will be identified on referral to participating acute stroke services and will be screened by the stroke team/stroke research team against clinical inclusion and exclusion criteria listed in section 10.

An eligibility screening form will be completed by the investigator to document participants' fulfilment of the entry criteria for all patients considered for the trial and subsequently included or excluded. For subjects/consultees who decline participation, this will document any reasons available for non-participation. Sites at which patients are being identified are full research sites.

11.2 Recruitment Procedure

If a patient fulfils clinical criteria, a clinician with delegation to take consent for the trial (and GCP trained) will explain the trial to the patient (if deemed to have capacity) or their next of kin or other appropriate consultee and invite them to participate. The relevant trial Patient Information Sheets (PIS) will be provided at this time and the patient/consultee allowed to consider it whilst clinical care towards delivering thrombectomy continues.

The clinician who approached the patient about participation will answer any questions they may have prior to informed consent.

This clinician will be listed on the site delegation log for this purpose.

11.3 Consent

A clinical investigator with delegated responsibility will verbally explain the exact nature of the trial and also provide each patient/relative/appropriate consultee with a written information sheet (PIS). This will include the known side-effects that may be experienced and the risks of participating in this clinical trial. Written informed consent will be obtained from each trial participant, alternatively, if the patient is unable to consent for themselves, then this will be provided from an appropriate consultee as required by each participating country. In England, a consultee will give an opinion on whether the patient would have wished to participate. Trial participants will be informed that they are free to withdraw their consent from

the trial or trial treatment at any time. In the case of patients who were enrolled in the trial by a consultee because they were unable to consent at the start of the trial, personal written informed consent will be confirmed once they regain capacity. A specific information sheet relevant to this situation will be provided to them at this time.

Due to the clinical urgency of acute stroke treatment and the need to undertake clinical thrombectomy the time for reflection is necessarily limited. The time constraints also preclude arranging official interpreters.

The original signed consent form will be retained in the Investigator Site File, with a copy in the clinical notes and a copy provided to the participant. The participant will specifically consent to their General Practitioner (GP) being informed of their participation in the trial.

The right to refuse to participate without giving reasons will be made clear.

12. Trial Intervention Details

12.1 Investigational Device Information

All devices should be used in accordance with the manufacturer's CE marked Instructions for Use (IFU).In the experimental arm, the initial attempt at thrombectomy will be with the "SOFIA"™ distal access catheter and the "ERIC"™ MVS devices ± clot aspiration (technique as per operator preference within device IFUs). If that fails to recanalises adequately then the neurointerventionist may elect to use any other CE-marked device approved for thrombectomy. Such devices will be those available as clinical routine at a site, and will not be supplied as part of the trial. The ERIC device used as allocated will be provided at a research rate by Microvention Terumo Inc. – one per patient (equivalent to $1500 USD).

The device make and model that is used for a procedure will be documented in trial documentation. In the control arm, the neurointerventionist is free to use preferred existing thrombectomy device(s) but should only use the "SOFIA" and "ERIC"™ MVS devices in exceptional circumstances if other devices have failed and in the best interests of the patient.

Devices with CE mark and approval for "stentriever" type thrombectomy are the following:

- Covidien ev3 Solitaire & derivatives
- Phenox BONNET & derivatives
- Phenox pRESET & derivatives

- PENUMBRA retriever/thrombectomy system & derivatives including aspiration catheter/pump
- Concentric Trevo/Trevo2 & derivatives
- Acandis Aperio
- Codman ReVive & derivatives
- Mindframe Capture device & derivatives

Other devices CE marked for ischaemic stroke thrombectomy may be approved for trial use by the Steering Committee after review of the relevant IFU.

13. Randomisation

Patients will be randomised to either novel thrombectomy device or standard stent based thrombectomy device (± clot aspiration).

Stratification will be by :

- age (18-65 vs >65)
- severity of stroke at presentation by NIHSS (6-15 versus 16+)

A central randomisation facility will allocate the randomised therapy per patient. The system, based at the Newcastle Clinical Trials Unit (NCTU) will be web based and accessed by sites using a secure password protected website link. Participants will be assigned a unique patient trial ID number. Patient details will be entered into the web-based system, which will return the allocation status.

Ratio of allocation to treatment groups will randomise on a patient basis and will be on a 2:1 ratio (SOFIA/ERIC to control).

Participants will not be informed of their allocated treatment group.

14. Blinding

Clinical outcome (Rankin Focused Assessment (RFA)) assessors will be blinded to device treatment allocation. Assessors will be medical or nursing or therapist with current Rankin assessment accreditation

Core lab neurointerventionist assessing TICI score (under modified STIR II criteria) at end of procedure will be blinded to treatment allocation.

In this trial emergency unblinding is not required as the same clinical intervention is undertaken in both arms and the operator is not blinded.

15. Trial Data

15.1 Assessments/Data Collection

Clinical evaluations will include standard neurological impairment and outcome scales as outlined in the trial flow chart in section 6.1 and the schedule of assessments below. In addition, at around 90 days post stroke the outcome will include the number of days spent at home in the first 90 days after stroke, an objective index of functional outcome that also contributes health economic data.

15.2 Schedule of Assessments

	Pre-Enrolment	Thrombectomy Procedure	0-24h	24h (22-36h) post treatment	72±8h post treatment (or hospital discharge if earlier)	Day 7(±2) post treatment (or at discharge if sooner)	~Day 90	Day 365 (±10)
Obtain Consent	X							
Review Inclusion/Exclusion Criteria	X							
Brain imaging (CT/MRI)	*			+				
MRI/MRA				X				
Vital Signs (temperature, blood pressure, heart rate)	*	*		*	+	+		
Post-thrombolysis Observations (BP, pulse) – if applicable		*	*					
Physical Examination - NIHSS	*	*		+	+	X		
Weight	*							
Haematology and Coagulation	+							
Bloods - Biochemistry	*			+				
Pregnancy Test (female patients of childbearing potential)	*							
mRS (RFA)	+						X	X
Adverse Events Evaluation		X	X	X	X	X	X	X
Home Time Evaluation							X	

X trial-specific procedure

* clinically routine procedure (data captured for trial)

+ procedure clinically routine in some/most patients

Visit 1: Pre Randomisation/Randomisation

Procedures that are part of routine patient care for assessment of eligibility for treatment of LVO strokes will be used also for assessment for eligibility of the trial, these include:

- Medical history, including symptom onset time, past history, medication, level of function or disability
- CT/A/P brain (or MRI/A)
- Blood samples for biochemistry (including estimated glomerular filtration rate (eGFR) and blood glucose) and haematology (including coagulation)
- Blood pressure, heart rate and temperature
- [Capillary] Blood glucose
- Weight
- Physical examination including NIHSS (see appendix B)

Trial specific procedures will take place following informed consent, these include:

- Pregnancy test for females of childbearing potential
- Web based trial entry
- Allocation of randomised treatment and patient unique trial number
- Completion of electronic Case Report Form (eCRF)

Visit 2: Thrombectomy Procedure

General anaesthesia or sedation may be used for the procedure as locally required. Intra-arterial mechanical thrombectomy will be undertaken using the CE marked MICROVENTION "SOFIA"**™** distal access catheter along with "ERIC"™ STROKE retriever Device (MSD) or other CE marked thrombectomy devices at the discretion of the Interventional Neuroradiologist. The procedure should commence (i.e. groin puncture) within 90 minutes of the onset of IV thrombolysis or confirmation of diagnosis of LVO stroke (whichever is later) and a guide catheter should be placed beyond the aortic arch within a maximum of 6h of stroke onset (9h for posterior circulation) and angiographic run performed to confirm LVO.

Procedure documentation will include drug administration (including anaesthesia or sedation), total duration, device used, number of passes, adverse events (AEs). If the "SOFIA"**™** and "ERIC"™ MSD fails to recanalise to TICI 2b or better after 3 passes, the neurointerventionist is free to use other CE marked thrombectomy device(s). In control arm standard stroke thrombectomy devices will be utilised as per local centre protocol. If after 3 passes these fail to recanalise to TICI 2b or better, the neurointerventionist is free to use other CE marked thrombectomy device(s) – including SOFIA &/or ERIC.

All assessments before discharge will take place in an acute stroke unit or neurointensive care facility and will be performed by the clinical stroke team with support from research nurses as required.

Post-treatment monitoring: will be documented on a trial worksheet for transcription into the eCRF. This includes the following items that are collected routinely in patients treated with IAT &/or IVT:

- Blood pressure hourly for 24 hours, then four hourly for 24 hours

Visit 3: 24 hours (22-36h) post treatment:

- Brain imaging will be with MRI and MRA (repeat CT and CTA only if MRI impossible)
- Vital signs
- NIHSS
- Blood samples for biochemistry
- Adverse event assessment
- Completion of eCRF

Visit 4: 72±8 hours post treatment (or hospital discharge if earlier):

- Vital signs
- NIHSS
- Adverse event assessment
- Completion of eCRF

Visit 5: 7(±2) **days post treatment (or hospital discharge if earlier):**

- Vital signs
- NIHSS
- Adverse event assessment
- Completion of eCRF

Visit 6: 30 days

- Adverse event assessment (by local team)
- Completion of eCRF
- Carried out by local trial team from medical records plus call to GP/patient if required

Visit 7: ~90 days (±3)

- mRS (by patient or carer)
- Home time evaluation (number of days spent at home in first 90 days after stroke)
- Adverse event assessment (by local team)
- Undertaken at standard clinic follow-up or if patient is unfit/unable to come to clinic then will be undertaken by telephone interview by local research team to complete RFA and home time evaluation

Visit 8: 365 days (±10)

- mRS (by patient or carer)
- Adverse event assessment (by local team)
- Completion of eCRF (by local team)
- Undertaken either by postal questionnaire, telephone interview or at clinic visit
- Trial completion

Modified Rankin Scale (mRS)

The mRS is a hierarchical ordinal scale used to assess disability in stroke trials, with seven discrete levels that range from No Symptoms (mRS=0) to death (mRS=6). Inter-observer agreement is significantly enhanced by use of a standardised structured interview. All investigators undertaking outcome assessment will document training in use of Rankin scoring.

Imaging

Routine brain imaging in acute stroke consists of brain CT, an X-ray based examination involving ionizing radiation. This identifies stroke caused by ICH with very high sensitivity and specificity, and may additionally show areas of established ischaemic damage that define eligibility for treatment. In patients with suspected LVO stroke centres undertaking regular

thrombectomy will undertake vascular imaging- usually CTA, but some may use magnetic resonance imaging (MRI), including MRA, as an alternative. Enrolment will occur after vascular imaging confirms eligibility.

CT angiography acquires thin axial sections during the first arterial passage of approximately 50ml of an iodinated contrast agent delivered via an IV cannula sited in a large forearm vein, delivered at a controlled rate (usually 4-6 ml/second) by a power injector. CTA acquisition that covers the arch of the aorta to the circle of Willis is recommended. Alternative vascular imaging is permitted (MRA or DSA).

Follow-up imaging at 24 (22-36) hours in patients treated with IV thrombolysis usually includes CT brain to define infarct size, haemorrhagic complications and brain swelling. For STABILISE trial-specific imaging will be MRI/MRA to define infarct better, and confirm vessel recanalisation and enable assessment of the role of early MRI as a possible predictor of long term outcome. Follow-up imaging may be with CT brain and CTA only in exceptional circumstances.

