

## **PRIORITY BRIEFING**

The purpose of this briefing paper is to aid Stakeholders in prioritising topics to be taken further by PenCLAHRC as the basis for a specific evaluation or implementation research project.

## **QUESTION DETAILS**

**Question ID:** 3

**Question type:** Implementation

**Question:** How should services be configured to obtain maximum benefit from thrombolysis for acute ischaemic stroke in the South West Peninsula in the present and future?

**Population:** All patients with suspected ischaemic stroke in the South West Peninsula

**Intervention:** Optimising service configuration to minimise the time between stroke onset and treatment via consideration of a range of options, including the introduction of more specific targets for time-to-treatment, would be beneficial for commissioning, service planning and delivery. Service modelling would also investigate the extent to which current services achieve the benefits shown in clinical trials and characterise the relationship between timing of treatment and effectiveness in the real life situation under a series of scenarios. Service modelling would also be used to investigate the impact of licensed changes in the 'therapeutic window' of rtPA (see note below) from three hours to four and a half hours to ensure the average time-to-treatment does not increase such that a greater number of patients are treated at a less effective time point.

**Control:** This modelling study would involve comparison of differing configurations of services.

**Outcome:** Patients to be treated at the earliest possible point after the onset of symptoms to maximise the benefits of rtPA treatment. Ensuring that the extension of the 'therapeutic window' of rtPA does not result in a relaxation (increase) of the time-to-treatment period.

### **Note on rtPA and terms:**

rtPA stands for 'recombinant tissue plasminogen activator'. It is a drug administered intravenously and used to dissolve the blood clot responsible for the stroke and reopen the artery. The current licensed 'therapeutic window' is three hours but findings of recent research are expected to extend the window to four and a half hours. Time (onset)-to-treatment time refers to the time that lapses between onset of stroke symptoms and the treatment received in hospital. Door-to-treatment time refers to the time that lapses between the patient's arrival at the hospital and onset of treatment.

## **Part 1: Research Background**

**Guidelines:** The National Clinical Guidelines for Stroke developed by the Royal College of Physicians (2008) state that all patients should be seen within three hours of an acute neurological syndrome suspected to be a stroke, and should be transferred directly to a specialised “hyperacute stroke unit” that will assess for thrombolysis and deliver it if clinically indicated. The Better Heart Disease and Stroke Care Action Plan (2009), active in Scotland, states that in those patients where the time of symptom onset can be established definitely, emergency medical services need to be configured to allow delivery of thrombolytic therapy within the required time period. The receiving unit must be in a position to rapidly assess and confirm suitability to start treatment as soon as potentially eligible patients arrive at the front door, and to give the treatment within an hour, at all times of day.

### **Research Summary:**

One systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS was identified.<sup>4</sup> This study (conducted in 2002) identified a number of barriers to effective implementation of thrombolytic and neuroprotective therapy including: the patient’s or family’s inability to recognize stroke symptoms and failure to seek urgent help; patient/family call the GP instead of an ambulance; inefficient process of emergency stroke care in hospital; and delay in neuroimaging. The study also identified some interventions that have been trialed to overcome these barriers including: an education programme for the public and healthcare workers; a training programme for paramedical staff to improve the accuracy of diagnosis; and reorganization of in-hospital systems to streamline acute stroke care. However, none of the evaluations of these interventions provided reliable estimates of effect. One of the main recommendations of this systematic review is to design research to determine the nature and cost of changes in NHS services that would be needed to deliver rtPA therapy safely and effectively to patients with acute stroke, including costs of service changes necessary to ensure that patients with suspected acute ischaemic stroke are admitted to hospital much more quickly.