MRI is a very common and safe clinical imaging investigation utilising radio waves within a powerful magnetic field to build up detailed structural images of the body. But due to the logistics and availability involved, MRI is underutilised in many stroke centres. Furthermore it is very rarely used as an early follow-up examination following a major stroke.

Image Processing and Analysis

Trial imaging studies will be transferred from clinical scanners or radiology archives after removal of individual identifiers from the DICOM file (patient name, date of birth, NHS number or similar unique identifier) which will be replaced with the site and trial specific patient ID number. Imaging studies will be uploaded to or forwarded on removable media for central review.

Blood Testing/Venepuncture

Additional blood testing for trial purposes is not required. Blood results relevant to acute stroke with thrombolytic treatment will be reviewed for trial purposes and routinely include the following:

- Biochemistry – blood glucose, urea and creatinine (and calculated estimated Glomerular Filtration Rate, eGFR), blood glucose
- Haematology – platelet count and coagulation studies (including prothrombin time, INR and activated partial thromboplastin time)

Because of the emergency nature of stroke treatment and the potential for patients to have been transferred from other hospitals for care, lab results may be derived from a number of different hospitals. Any EU acute care hospital laboratory will be acceptable as the source of pre-treatment blood results.

15.3 Data Handling & Record Keeping

An electronic case report form (eCRF) will be used to collect trial data. The eCRF will be developed by the Newcastle University Clinical Trials Unit and Newcastle University Institute for Ageing and Health and access to the eCRF will be restricted, with only authorised site-specific personnel able to make entries or amendments to their patients' data. It is the investigator's responsibility to ensure completion and to review and approve all data captured in the eCRF.

All data handling procedures will be detailed in a Trial Specific Data Management Plan. Data will be validated at the point of entry into the eCRF and at regular intervals during the trial. Data discrepancies will be flagged to the trial site and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with International Conference on Harmonisation of Good Clinical Practice (ICH GCP), local regulations, or as specified in the Clinical Trial Agreement, whichever is longer. Data will be retained at the Data Centre for a minimum of 5 years.

Data will be recorded by authorised site staff on electronic Case Report Forms (eCRF). Data transferred from site to the secure validated database by remote access will be secure and encrypted. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable data will leave the trial site. The quality and retention of trial data will be the responsibility of the CI. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

16. Statistical Considerations

16.1 Statistical Analysis

The trial will have a comprehensive Statistical Analysis Plan, which will govern all statistical aspects of the trial, and will be authored by the Trial Statistician and agreed by the Trial Steering Committee (TSC) before any comparative analysis is undertaken or any unblinded data is released.

As an early phase trial the majority of the statistical analysis will be descriptive carried out on an intention to treat basis retaining patients in their randomised group and including any ineligible patients or protocol violators.

The primary outcome measure is the proportion of patients in each randomised group who achieve good recanalisation at end of procedure as a proportion of all randomised patients based on independent core lab adjudication (blinded to allocation to experimental or control arm) and defined as STIR II modified TICI grade 2b/3.

Secondary outcome measures (defined in section 2) will be summarised (overall and by randomised group) according to their data type: categorical measures will be summarised as proportions of the total number of randomised patients, continuous measures will be summarised as means (sd), integer continuous measures as medians (IQR).

Specifically, the mRS score at day 90 ($\pm$7) will be treated as a continuous ordinal variable and also categorised as favourable (scores of 0-2) or unfavourable (scores 3-6) and by change from baseline pre stroke mRS.

Safety data (serious adverse events) – both numbers of subjects and events – will be summarised by randomised group and overall using descriptive statistics, including mortality rates within 365 days. Feasibility will be reported descriptively as i) acceptability to patients defined as the total number of patients randomised as a proportion of those identified as eligible to participate; ii) feasibility of the procedure defined as time to thrombectomy and duration of thrombectomy; iii) compliance to data collection procedures at 3 and 12 months.

Summary statistics of the primary and secondary outcome measures will be presented by stratification factors, specifically age cohort (50-65 versus >65y) and also clinically relevant groups according to type of occlusion (internal carotid artery, basilar artery, proximal middle cerebral artery, MCA distal). The relationship between age (as a continuous measure) and other clinical variables will be explored descriptively as well as investigating the risk associated with increased age as a potential predictor of the primary outcome.

16.2 Sample Size Calculation

It is intended that this phase II early clinical trial will gather feasibility, safety and provisional outcome data which will inform the design of a subsequent powered, definitive phase III trial. We intend to recruit between 120 patients over 24-30 months to do this.

The number of patients is predominantly based on pragmatic considerations, around feasible recruitment of patients given available time and resources. The design is a randomised controlled trial randomising patients to the novel SOFIA/ERIC devices on a 2:1 basis in favour of SOFIA/ERIC. In this design the control device group will provide an indication of activity and adverse effects in patients receiving current standard of care. This trial is not designed or powered to statistically compare the control and experimental groups using formal hypothesis testing. The control group are recruited primarily to provide an unbiased 'benchmark' of activity and adverse events, hence the justification for the 2:1 randomisation.

The primary outcome measure for this early phase trial is recanalisation rate (as a shorter-term surrogate for longer term outcome measures of function more suitable for phase 3 trials). The number of patients is based on achieving a specified recanalisation rate in the experimental device group, with acceptable error levels, which would justify further research of the device. As an indication, assuming a recanalisation rate to reject SOFIA/ERIC (p0) <75% and a recanalisation rate to justify investigating SOFIA/ERIC further (p1) >90%, recruiting a minimum of 67 patients to the SOFIA/ERIC arm would allow alpha and beta error levels of 2.5% and 10% respectively (Fleming-A'Hern single stage early phase trial methodology). Assuming a conservative anticipated drop-out rate of up to 20% over 6-months increases the recruitment target for the experimental device arm to 80 patients. An additional 40 patients will be randomised to the control device on as 2:1 basis total recruitment target of 120 patients. There is no formal comparison between the two groups and the trial data will be presented as per the single-arm Fleming-A'Hern design. However the dropout rate has been 0 to date, so as few as 100 patients may be required.

The overall aim is to move through the clinical trial pathway, to later phase studies, quickly. This trial will provide initial estimates of therapeutic activity, and incorporate planned investigation of stratification subgroups and biomarkers to inform future trials. At the end of the trial we will be in a position to make an informed decision regarding progression of the SOFIA/ERIC devices into definitive phase III trials.

Management and Delivery

The Newcastle University Clinical Trials Unit, a fully registered UK Clinical Research Network (CRN) Clinical Trials Unit, in conjunction with CIs and Trial Steering Committee, will manage the trial and analyse/report the interim and final trial data.

17. Compliance and Withdrawal

17.1 Participant Compliance

Where feasible, trial visits will coincide with routine clinical follow-up, to enhance the likelihood of good compliance. Visit windows as outlined in the table in section 15.2 should ensure visit attendance; non-attendance for trial visits will prompt follow-up by telephone.

Data collected for routine clinical care will be used for clinical trial documentation (e.g. blood results, NIHSS score, imaging findings). Consent will specifically include the use of clinically routine data for trial purposes, and for review of imaging studies by independent observers.

17.2 Withdrawal of Participants

Patients have the right to withdraw from the trial at any time for any reason, and without giving a reason.

It is understood by all concerned that an excessive rate of withdrawals can render the trial uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the trial, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

Consent will be sought from patients to retain data collected up to the point of withdrawal. Patients will be asked if they would be happy for the reason for the decision to withdraw to be recorded.

18. Data Monitoring, Quality Control and Quality Assurance

18.1 Discontinuation Rules

The trial may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Data Monitoring & Ethics Committee and/or Trial Steering Committee, Sponsor, Regulatory Authority or Ethics Committee concerned.

18.2 Monitoring, Quality Control and Assurance

Routine Management of Trial: Trial Management Group (TMG)

The trial will be coordinated by a Trial Management Group that will include those individuals responsible for the day-to-day management of the trial; namely the CIs, clinical research fellow, statistician, trial manager and database manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC should:

- agree the trial protocol and any protocol amendments
- provide advice to the investigators on all aspects of the trial
- have members who are independent of the investigators, in particular an independent chairperson

Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the TSC.

Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The IDMC will be independent of both the investigators and the funder/sponsor and will be the only body that has access to unblinded data. It will make recommendations to the TSC.

18.3 Trial Monitoring and Auditing

Trial monitoring visits will be conducted as appropriate by NHS Sponsor designated Monitor(s) e.g. from Newcastle Clinical Trials Unit. The level of monitoring will be based on the outcome of the completed monitoring risk assessment; however, the minimum requirement per site will be an initiation visit following the issue of all approvals, and prior to the start of recruitment and a close out visit at each site after the last patient has completed the last visit.

Prior to commencement of the trial a Monitoring Plan will be written by the monitors and approved by the Sponsor's Research Governance Manager. In addition, the trial may be subject to routine or for-cause audit visits. Investigators and site staff will notified in advance of any audit and/or monitoring visits.

19. Adverse Event Monitoring and Reporting

19.1 Definitions

- **Adverse Event (AE) –** Any untoward medical occurrence in a subject to whom a trial intervention or procedure has been administered, including occurrences which are not necessarily caused by or related to that intervention/procedure.

- **Serious Adverse Event (SAE) -** Any untoward occurrence that:
    a. results in death
    b. is life threatening
    c. requires hospitalisation or prolongation of existing hospitalisation
    d. results in persistent or significant disability or incapacity
    e. consists of a congenital anomaly or birth defect
    f. is otherwise considered medically significant by the investigator

- **Causality** - AEs should be assessed for causality and whether the event was **related** or **unrelated** to the intervention under trial.

- **Severity –** the term 'severe' is used to describe the intensity of a specific event:
    - **Mild:** discomfort is noticed, but there is no disruption of normal daily activities
    - **Moderate:** discomfort is sufficient to reduce or affect normal daily activities
    - **Severe:** discomfort is incapacitating, with inability to work or to perform normal daily activities

19.2 Expected Adverse Events

The following AEs are considered to be expected:

- *AEs related to acute stroke:*
    - Brain swelling / brain oedema (including brain herniation, raised intracranial pressure, mass effect, "malignant oedema")

- Haemorrhagic transformation of the infarct (symptomatic and asymptomatic)
- Recurrent stroke (new or extension)
- Neurological deterioration
- Seizures
- Infections, including pneumonia, urinary tract infection, cellulitis, C. Difficile
- Complications of immobility (deep vein thrombosis, pulmonary embolism, falls, fractures, pressure sores, spasticity, joint immobility or pain)
- Troponin T elevation without criteria of myocardial infarction
- Myocardial infarction
- Depression & other related psychological sequelae
- Frailty
- Death

- *AEs related to thrombolytic drug administration (these are detailed in relevant SmPCs):*
  - Intracranial haemorrhage (symptomatic and asymptomatic)
  - Angio-oedema
  - Anaphylactoid reaction
  - Hypotension
  - Systemic bleeding eg. GI haemorrhage, epistaxis
  - Convulsions
  - Fever
  - Rash
  - Venous or arterial thrombosis (failure of response or subtherapeutic)
- *AEs related to thrombectomy devices and associated guiding catheter(s)/balloons:*
  - Intracranial haemorrhage (symptomatic and asymptomatic), including subarachnoid haemorrhage
  - Vasospasm
  - Dissection
  - New stroke
  - Arterial wall damage including arterial laceration, puncture and dissection

- Femoral/Brachial/Radial arterial puncture site haematoma, pseudoaneurysm or haemorrhage
- Device fracture
- Device embolism
- Failure to withdraw device successfully
- Failure to retrieve some / all of the thrombus
- De novo arterial stenoses / occlusions

19.3 Protocol Specifications

19.4 Recording and Reporting of Adverse Events

AEs (from randomisation to 365 days) will be identified by observation and/or enquiry at trial visits. AEs that do not meet criteria for seriousness will be recorded in the medical notes only. Details of SAEs will be recorded to the eCRF in addition to the medical notes and followed until resolution. Expected SAEs as listed above (section 19.2) should be followed until resolution. The relationship with the trial procedures will be assessed for any unexpected SAEs: if possibly or definitely related, unexpected SAEs will be communicated by local PI to the Chief Investigator (CI) for review and will be reported to the Research Ethics Committee (REC) as detailed below. Unrelated and unexpected SAEs will be followed until resolution.

Reporting to Sponsor

All unexpected SAEs arising during the trial must be reported by the Principal Investigator (or designee) to the Sponsor and NCTU via fax using the SOHO 66 system as soon as reasonably practicable and in any event within 24 hours of first becoming aware of the event. Any follow up information should also be reported.

The initial report can be made verbally, but must be promptly followed with a detailed, written SAE report faxed via SOHO 66. The SAE form should be completed and faxed using SOHO 66 (Fax No: tbc)

Reporting to the Research Ethics Committee (REC):

Any SAE occurring to a research participant will be reported to the main REC (i.e. the REC that gave a favourable opinion of the trial) where in the opinion of the Chief Investigator (CI), the event was:

- "Related" – that is, it resulted from administration of any of the research procedures, **and**
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted to the REC **within 15 days** of CI becoming aware of the event, using the 'report of serious adverse event form' for non-CTIMPs published on the National Research Ethics Service (NRES) website.

http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

The form should be completed in typescript and signed by the CI (or designee). The Sponsor will assist in the preparation and submission of the report.

The co-ordinator of the main REC will acknowledge receipt of safety reports within 30 days.

Annual Progress Report

The CIs are also responsible for providing an annual progress report to the REC using an NRES "Annual Progress Report form for all other research". This form is available at:

http://www.hra.nhs.uk/resources/during-and-after-your-study/nhs-rec-annual-progress-report-forms/

The report will be prepared by the Trial Management Group. A section on the safety of patients is included in this report. The Sponsor will assist in the collation of the safety information required for the report.

Reporting to Local Research and Development (R&D) Departments

The Principal Investigator at each site is responsible for the provision of reports to their local R&D department per the conditions of Management approval.

20. Ethics & Regulatory Issues

The trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]).

Favourable ethical opinion will be sought from the relevant REC before patients are entered into this clinical trial. Patients will only be allowed to enter the trial once they have provided written informed consent or it has been given by an appropriate consultee.

The CI will be responsible for updating the REC of any new information related to the trial.

20.1 Protocol Amendments

Any change in the trial protocol will require an amendment. Any proposed protocol amendments will be initiated by the CIs following discussion with the TSC and any required amendment forms will be submitted to the Regulatory Authority, Ethics Committee and Sponsor. The CIs and the TSC will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor's representative (NUTH R&D). Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC, and participating site Research and Development (R&D) office.

21. Confidentiality

Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by their initials and a unique trial identification code only. The trial will comply with the Data Protection Act, 1998. All trial records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access.

22. Insurance and Finance

The STABILISE trial is sponsored by Newcastle Upon Tyne Teaching Hospitals (NUTH). The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

Indemnity in respect of potential liability arising from negligent harm related to trial design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with the University. This is a non-commercial trial and there are no arrangements for non-negligent compensation.

23. Trial Report/Publications

An annual progress report will be submitted to the funders, the first being submitted 12 months from the date that all trial related approvals are in place. Annual reports will be submitted to the ethics committee, regulatory authority and sponsor with the first submitted one year after the date that all trial related approvals are in place.

The trial will be submitted for adoption by the Stroke Research Network (SRN). It will be disseminated via SRN, presentations at relevant professional meetings and publications in peer reviewed journals. SRN will aid with dissemination to the wider public as will Newcastle University. All manuscripts, abstracts or other modes of presentation will be reviewed by the Trial Steering Committee and Funder prior to submission. Individuals will not be identified from any trial report.

The data will be the property of the Chief Investigators, Co-Investigators and Principal Investigators. Publication will be the responsibility of the Chief Investigators and published under the authorship agreed with the Co-Investigators and all the Principal Investigators who have entered patients into the trial.

Participants will be informed about the results at the end of the trial, including a lay summary of the results.

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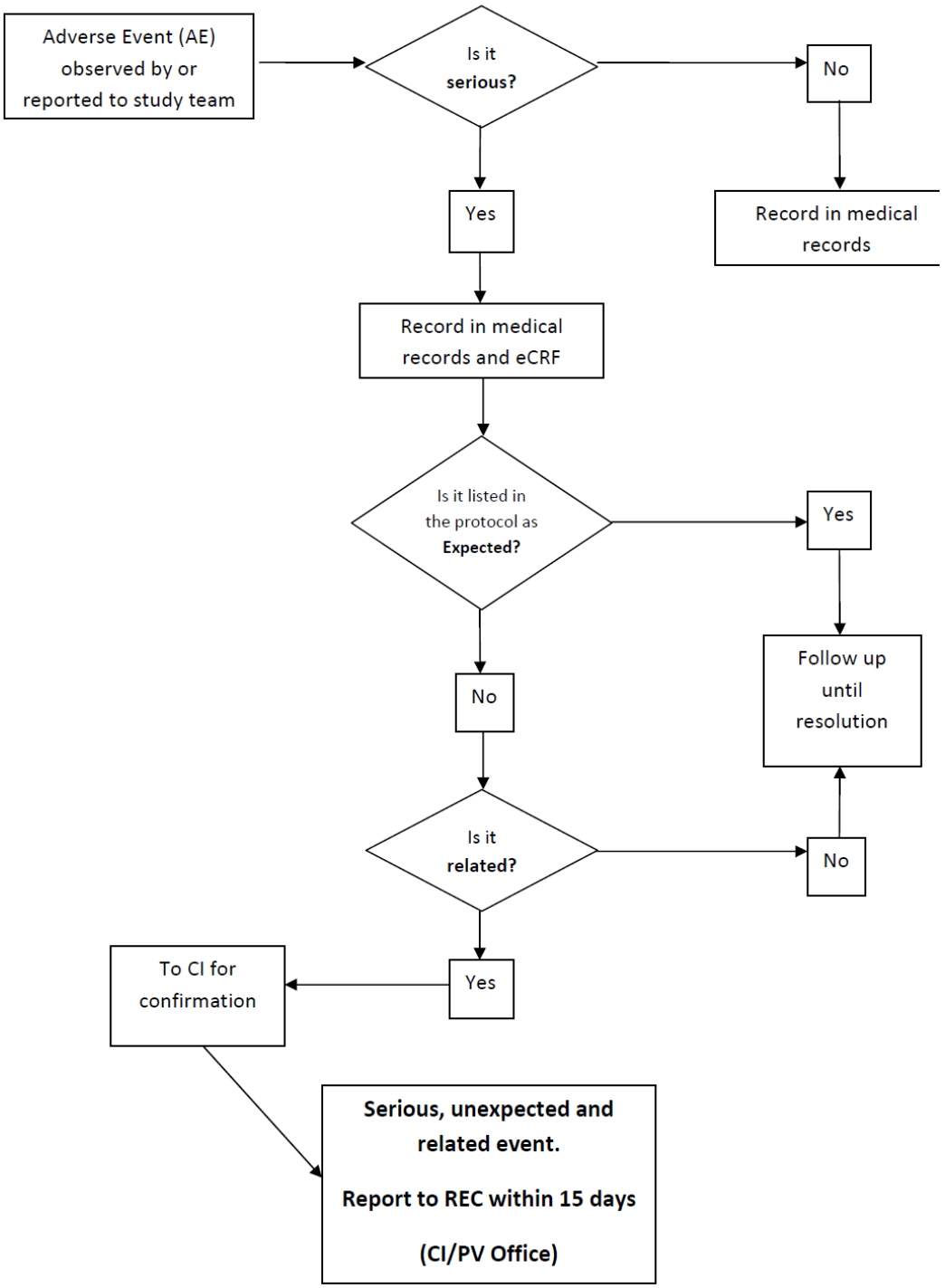
25. Appendices

Appendix A: Flowchart for Assessing and Reporting Adverse Events



Appendix B: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic Principles for All Medical Research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the trial on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the trial and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the trial or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research Combined with Medical Care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the trial, every patient entered into the trial should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the trial.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a trial must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix C: NIH Stroke Scale

0	No Stroke Symptoms
1-4	Minor Stroke
5-15	Moderate Stroke
16-20	Moderate to Severe Stroke
21-42	Severe Stroke

Appendix D: Modifed Rankin Scale (mRS)

Provided by the Internet Stroke Center — www.strokecenter.org

MODIFIED **Trial ID**: _____

RANKIN **Rater Name:** _____

SCALE (mRS) **Date:** _____

Score 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

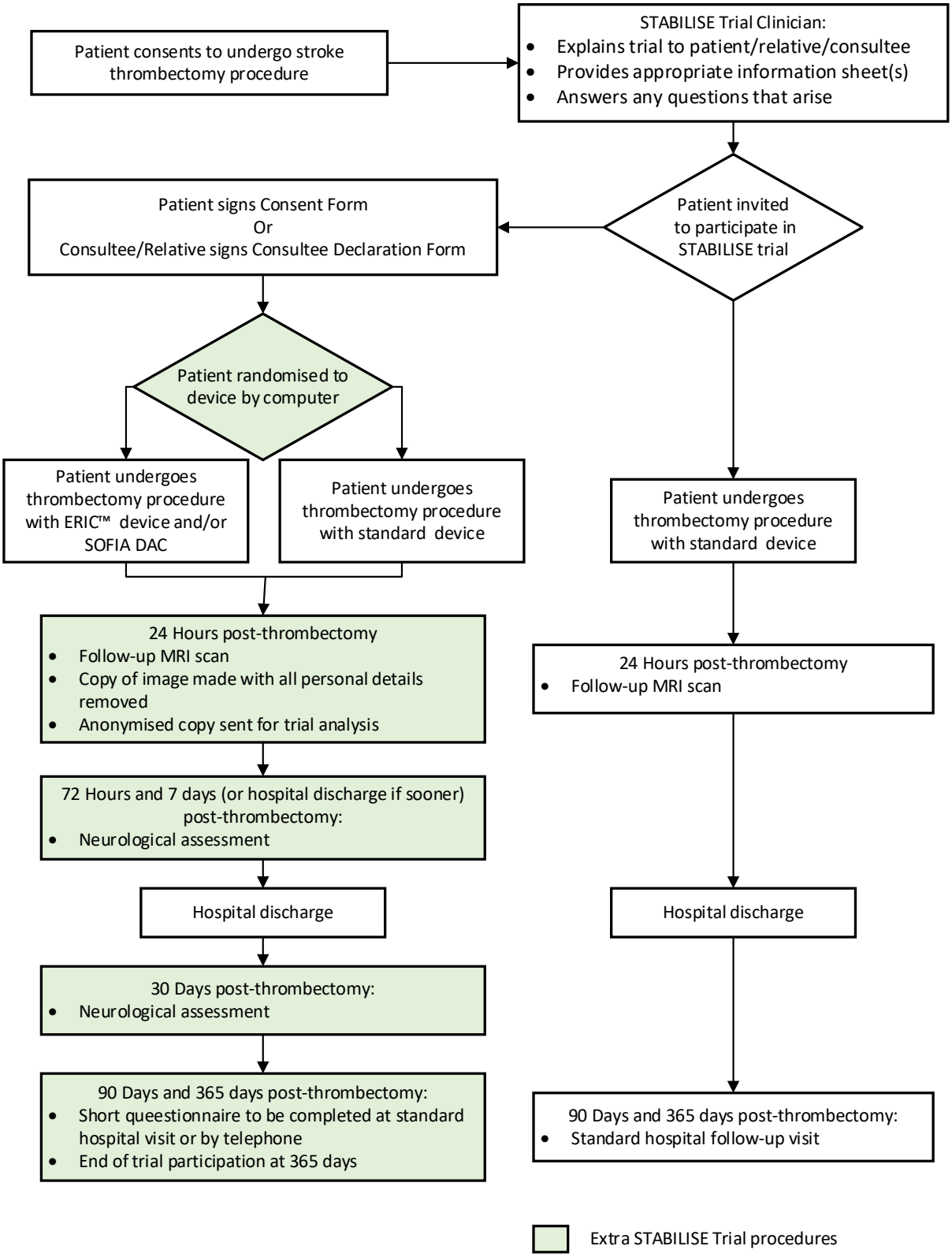
4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 Dead