A number of trials have been conducted around the structure of services for improved acute stroke care. Most agree that to reduce the burden of illness due to stroke, efforts at primary prevention are essential and likely to have a greater impact than even the best interventions after the event. In the absence of good primary prevention, whatever is possible must be done to reduce the sequelae of stroke.<sup>1</sup> Despite evidence of the beneficial effects of thrombolysis, it is reported that its implementation throughout the UK is patchy.<sup>3,7,8</sup> Studies that have looked at barriers to the timely implementation of treatment for acute stroke<sup>5</sup> identify a lack of skills, nursing knowledge and ‘fast track’ organisation relating to thrombolysis, fears of intracranial bleeding, lack of appropriate stroke unit beds

and issues of consent as some of the main barriers to overcome. Scarborough District General Hospital developed a multidisciplinary model with their Coronary Care Unit to deliver stroke treatment with positive results.<sup>5</sup> Some studies<sup>6</sup> suggest that the emergency departments within hospitals are the ideal location for the delivery of thrombolysis for stroke as the skills and resources are readily available and as such emergency physicians should be included in the development of protocols for the delivery of thrombolysis alongside stroke physicians and radiologists. Other studies suggest the dissemination of a simple guideline/referral protocol can improve the speed at which treatment is received.<sup>8</sup>

**Ongoing Research:**

One trial investigating the efficacy of a high intensity implementation strategy (in comparison to a regular intensity strategy) to promote thrombolysis for ischaemic stroke and identifying barriers and success factors to thrombolysis implementation in the Netherlands has been identified. The study began in 2005 and was expected to complete in 2007 but no resulting evidence/publications can be found. The outcomes of interest were how patients were treated with thrombolysis care and how many patients were treated within three hours of onset of symptoms. The study was sponsored by Netherlands Organisation for Health Research and Development.

## **Part 2: Prioritisation Information**

### **1. The health problem**

#### **Epidemiology:**

The most common form of stroke is caused by a clot narrowing or blocking blood vessels so that blood cannot reach the brain, which leads to the death of brain cells due to lack of oxygen (ischaemia). Symptoms commonly include numbness, weakness or paralysis, slurred speech, blurred vision, confusion and severe headache.

Stroke is a major health problem in the UK. It accounted for over 56,000 deaths in England and Wales in 1999, representing 11% of all deaths. Most people survive a first stroke, but often have significant morbidity. Each year in England, approximately 110,000 people have a first or recurrent stroke and a further 20,000 people have a TIA (an episode that resolves in 24 hours). More than 900,000 people in England are living with the effects of stroke, with half of these being dependent on other people for help with everyday activities. In England, stroke is estimated to cost the economy around £7 billion per year. This comprises direct costs to the NHS of £2.8 billion, costs of informal care of £2.4 billion and costs because of lost productivity and disability of £1.8 billion.

There are approximately 2700 admissions with acute stroke to hospitals of Devon and Cornwall annually. Currently around 1.5% are treated with rtPA.

### **2. Identification of the topic as a priority**

National Stroke Strategy (2007) highlights service improvement and stroke as a medical emergency as two key target areas. The strategy requires that services work together in networks, looking across all aspects of the care pathway. Regular local and national audit and increased participation in clinical trials will also drive improvements in stroke care. The strategy also emphasizes the need for patients to get to the right hospital quickly and suggests the provision of centres that supply 24 hour access to scans and specialist stroke care.

In Scotland the 'Better Heart Disease and Stroke Care Action Plan' (2009) suggests that NHS Boards, with advice from their stroke MCNs (Managed Clinical Network), should consider appropriate models to facilitate access to thrombolysis for stroke patients, particularly in areas with limited medical cover.

SIGN (Scottish Intercollegiate Guidelines Network) clinical guidance for Scotland also suggests the emergency services should be redesigned to facilitate rapid access to specialist stroke services.

National targets are for thrombolysis to be achieved in 10% of patients with acute stroke.

**SW SHA Priorities framework 2008-11**

- reduce mortality rates from heart disease and stroke in people under 75 to 65 per 100,000 by 2013
- full implementation of the National Stroke Strategy
- 95% of people who have suffered a stroke will receive brain imaging within 30 minutes of arrival at hospital 7 days a week by March 2010

**3. Local perspective**

Improved thrombolysis for acute stroke is a priority for Cornwall and Devon PCTs.

**Tractability:**

Potential for service simulation study to be taken forward within PenCLAHRC.

**An overview of the local context:**

No other information available

## References

(1) Heller, R. F., P. Langhorne, et al. (2000). "Improving stroke outcome: the benefits of increasing availability of technology." *Bulletin of the World Health Organization* 78(11): 1337-43.