TOTAL (0–6): _____

Appendix L - Stabilise Trial - Patient Pathway Flowchart



Appendix M – STABILISE DMC Charter

STABILISE DMC Charter

Title pages

Sponsor representative	Susan Ridge Research Governance Manager, Joint Research Office, Regent Point, Regent Farm Road, Newcastle upon Tyne, NE3 3HD Tel: 0191 282 4823 Fax: 0191 282 4524 Email: Susan.Ridge@nuth.nhs.uk
Funders	NIHR Newcastle Biomedical Research Centre MicroVention Terumo Inc
Sponsor Reference Number	R&D number: 6893
REC Reference	14/NE/0113
ISRCTN Number	15698516
Version Number and Date	Version 1.0: 24-Aug-15
Chief Investigators	Prof Phil White Prof Gary Ford
Trial Manager	Andrea Bell
Trial Office	Newcastle CTU 1-4 Claremont Terrace, NE2 4AE

STABILISE DMC Charter

DMC chair	Prof Rustam Al-Shahi Salman Professor of clinical neurology, University of Edinburgh Honorary consultant neurologist, NHS Lothian UK Email: rustam.al-shahi@ed.ac.uk
Other DMC members	Dr Andy Molyneux Oxford University Neurosurgery and Neuroradiology Research Unit UK Email: jane.armitage@ctsu.ox.ac.uk
	Dr Andy Vail (biostatistican) Manchester University Email: andy.vail@manchester.ac.uk
Un-blinded trial statistician	tbc

STABILISE DMC Charter

Approval signatures

The following individuals, by providing their signatures, indicate their understanding of, and willingness to comply with, the roles and responsibilities assigned to them in this DMC charter.

Name	Role	Signature	Date
Prof Rustam Al-Shahi Salman	Chair		
Dr Andy Molyneux	Member		
Dr Andy Vail	Member		
Prof Phil White	Chief investigator		
Prof Gary Ford	Chief investigator		
Ms Susan Ridge	Co-sponsor representative		

STABILISE DMC Charter

Table of Contents

STABILISE DMC Charter

Introduction

Purpose

The purpose of this document is to describe the roles and responsibilities of the independent Data Monitoring Committee (DMC) for STABILISE, the specific purposes and functions of the DMC and those supporting its activities, the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees. This charter has been written to comply with the structure proposed by the DAMOCLES Study Group.[1]

Trial objectives

STABILISE is a multicentre prospective phase 2 single-blinded randomised controlled trial of novel endovascular device system for mechanical clot retrieval (SOFIA and ERIC) versus standard thrombectomy device(s) (see trial flowchart on page 12). The primary objective is to determine if the novel thrombectomy system can be used safely and successfully in people with large vessel occlusion (LVO) acute ischaemic stroke. The secondary objectives are a) to investigate the efficacy (recanalization rate) and safety of the thrombectomy devices and inform design of a phase III clinical trial; b) to determine the procedural safety of thrombectomy in a wider stroke population; c) to investigate the use of early MRI post thrombectomy as a surrogate marker of clinical outcome.

Composition

The DMC comprises three members (see page 2): two senior clinicians with interests in stroke and interventional neuroradiology as well as prior clinical trial and DMC experience, and a statistician with clinical trial and prior DMC experience. DMC members were chosen for their independence, likelihood of being constructively critical of the ongoing trial, and their support for the aims and methods of the trial. The Sponsor has approved all DMC members.

All DMC members are expected to serve from the start of the trial until the trial is completed (i.e. final database lock). Should it be necessary for a member to resign, the member must submit the effective date of resignation in writing to the Sponsor, DMC chair, and chief investigator. In the event a member resigns, the Sponsor, DMC chair and chief investigator will initiate the process to identify a replacement member. If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DMC. If a member does not attend a third meeting, they should be replaced.

Competing interests

DMC members will not be involved as principal investigators or delegated physicians in STABILISE. In addition, DMC members must not have a scientific, financial, or regulatory conflict of interest that would bias their review of trial data (e.g. DMC members must not have a financial interest that could be substantially affected by the outcome of the study, relationships with individuals in trial leadership positions that could be considered reasonably likely to affect their objectivity, or involvement in any potential competing trial). DMC members will be reimbursed for travel and accommodation, but there are no other payments. None of the members has declared a competing interest.

STABILISE DMC Charter

Roles and responsibilities

The DMC is an independent expert advisory group, which has been commissioned and charged with the responsibility of evaluating cumulative safety and efficacy data, as well as clinical trial conduct, at regular intervals. The DMC will act in an advisory capacity to the TSC to review un-blinded interim analyses of safety and efficacy in STABILISE in order to (a) provide an independent overview of the safety of trial participants and (b) make recommendations about the continuation, termination or other modifications to the trial. The DMC will function independently of all other individuals and bodies associated with STABILISE, including the TSC, funder, and investigators.

DMC members

The DMC members are authorised and expected to perform the following functions:

Principles

- Provide approval for, and operate in accordance with, this DMC charter.
- Always have as their primary function the safeguarding of the interests of trial participants.
- Participate in and vote on DMC recommendations bearing in mind the fact that ethical considerations are of prime importance.
- Keep all information received relating to the trial confidential (i.e. it should not be shared with anyone outside the DMC, including the chief investigator).
- Ensure hard copy meeting documents or closed session minutes are shredded and electronic versions are password-protected.
- Disclose competing interests.

Practical functions

- Monitor the safety and efficacy of the trial intervention, through scheduled review of accumulating clinical data from the ongoing clinical trial
- Take into account accumulating data from similar ongoing clinical trials, and share STABILISE's emerging data in confidence with the DMCs of similar ongoing clinical trials.[2]
- Consider the need for additional unscheduled reviews of study data.
- Review and evaluate the content of all un-blinded trial data reports received.
- Make clear advisory recommendations, via the DMC chair, about stopping or continuing the trial to the TSC and Sponsor. However, the DMC will not be asked to provide any recommendation about whether the trial should be stopped on the basis of futility
- Contribute to enhancing the integrity of the trial.
- The DMC may also formulate recommendations relating to the selection, recruitment, or retention of participants, or their management, or to improving their adherence to protocol-specified regimens, and the procedures for data management and quality control.
- In the event of further funding being required, to provide the TSC and funder(s) with appropriate information and advice on the data gathered to date in a manner that will as far as possible protect the integrity of the trial.

DMC chair

Throughout the trial, the DMC chair will take responsibility for the DMC's operation and will be authorised and charged with the following responsibilities:

- Chair all DMC data review meetings, facilitate and summarise discussions.
- Ensure that all relevant data that have been provided to the DMC have been reviewed by the DMC members and that all issues have been addressed.
- Ensure that blinded individuals (i.e. DMC contacts and DMC consultants) are not inappropriately exposed to confidential and/or un-blinded trial data.
- Ensure that only DMC members are present for deliberations over un-blinded data, when DMC recommendations are discussed and when DMC voting procedures are conducted.
- Ensure the accuracy of confidential, written minutes of all closed sessions of any DMC meetings and maintain these minutes as confidential to DMC members only, until the final (end of study) database lock is complete.
- Ensure the accuracy of minutes of open and final sessions of all DMC meetings.
- Communicate, author, sign, and provide the official, final recommendations of the DMC within specified timelines and according to the specifications outlined in this charter. If the DMC is divided in opinion on any major issue affecting the DMC's recommendation to the Sponsor and TSC, the DMC chair is responsible for assembling and presenting the majority and dissenting opinions for all recommendations considered.
- Arrange for consultation(s) and/or request additional data, as deemed necessary.
- Elect to involve the un-blinded trial statistician in closed session meetings. If the un-blinded trial statistician is not involved in closed session meetings, the DMC chair will minute them.

Relationships

Chief investigator (on behalf of the Sponsor)

The chief investigator, on behalf of the Sponsor, will have the following responsibilities with respect to the DMC:

- Provide final approval of the DMC chair and members to serve on the DMC.
- Provide a primary contact representative to receive recommendations from the DMC.
- Provide an un-blinded trial statistician to support the DMC.
- Ensure relevant external clinical or other data on the safety of study interventions are provided to the DMC.
- Ensure that DMC members are informed of trial progress and any other relevant issues at least annually.
- In preparation for data review meetings, ensure that the DMC receive a general summary of the status of the trial and any relevant clinical issues.
- Attend all open and final sessions of DMC meetings, as needed.
- Respond to the DMC's comments on the protocol, proposed amendments to it, and recommendations unrelated to the protocol.
- Maintain ultimate responsibility for safe study conduct.

Un-blinded trial statistician

The responsibilities of the un-blinded trial statistician are as follows:

- Provide approval for and operate in accordance with the specifications outlined in this DMC charter.
- Coordinate the implementation of the schedule for preparation and distribution of data reports to DMC members.
- Ensure that all data required by the DMC are provided according to an agreed time frame.
- Work with DMC members to confirm which data are necessary for the DMC data reports.
- Provide a mock-up of the data report for approval prior to the first DMC meeting at which data will be reviewed (distributed by secure means e.g. encrypted/password-protected).
- Create software applications/queries/analysis code to generate the DMC data report and transfer the reports to DMC members in a secure and confidential manner.
- Ensure that the content of un-blinded trial data reports or details of discussions at DMC meetings are treated in the strictest confidence and are not revealed to any non-DMC member prior to study closedown, without the written approval of the DMC chair.
- Maintain a secure and confidential archive of electronic copies of datasets and related programs provided to the un-blinded trial statistician.
- Provide consultation regarding the information presented in the DMC data reports, as requested by the DMC members.

Ad hoc advisors

The DMC may, with prior approval from the Sponsor, contact and involve selected expert advisors who may, in strict confidence, provide additional, relevant insight or expertise to the DMC, regarding any specific issues that may arise. Ad hoc advisors are not considered to be members of the DMC. As a rule, ad hoc advisors must not attend closed sessions of DMC data review meetings. These advisors would typically be un-blinded to only relevant data, unless the DMC chair deems it necessary for them to be un-blinded to any or all other data to provide fully informed advice. Not only would the content of such discussions be confidential, but every effort should be made to ensure that the fact that their advice has been sought also remains confidential.

Organisation of DMC meetings

Before or early in the trial

An early meeting of the DMC will be beneficial to allow the members to get to know one another, and to consider the protocol in detail, any analysis plan, future meetings, how the DMC might respond to hypothetical situations, and to clarify aspects of the protocol with the chief investigator. The DMC should meet within one year of recruitment starting at the latest. The first meeting should ideally be face-to-face.

Subsequent meetings

Subsequent DMC meetings should ideally be face-to-face, but by teleconference if convening a DMC meeting in person is difficult. Meetings should take place annually at the latest. Meetings should take place as soon as reasonably possible after the DMC members have received data from the un-blinded trial statistician; discussions must include at least 2/3 members. The meeting will

be organised by the DMC Chair in conjunction with unblinded statistician and will start with an 'open' session which will also be attended by the chief investigator (or representative) who will give an update on the trial's recruitment and data quality. This will be followed by the 'closed' session attended by DMC members only, which will address efficacy and safety data by treatment group. Interim data should be kept confidential and restricted to the DMC. 'Open' session minutes will be taken by a member of STABILISE team & circulated for approval; 'closed' minutes and recommendation(s) will be drafted by either the un-blinded trial statistician (and checked by the DMC chair) or the DMC chair, and agreed by the DMC members. The DMC chair will report to the chief investigator.

Trial documentation and procedures to ensure confidentiality and proper communication

Data reports

The DMC will receive data reports directly from the un-blinded trial statistician at least two weeks in advance of scheduled data review meetings. Data included in each DMC data report will be cumulative-to-date at the time of the established data cut-off. The cut-off date for the data included in the data reports, as well as the current enrolment figures, will be stated in the report. The DMC may request additional information on individual patients, as needed.

Open sessions

These will describe accumulating information relating to recruitment and data quality (e.g. treatment device, response rates, data completeness) and pooled data from both treatment device allocation groups on numbers of events for the primary and other outcome measures, at the discretion of the DMC, as follows:

- Trial status
  - Timeline for trial
  - Number of patients randomised
    - By centre (by month and total)
  - Cumulative recruitment graph
  - Numbers of crossovers / drop-in / drop-out
  - Completeness of clinical data
- Baseline (pre-randomisation data)
  - Age / sex
  - Co-morbidities
  - NIHSS / mRS
  - Brain imaging (CT+CTA or MR+MRA)
  - LVO location
  - Time from symptom onset to brain imaging
  - Time from CTA to randomisation
  - Time from symptom onset to groin puncture
  - Time from symptom onset to target vessel recanalization
  - Completeness of radiographic imaging
    - Baseline CT/CTA diagnostic imaging
    - Thrombectomy procedure
    - F/U MRI/MRA
- Numbers of primary and secondary outcomes

- Numbers of serious adverse events

Closed sessions

In addition to all the material available in the open session, the closed session material will include efficacy and safety data by allocated treatment group. The un-blinded trial statistician will perform interim analyses on major outcome events along with any other analyses that the DMC may request. All information about benefits and risks will be presented in a balanced and accessible way. Data reports for review by the DMC will be presented on a Group A, Group B basis (in case the reports are lost; the DMC members will be informed separately of the true treatment assignments associated with the groups). With respect to relative safety and efficacy the following outcomes in particular will initiate discussion and minuting of detailed reasons for recommending early stopping or continuation of the study

Further steps to ensure confidentiality

DMC members are obliged to store the papers and electronic documents securely after each meeting so they may check the next report against them. After the trial is reported, the DMC members should destroy all interim reports. The DMC may discuss issues from their involvement in the trial 12 months after the primary trial results have been published, or when permission is granted by the chief investigator.

Decision making

Recommendations

The DMC will make advisory recommendations (rather than executive decisions) based primarily on safety and efficacy considerations, guided by statistical analyses. In making any recommendation, the DMC will consider the overall internal and external evidence, the multiplicity of testing and the possibility that the trends in the data might be reversed with longer follow-up or increased recruitment.

Early stopping rules

Interim analyses of un-blinded data will be based on recanalisation rates (1) the primary outcome, and (2) all serious adverse events. In the light of these analyses, the DMC will advise the chair of the TSC and Sponsor (via the chief investigator) if, in their view, the trial can safely continue.

- Treatment effects are to be assessed in the following key subgroups defined at randomisation:
- Participant age at randomisation (<65 years versus 65 years or older)
- LVO location (anterior versus posterior circulation)
- Time since AIS (acute ischaemic stroke) symptom onset (0 – 4.5 hrs, 4.5 – 6/9 hrs)
- Recanalisation rates according to STIR II modified TICI scale
    - Poor (score 0 - 2a)
    - Good (score 2b - 3)
- Time from symptoms onset to recanalization

Voting

Every effort should be made for the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken and the decision will go with the majority vote, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. For the avoidance of doubt, the un-blinded trial statistician and ad hoc advisors cannot vote.

Absent DMC members

The DMC will be quorate for decision making provided at least two members are present and all absent members have communicated their opinions to the chair. Members who cannot attend in person should be encouraged to attend by teleconference. DMC members who are not able to attend the meeting may pass comments to the DMC chair for consideration during the discussions. If the DMC is considering recommending major action after such a meeting, the DMC chair should talk with the absent member(s) as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMC.

Reporting

After the review of each data report has been completed, the DMC chair will provide the official DMC recommendation, usually within three weeks, to the Sponsor via the chief investigator and to the chair of the TSC regarding the appropriateness of continuing the study, from a safety and efficacy perspective, as well as any other recommendations relevant to study conduct and/or patient safety. Unless indicated otherwise by the DMC chair, this letter will not be considered confidential. This should be copied to the un-blinded trial statistician and trial manager, and should be sent in time for consideration at the next TSC meeting. If the trial is to continue largely unchanged then it would be useful for the report from the DMC to include a summary paragraph suitable for trial promotion purposes.

Following a report from the DMC, the TSC will decide whether to modify entry to the study (or seek extra data). Otherwise, the TSC, the collaborators and central administrative staff will remain ignorant of the interim results.

If the DMC has serious problems or concerns with the TSC decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting should be chaired by an external expert who is not directly involved with the trial.

After the trial

Records retention

The DMC un-blinded statistician will ensure a copy of DMC files (i.e. copies of all reports reviewed by the DMC and copies of final minutes of all sessions of any DMC meeting) is sent to the chief investigator after the end of the study. It will be the responsibility of the chief investigator, on behalf of the Sponsor, to arrange for long-term archiving.

Publication of results

DMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. The DMC will have the opportunity to approve publications, especially with respect to reporting of any DMC recommendation regarding termination.

Indemnification and liability

The Sponsor shall indemnify, defend and hold harmless each DMC member (and their employer where their DMC member duties are undertaken in the course of their employment), from and against any and all losses, damages, liabilities, reasonable lawyer's fees, court costs, and expenses (collectively "Losses") resulting or arising from any third-party claims, actions, proceedings, investigations or litigation relating to or arising from or in connection with the performance of responsibilities by such DMC member contemplated herein, except to the extent any such Losses have resulted from a breach of such DMC member's obligations hereunder or from any wilful or intentional misconduct of the DMC member seeking indemnity hereunder.

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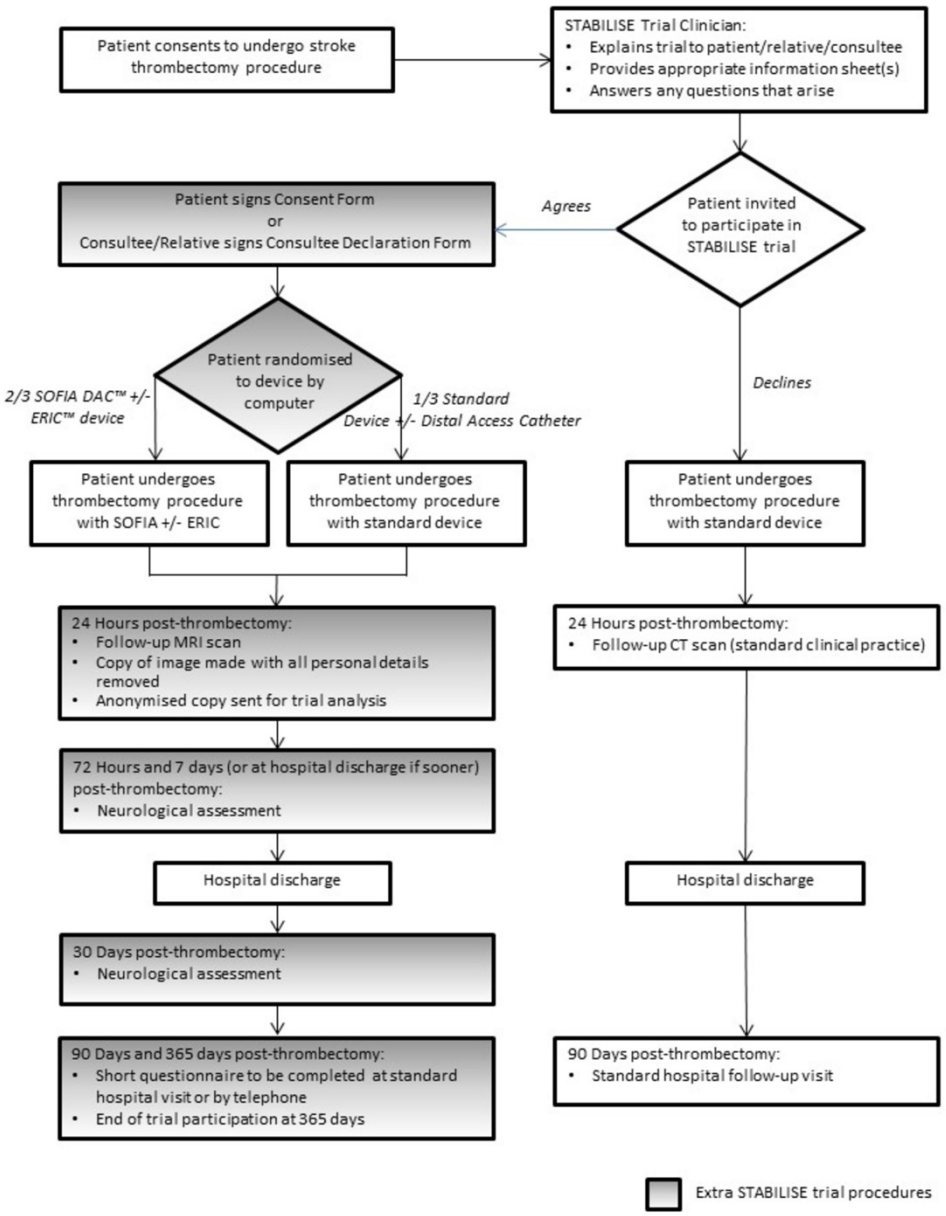
STABILISE DMC Charter

STABILISE Trial – Patient Pathway Flowchart



Appendix N – CTA Training Day Agenda

Registration: 09:00-9:15

Introduction: 9:15-9:30 - Setting out the Priorities for the Training Day

9:30-10:00 – Radiographic considerations for CT Angiograms in acute stroke patients

10:00-10:30 – Evidence for performing immediate CT/CTA imaging: review of recent thrombectomy trials

10:30-11:00 - How to read CT and CT Angiograms in acute stroke cases: applied vascular anatomy and implications on decision making

11:00-11:40 – Cases: Hands-on session at reading intracranial CT and CT Angiogram scans

Coffee break - 11:40-11:55

11:55-12:15 – Cases Review and Discussion

12:15-13:00 – Cases: Hands-on session at reading intracranial CT and CTA scans

Lunch Break – 13:00-14:00

14:00-14:20 – Cases Review and Discussion

14:20-15:00 – Cases: Hands-on session at reading intracranial CT and CTA scans

Coffee break - 15:00-15:15

15:15-15:30 - Cases Review and Discussion

15:30-16:00 - Cases: Hands-on session at reading intracranial CT and CTA scans

16:00-16:30 - Cases Review and Discussion

16:30 – 17:00: Feedback and Collection of Certificate

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CTA in acute stroke: short intensive training intervention is highly effective in improving radiologists' performance

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ARTICLE INFORMATION

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AIM: To determine whether focussed radiology training in reporting stroke computed tomography angiography (CTA) improved diagnostic performance of general radiology specialty trainees staffing regional on call rotas.

MATERIALS AND METHODS: A validated case archive (VCA) consisting of 50 hyperacute stroke CTA cases was developed for a full day course on CTA interpretation. Training days were organised ensuring all local trainees had a chance to attend. The rate of major and minor amendments by neuroradiology consultants were reviewed in 252 on-call radiology trainee reports.

RESULTS: Before training, radiology trainees had a total discrepancy (reporting error) rate of 37%: 12% major, 25% minor. Following CTA training, the total discrepancy rate was not significantly reduced (34%) but there was a substantial reduction in major discrepancies to 4% (p=0.037; odds ratio = 3.30, 95% confidence interval [CI]: 1.08 to 10.12).

CONCLUSION: An intensive training course based on a hyperacute stroke VCA significantly reduced major discrepancies in stroke CTA interpretation for radiology trainees. The ability of radiology trainees to recognise large vessel occlusions and other significant findings improved.

Introduction

Stroke is the second commonest cause of death worldwide affecting 6.7 million patients and representing 11.9% of all deaths.[1] In the UK, stroke is the largest cause of disability in adults; half of all stroke survivors are dependent on carers with activities of daily living.[2] Until recently, intravenous thrombolysis (IVT) was the only available hyperacute treatment, but mechanical thrombectomy is now a proven therapeutic option for patients presenting with acute ischaemic stroke caused by proximal large artery occlusion (LAO). There have been eight recently published positive mechanical thrombectomy trials.[3–10] NICE (National Institute for Health and Care Excellence) has approved thrombectomy for use in the NHS (National Health Service).[11] Proximal LAO accounts for ~40% of ischaemic strokes[12] and this group of stroke patients

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0009-9260/

present with the biggest deficits (so often present quickly) but respond least well to IVT with a disproportionately high disability burden as a result.[13]

Fast and accurate assessment of patients potentially suitable for acute interventional management is critical to offer the best treatment. In regional teaching hospitals, out of hours CT/CTA are provisionally reported by a general radiology (specialist) trainee. The supervising on-call neuroradiology consultant, although available for giving a second opinion at any time, will review all scans and document any disparities within 1–12 hours.

Traditional preparation for starting radiology on-call consists of the usage of teaching collections, lectures, and rotations into the different radiological specialties. In a traditional teaching file, only key images are provided, which allows many disease entities to be presented in a limited time. Simulation training enables users to experience a more real-life experience of reporting cases and using different visualisation tools (e.g., windowing, reconstructions) to accurately interpret the imaging examinations. This method of training has become widely used in interventional specialties, including interventional radiology. With digital imaging now ubiquitous, it is much easier to implement digital simulation teaching resources into diagnostic radiology. The opportunity to participate in training within a safe environment where trainees can review and report entire examinations promotes confidence, especially at the beginning of on-call commitments.

The purpose of this study was to develop simulated radiology training for reviewing CTA examinations of patients presenting with hyperacute ischaemic stroke. A validated case archive (VCA) was used together with a few short presentations on relevant anatomy, the CTA technique, and CTA reporting tips to create a full day training course. The reports of the radiology trainees were then reviewed pre- and post-CTA training day to assess whether it had impacted on their reporting performance and confidence.

Materials and methods

Validated case archive development

As a first step, the scans of 364 patients presenting over a period of 7 months with clinical details of acute stroke symptoms were reviewed. From these, all CTA images were reviewed and assessed for their image quality. Fifty cases were subsequently selected for the development of a VCA. The intention was to have a mixture of normal scans, which would be used to practise and develop a methodology of assessing these examinations, a few cases with normal

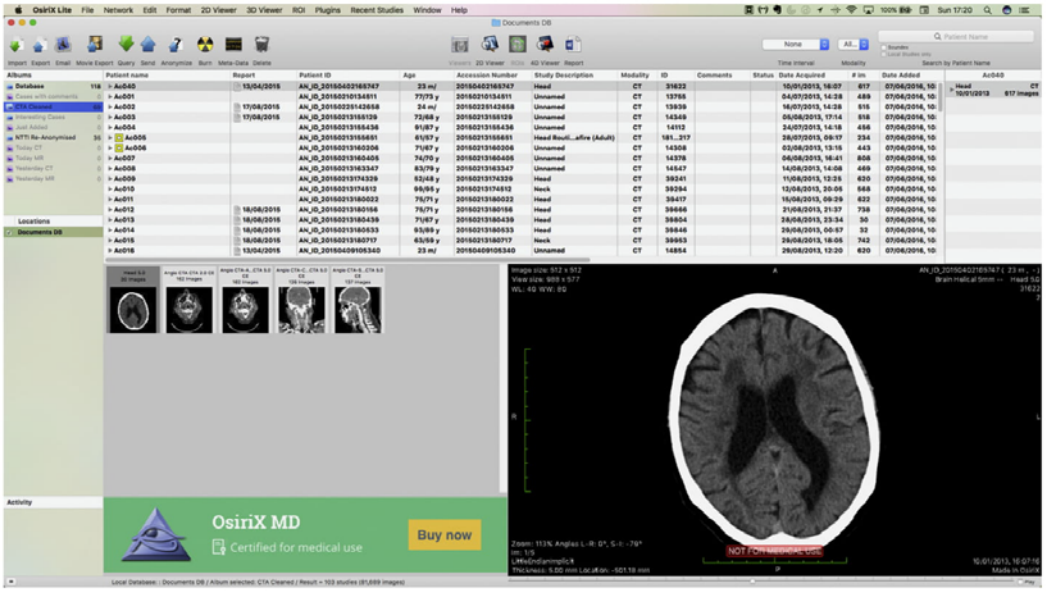

Figure 1 Osirix user interface. Main window with all the expected menu options at the top, including "ROI" (region of interest) and "Plug-ins", with each one of these having further sub-menus. All the basic study functions are present in a toolbar, including import/export, anonymisation, report, search function, and these can be customised to your preferences. On the left side the "Albums" and the "Locations" as well as any current "Activity" are shown. The main database window shows the different cases available. Under this, once a case is clicked on, the quick viewer window shows the different sequences available on the left and on the right the selected series can be scrolled through for a quick overview. To open the viewer window, either double click a patient or a series from the quick viewer window.

anatomical variants, which are important to recognise, and finally, a mix of stroke and non-stroke disease cases that are typically encountered. Seven of the VCA cases were normal with common normal anatomical variants. The other 43 images had significant primary vascular disease responsible for the patient's symptoms and six images were included because they also had secondary incidental but significant findings. These 50 CTA cases were validated by three neuroradiologists (two consultants, one fellow) who reviewed all images and recorded all the findings. Two neuroradiologists reviewed any discrepancies and a consensus was obtained to create a reference standard based on a combination of the consensus imaging findings, clinical findings, and clinical course plus evolution on any subsequent imaging.

After obtaining permission from the Trust Caldicott guardian, the anonymised CT brain/CTA image digital imaging and communications in medicine (DICOM) data sets were exported to Osirix.[14] In order to allow the reporting experience to be as close to real life as possible, the (anonymised) presenting clinical details and key past medical history of each patient were noted by transcription from electronic patient records and by obtaining patient's notes in selected cases.

A report type document was attached to every single examination in Osirix. This report included the clinical presentation along with any relevant medical history, the reference standard findings (noting findings both on the unenhanced brain and the CTA sequences), and finally, any acute treatment given to the patient as well as the medium-term clinical outcome (3–6 months).

Osirix MacLab

The training days were delivered in a purpose-built radiology training centre, which has 12 Apple 27″ retina iMacs each running Osirix 64 bit.[14] This software has the capability to handle large datasets, it allows the user to view and manipulate DICOM files, and it has all the standard PACS functions built in, including more complex functions such as multiplanar reformats, volume rendering, and vessel analysis (Figs 1 and 2). Video tutorials on how to use Osirix and its capabilities are freely available online at http://www.osirix-ukusergroup.org/video-tutorials. The networked set-up allows for lectures and cases to be displayed on each individual workstation and on the large wall mounted monitor. This allows trainers to demonstrate subtle and complex findings to the trainees.

Radiology trainee participation

A full training day, consisting of three 30-minute lectures followed by simulation training, was developed (see Electronic Supplementary Material Appendix S1 for details of the day). The lectures covered the importance of acute stroke imaging including a review of recent evidence for

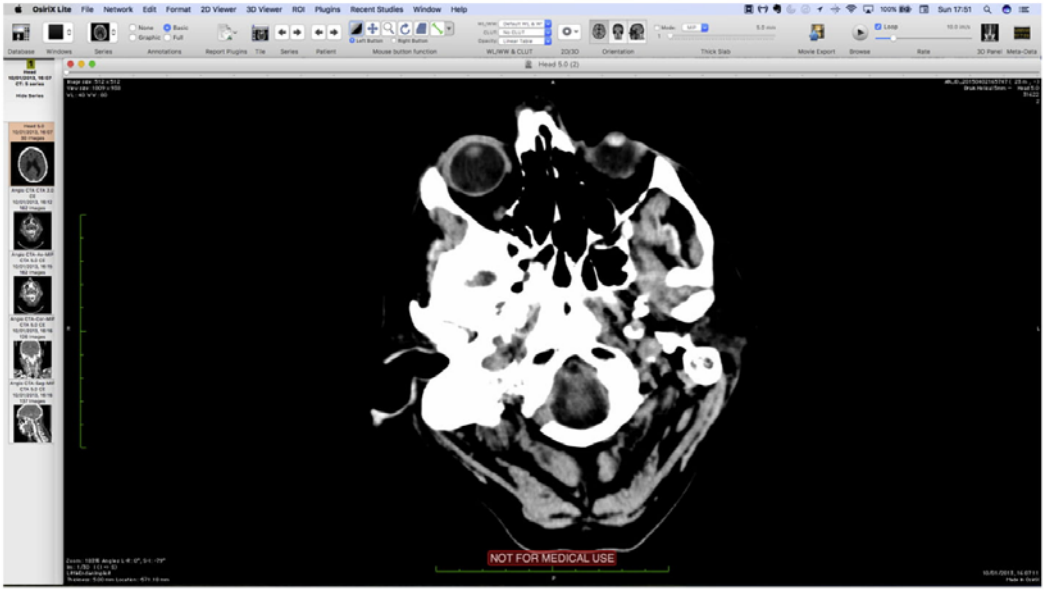

Figure 2 Osirix viewer. This has a similar interface, with the menu bar at the top and the toolbar underneath, which has all the expected basic functions such as windowing, zooming, measuring, and more advanced functions such as reconstructions and vessel analysis. The toolbar can be customised and further more advanced plug-ins can also be downloaded and added to Osirix. The scan series are displayed on the left side and once you click on one, this will open in the main viewing window on the right side.

imaging in acute stroke, the technical requirements, neurovascular anatomy, and a methodological approach of how to interpret and report these scans. For the remainder of the day, trainees worked at their own pace through suggested VCA cases before reviewing them with the facilitator (neuroradiology fellow and/or consultant). Trainees evaluated 15–20 VCA cases during the course of the day.

Between September 2015 to September 2016, all radiology trainees performing on-call duty at the institution attended this course. In total, 44 trainees attended one of 4 training days. The training days were organised according to neuroradiologists' availability and typically two trainers delivered the programme on each day.

Assessment of performance

Radiology trainees' reports pre- and post-CTA training were reviewed and assessed objectively for amendments to the original provisional reports. The amendments added by consultant neuroradiologists were then categorised as major or minor.

A major discrepancy (error) was defined as a significant finding, which if mentioned on the initial report definitely/probably would impact on the patient's management such as acute infarcts, intracranial haemorrhage, large vessel occlusion, dissection and significant atheromatous disease (e.g., >70% ICA stenosis).

A minor discrepancy was defined as a clinically insignificant reporting error, which would definitely/probably not have any impact on the acute management for the patient, e.g., old strokes, <50% internal carotid artery (ICA) atheroma, and/or stenosis, other incidental findings such as small aneurysms, small meningioma, thoracic lymph nodes, etc. Figs 3–4 demonstrate examples of both major and minor discrepancies.

Data collected included the date of scan, patient ID, age, sex, provisionally reporting trainee, year of training, time of report, CTA training status (pre/post), any neuroradiologist amendments and any other relevant report details. Simple logistic regression analyses were performed using IBM SPSS Statistics, version 23 (IBM, Armonk, NY, USA) to assess the

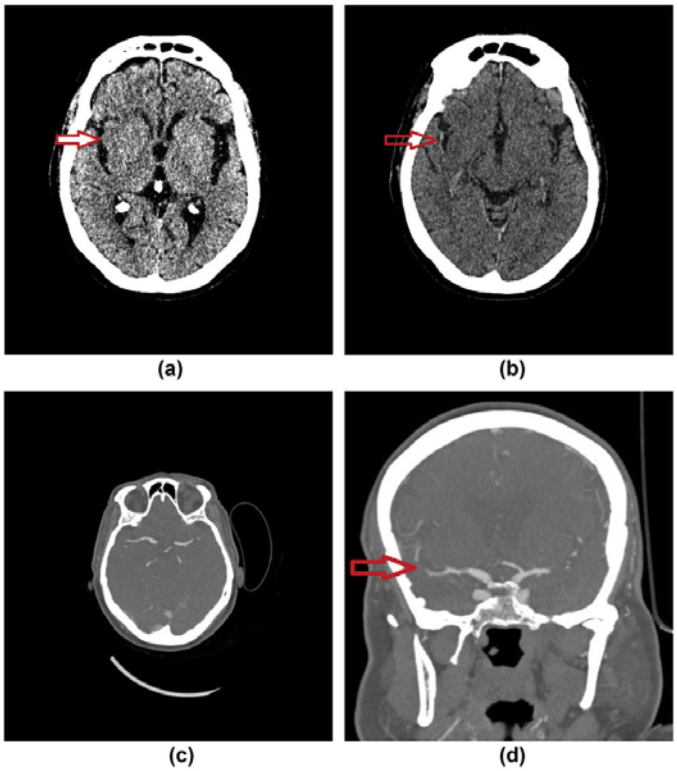

Figure 3 Major error example. An 83-year-old woman who presented acutely with left-sided neglect, left arm and leg weakness, dysarthria, and dysphagia. The provisional report did not identify the low attenuation changes in the right insula (a), the dense M2 vessel on the pre-contrast scan (b) or the M2 MCA thrombus on the CTA images (c,d). This was classified as a major error.

pre- and post-training error rates, including total, minor, and major error rates.

Results

Forty-eight radiology trainees had their reports reviewed retrospectively over a period of 1 year. As the CTA training was delivered over a period of time (four sessions) and typically trainees rotate through different hospitals, reports were assessed from 21 trainees who had attended the CTA training and 27 trainees who had not. Six of the 48 registrars had both pre- and post-CTA training reports and this group was analysed as a subset. In total, 252 reports were reviewed: 147 of them being done pre- and 105 done post-CTA training.

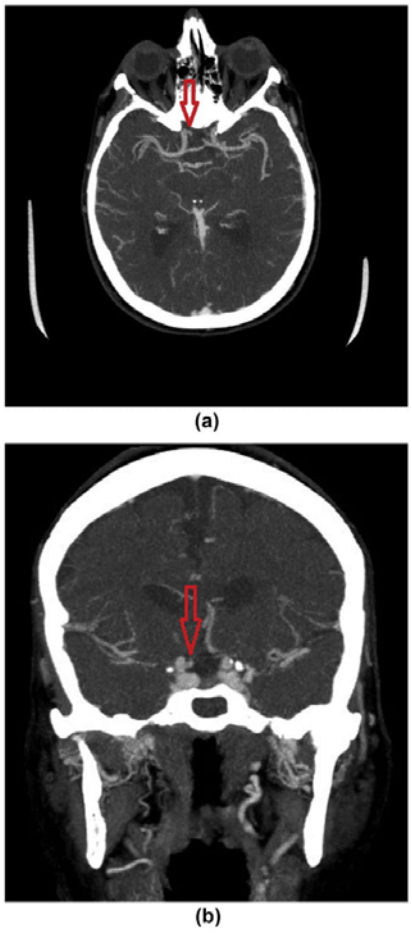

Figure 4 Minor error example. A 73-year-old lady with new right-sided acute visual symptoms. No acute findings were present on the scan, but a 3 mm right paraopthalmic aneurysm (arrowed) was not identified on the provisional report. This was classified as a minor error.

Examining trainees' seniority, slightly more in the pre-CTA training group of reports (58% versus 51%) were by more experienced trainees, years 4 and 5. This is because CTA training was preferentially first delivered to the most junior registrars (years 2 and 3) who are on-call.

In the control (pre-CTA training) group 57 out of 147 reports on CT/CTA examinations were amended due to a perceptual/reporting discrepancy (error), a total discrepancy rate of 39%. In the intervention group (post-CTA training) 36 out of 105 reports were amended, a total discrepancy rate of 34%.

In the control group there were 17/147 reports on CT/CTA examinations with major discrepancies, a rate of 12%. In the intervention group, there were 4/105 major discrepancies, a rate of 4%.

In terms of minor discrepancies, the control group reports had 40/147 discrepancies, a minor discrepancy rate of 27%; the intervention group reports had 32 minor discrepancies out of 105 examinations reviewed, a minor error rate of 30%.

The improvement in total errors was not statistically significant (p=0.467, odds ratio [OR] = 1.214, 95% confidence interval [CI] = 0.720 to 2.046). The reduction in the major discrepancy rate was statistically significant (p=0.037, OR = 3.302, 95% CI = 1.078 to 10.118). The small increase in minor errors was not significant and simple logistic regression demonstrated (p=0.572, OR = 0.853, 95% CI = 0.491 to 1.481).

Subset analysis on six trainees with both pre- and post-CTA training reports was performed, who in total reported 69 examinations (Fig 5). Thirty-three reports were done pre-CTA training and 36 reports post-training. The maximum time lapse between training and the assessed on-call reports were between 4–6 months. The total discrepancy rate pre-CTA training was 48% (16/33), which improved to 25% (9/36) post-training (p=0.046, OR = 2.824, 95% CI = 1.021 to 7.810). The major discrepancy rate substantially improved from 15% (5/33) to 0% (0/36). Logistic regression was inappropriate for analysing major discrepancy rate because zero cases had major discrepancies post-training. Similarly, this prevented the calculation of an OR. A Fisher's exact test was used to calculate significance (p=0.021). The minor discrepancy in this trainee subset was 33% (11/33) pre-training, improving to 25% (9/36) post-CTA training, a non-statistically significant improvement (p=0.447, OR = 1.5, 95% CI = 0.527 to 4.267). Overall, 73% of trainees reported feeling more confident with reporting CTAs after attending the VCA training.

Discussion

The rate of major discrepancies in the present study is in line with professional society rates of 3–30%.[15] Registrar attendance to a focussed 1-day stroke CTA course built around a VCA to provide simulation training significantly

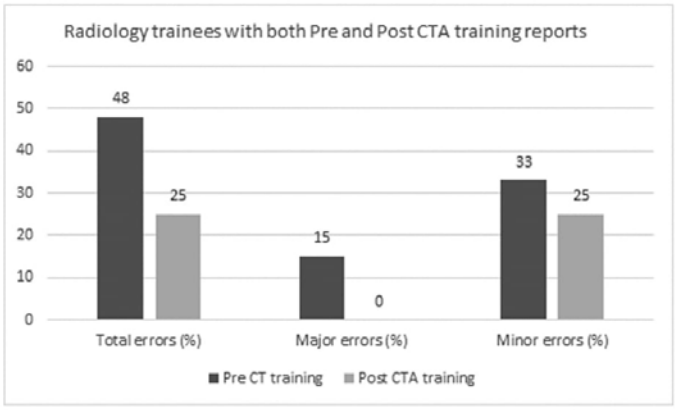

Figure 5 Discrepancy rates in subset of trainees with reports assessed pre- and post-CTA training.

decreased the rate of major errors from 12% to 4%, which is within the lower range of accepted radiology discrepancy rates. Similarly, the subset of registrars that attended the course and had both pre- and post-CTA training reports, improved their major discrepancy rate from 15% to 0%. Overall, the CTA training intervention had a significant impact on the major discrepancy rate. This is the most important aspect as these radiology trainee provisional reports are the imaging interpretation that will immediately impact hyperacute stroke patient management. It is important for radiology trainees to have adequate experience and a good method of assessing stroke CT examinations if they are to safely, accurately, and expeditiously report acute on-call stroke examinations. The time pressure in hyperacute stroke management dictates that considerable weight is given to the initial CT/CTA report, particularly out of hours.

Ultimately this training has led to improved acute identification of patients who may benefit from thrombectomy. This intervention allows the registrars to have an educational tool that closely mimics on-call in a safe learning environment with review of entire CT/CTA study and ability to manipulate images by windowing, zooming, etc., as they would in the on-call setting. This has the advantage of allowing trainees to independently evaluate the scan and find the relevant disease rather than just pointing to them the findings of interest. This is more challenging and every trainee has the opportunity to assess and go through the images at their own time, not just observing reporting. In terms of both building confidence and more objectively in diagnostic performance (assessed prospectively by discrepancy rates) the intervention has proved successful. The feedback from the radiology trainees was excellent and an online resource to complement the training day has been developed. The CTA interpretation intervention has also been used for other groups including consultant radiologists, radiographers, and stroke physicians. Based on published experience in studies examining stroke imaging interpretation, the training benefit is not expected to be limited to radiologists (whatever their experience), but also to extend to stroke physicians, neurologists, etc.[16] This approach could be used to train general consultant radiologists working in district general hospitals (DGHs) or working for outsourcing companies and a similar model of assessment could be implemented to assess discrepancies.

One of the limitations of the present study is the relatively small study size. Another is the staggered training period of 1 year due to the off-site location of the training facility and the availability of trainee and neuroradiology staff. Due to this and because trainees move in and out of the on-call rota on rotation to other hospitals a group comparison was performed.

A previous large study on resident on-call discrepancy rates has identified neuroradiological head CT studies as having the highest overall major discrepancy rates.[7] The same study showed that focussed teaching on the specific topics that had the largest number of discrepant reports, led to a statistically significant improvement in subsequent trainee reports.[17] Similarly, in the present study, it was shown that focused stroke CTA training significantly improved major discrepancy rate. The next question is whether one session is enough, or whether refresher sessions need to be organised to keep up this skill in radiologists who do not routinely report stroke CTA examinations.

A stroke CTA training intervention using a validated case archive within a simulation facility has proved highly successful in one English region. The reporting accuracy of general radiology trainees with a range of experience improved. Most importantly, the major discrepancy rate significantly decreased. This is a very useful tool in the training of professionals in CTA interpretation for hyperacute stroke symptoms. It indicates that most radiologists undertaking such a learning process likely do not need extensive training to reach acceptable competency levels in stroke CTA (very low major error rate).

Acknowledgements

The authors thank Dr Richard Francis for the advisory help provided for the statistical analysis, and Dr R. Ramaswamy, Dr D. Minks, Dr J. Hall, and Dr A. Gholkar for their help with delivering the training days. The radiology training centre in the North East was funded by Health Education North East to provide radiology simulation training to the radiology specialty trainees of the region. This work was subsidised by a grant for the STABILISE trial — funded jointly by Newcastle University Biomedical Research Centre and Microvention Terumo Inc (BH136733).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.crad.2017.04.015.

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Appendix P – Thrombectomy Technical Difficulty Index (TTDI)

Minimal Difficulty ≤ 4

Mild to Moderate > 4 and < 8

Severe Difficulty ≥ 8

A) Aortic Arch Elongation / Atheroma Classification

Elongation Classification	Score
Grade I	1
Grade II	2
Grade II + appreciable atheroma or Grade III	3
Grade III + appreciable atheroma	4

B) Target Vessel (TV) Tortuosity

TV proximal (Beneath skull base)	Score	&	TV (Intracranial)	Score
None / Mild	0		None / Mild	0
Moderate	1		Moderate	1
Severe	2		Severe	2

Score: (TV Proximal + TV Distal) / 2

C) Stenosis along target vessel

Stenosis grade	Score
Mild <50%	0
Grade I – 50 - 70%	1
Grade II – 70 – 95%	2
Grade III – acute occlusion / critical stenosis	3

D) Abbreviated Clot Burden Score*

Anterior Circulation	**Score**	**or**	**Posterior Circulation***	**Score**
Mild (CBS ≥8)	0		Mild	0
Moderate (CBS 6-7)	1		Moderate	1
Severe (CBS ≤5)	2		Severe	2

E) Any other extra problems - to add another 1 point.

E.g. tandem stenosis/occlusion, aortic coarctation, common brachiocephalic trunk (bovine arch), variant origin of the vertebral artery (if target artery), right aortic arch, double aortic arch and any other variant anatomy / pathology which is presumed to add complexity to the case - including known severe PVD, INR/PT significantly prolonged or other arterial access problem.

Total Score = A + B + C + D + E

Appendix Q – Awards, Publications, Presentations, Teaching, Conferences and Courses Attended Throughout my Ph.D. Studies

Awards

Travel Award Program for Students, Radiological Society of North America 2018, USA

1st Place, trainee research project, Canadian Association of Radiologists ASM 2018, Canada

Best trainee oral presentation, British Society of Neuroradiologists ASM 2016, UK

Publications

Drake B, Patro S, Quateen A, **Cora EA**, Finitsis S, Sinclair J, Iesiuk H, Iancu D. Metameric Spinal AVM: Long-Term Symptomatic Relief Achieved by Embolization of the Extradural Component. Interventional Neuroradiology, 2019 Mar.

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Cora EA, Finitsis S, Woulfe J, Essbaiheen F, AlQahtani H, Drake B, et al. Stent-assisted coiling of posterior inferior cerebellar artery aneurysm complicated by arterial avulsion. Interv Neuroradiol, 2018 Aug.

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;2(4):308–18.

Cora EA, Ford GA, Flynn D, Gonsalves P, White P. CTA in acute stroke: short intensive training intervention is highly effective in improving radiologists' performance. Clin Radiol. The Royal College of Radiologists; 2017;72(10):871–7.

Cora EA, White PM, Wardlaw JM. Stroke imaging in the age of thrombolysis. Imaging. 2016 Feb 12; 20120004.

Presentations

Acute Thrombectomy in the Ageing Population: A retrospective analysis of radiological and clinical outcomes in acute thrombectomies performed in patients 80 years and older with an intention to treat analysis

24-30/11/18 Poster presentation, Radiological Society of North America 2018, Chicago, USA
Selected for the Student Travel Award

Acute thrombectomy in the Ageing Population: A retrospective analysis of radiological and clinical outcomes in acute thrombectomies performed in patients over 80 years in a multicentre study

17-20/10/18 Oral presentation, World Stroke Conference 2018, Montreal, Canada

Acute thrombectomy in the ageing population: a retrospective analysis of radiological and clinical outcomes in acute thrombectomies performed in patients ≥ 80 years of age

28/04/2018 Oral presentation, Canadian Association of Radiologists ASM 2018, Montreal, Canada
Awarded 1st place for trainee research project

Development of a technical scoring tool to assess the predicted thrombectomy difficulty in patients with acute ischaemic stroke

8/10/2016 Oral presentation, British Society of Neuroradiologists, York, UK

Using a validated case archive to train radiology SpRs in reporting acute CT angiograms in patients with suspected ischaemic stroke due to large vessel occlusion

7/10/16 Oral presentation, British Society of Neuroradiologists, York, UK
Awarded best trainee oral presentation

STABILISE Trial and Research Outputs

30/6/16 Poster presentation, NAHP, Newcastle University, Newcastle, UK

CT Angiography in Acute Ischaemic Stroke: A Validated Case Archive Based on an Audit of Local Practice

11/2015 ION Poster Evening, Newcastle University, Newcastle, UK

CT Angiograms in Patients with Suspected Acute Ischaemic Stroke - Audit

06/2015 Oral presentation, Northern Radiologists ASM, Durham, UK

Stroke: an evaluation of thrombectomy in the ageing brain – [including] where IV thrombolysis fails or is contraindicated [STABILISE]

04/2015 Poster presentation, European Stroke Organization Conference, Glasgow UK

12/2014 Poster presentation, UK Stroke Conference, Hull, UK

12/2014 Poster Presentation, Newcastle University, UK

Update on UK led thrombectomy trials

10/2014 Oral presentation, British Society of Neuroradiologists, Belfast, Ireland

CT angiography in acute ischaemic stroke: a validated case archive based on an audit of local practice

04/2015 Poster, European Stroke Organization Conference, Glasgow, UK

Teaching

Neuroradiology Teaching

2014 – 2019 Bi-monthly informal junior doctors teaching

Thrombectomy and Care of the Post-thrombectomy Patient

Presented to intensive care nurses from the Ottawa hospital and from the Champlain Local Health Integration Network

26/10/2018 Civic Hospital, Ottawa, Canada

Radiology Resident Teaching – Neuroradiology cases

25/04/2018 Formal trainee teaching, The Ottawa Hospital, Canada

Acute Thrombectomy and Stroke Therapy Trials and Implementation Day

Organized, presented and helped to deliver a one-day course aimed at Consultant Physicians and Radiologists

14/02/2017 London, UK
Recognized by RCR UK for 6 CPD points

Developed CTA Course at the Durham MacLab for Radiologists and Physicians

2016 – 2017 4 Full day sessions delivered in Durham, UK
Recognized by RCR UK for 6 CPD points

Future of Neurological Interventions: Recent Advances and Concepts in Neuroradiology

07/2015 Invited Lecturer, International Medical Summer School, Manchester, UK

Neuroradiological Emergencies for Radiology Registrars

07/07/2015 Lectures and simulated training on Osirix, MacLab, Durham, UK

Courses and Conferences

Radiological Society of North America Annual Meeting
27/11/2018 – 29/11/2018 Chicago, USA

Advanced Neurointervention for Hemorrhagic Conditions and Acute Ischaemic Stroke Treatment - Fellows Course
19/11/2018 – 20/11/2018 Toronto, Canada

World Stroke Congress 2018
17/10/2018 – 20/10/2018 Montreal, Canada

AVM 2018 World Congress
14/10/2018 – 16/10/2018 Montreal, Canada

Canadian Interventional Neuro-Group 2018 Meeting
12/10/2018 – 14/10/2018 Montreal, Canada

Canadian Neurological Sciences Federation Congress
24/06/2018 – 27/06/2018 Halifax, Canada

American Society of Neuroradiology Annual Meeting 2018
02/06/2018 – 07/06/2018 Vancouver, Canada

Canadian Association of Radiologists 2018 Annual Scientific Meeting
26/04/2018 – 29/04/2018 Montreal, Canada

Ottawa Stroke Summit
17/11/2017 Ottawa, Canada

International Neuroradiology Symposium and 3rd Terbrugge Lectureship
15/09/2017 – 16/09/2017 Toronto, Canada

Canadian Interventional Neuro-Group 2017 Meeting

07/09/2017 – 09/09/2017 Alberta, Canada

Practical Statistics 1

06/03/2017 – 07/03/2017 Newcastle University, UK

European Course in Minimally Invasive Neurological Therapy

12/12/2016 – 16/12/2016 Oxford, UK

UK Neurovascular Group Meetings

25/11/2016 – 26/11/2016 Hull, UK

10/06/2016 – 11/06/2016 Manchester, UK

British Society of Neuroradiologists Annual Meeting

6/10/2016 – 8/10/2016 York, UK

Newcastle University Institute for Ageing Research Day

30/06/2016 Newcastle, UK

Brainstorm Neurointerventional Meeting

13/06/2016 – 15/06/2016 Edinburgh, UK

European Stroke Conference

17/04/2015 – 19/04/2015 Glasgow, UK

Radiological Society of North America Annual Meeting

30/12/2014 – 05/12/2014 Chicago, USA

British Society of Neuroradiologists Annual Scientific Meeting

10/10/2014 – 11/10/2014 Belfast, Ireland

UK Neurovascular Group Meetings

12/06/2015 – 13/06/2015 Liverpool, UK

13/06/2014 – 14/06/2014 Liverpool, UK

04/04/2014 London, UK

Brainstorm Neurointerventional Meeting

02/06/2014 – 04/06/2014 Edinburgh, UK

Hull Interventional Neuroradiology Course

15/05/2014 – 16/05/2014 Hull, UK

Advanced Stroke Neurovascular Intervention

20/03/2014 – 21/03/2014 Newcastle, UK