**INTRODUCTION:** A decision analysis was performed to explore the potential benefits of interventions to improve the outcome of patients admitted to hospital with a stroke, in the context of the technology available in different parts of the world. **METHODS:** The outcome of death or dependency was used with a six-month end-point. **RESULTS:** Four settings were identified that would depend on the resources available. The proportion of stroke patients who were dead or dependent at six months was 61.5% with no intervention at all. Setting 4, with the only intervention being the delayed introduction of aspirin, produced a 0.5% absolute improvement in outcome (death or dependency), and the addition of an organized stroke unit (Setting 3) produced the largest incremental improvement, of 2.7%. Extra interventions associated with non-urgent computed tomography and thus the ability to avoid anticoagulation or aspirin for those with a haemorrhagic stroke (Setting 2), and immediate computed tomography scanning to allow the use of thrombolytics in non-haemorrhagic stroke (Setting 1), produced only small incremental benefits of 0.4% in each case. **DISCUSSION:** To reduce the burden of illness due to stroke, efforts at primary prevention are essential and likely to have a greater impact than even the best interventions after the event. In the absence of good primary prevention, whatever is possible must be done to reduce the sequelae of stroke. This analysis provides a rational basis for beginning the development of clinical guidelines applicable to the economic setting of the patient.

(2) Marx, P., A. Hartmann, et al. (2001). "[Prerequisites, indications and contraindications of IV-lysis of ischemic stroke with rt-PA]." *Fortschritte der Neurologie-Psychiatrie*(8): 346-52.

**BACKGROUND AND PURPOSE:** To evaluate prerequisites, safety, and efficacy of i.v.-thrombolysis of ischemic stroke with rtPA in an academic medical center. **METHODS:** Over a period of 2 years and 10 months all patients admitted with a diagnosis of stroke were recruited. Inclusion and exclusion criteria for i.v.-thrombolysis were combined from large scale randomized controlled trials, the time window, however, could be extended up to 4 hours in subjects with a negative CT-scan. Prespecified outcome parameters were the modified Rankin Scale (mRS) and the Barthel Index (BI) at 3 months, and symptomatic hemorrhagic complications. Additionally, time parameters, such as onset-admission-time, door-Ct-time, door-needle time, and onset-needle time were recorded. **RESULTS:** During the reported period 103 patients underwent i.v.-thrombolysis, corresponding to 14.9% of all patients with ischemic stroke, and 47% of patients with ischemic stroke arriving in < 3 hours after symptom onset. The mean baseline NIHSS was 14, the mean mRS 13 (3-34), the mean age 70 (+/- 12) years. The following time intervals were observed: Onset-admission-time 64 min., door-CT-time 27 min., admission-needle-time 80 min., and onset-

needle-time 142 min. There were 4 symptomatic intracerebral hemorrhagic transformations, including 3 parenchymal hemorrhages, 2 of them lethal, and one with almost full recovery. According to the mRS, 39% of patients had a good (mRS 0-1), 72% a good to moderate recovery (mRS 0-2). The corresponding figures for the BI were 60% BI 95-100 and 72% BI > 90. The mortality was 15%. CONCLUSION: The i.v.-thrombolysis of ischemic stroke with rt-PA demands appropriate organisation of the pre- and in-hospital phase and can be performed safely and efficaciously in daily clinical routine if inclusion and exclusion criteria as well as all safety measures during the critical phase after therapy are strictly obeyed.

(3) Lindley, R. I. and R. I. Lindley (2002). "Thrombolysis for acute stroke in the United Kingdom." *Age & Ageing* 31 Suppl 3: 28-30.

The publication of the National Institute of Neurological Disorders and Stroke trial of thrombolysis has not led to the widespread implementation of alteplase for acute ischaemic stroke in the United Kingdom. However, the Cochrane systematic review of thrombolysis for acute ischaemic stroke suggests that alteplase is the most promising treatment for acute ischaemic stroke. Successful implementation of thrombolysis in the United Kingdom will depend on continued investment in acute stroke services, attention to the known barriers to treatment, further data from randomized controlled trials and the licensing of alteplase for this indication.

(4) Sandercock, P., E. Berge, et al. (2002). "A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. Thrombolytic therapy in acute ischaemic stroke (Brief record)." *SO: Health Technology Assessment*(26): 1-25.

(5) Carty, R., R. Mooraby, et al. (2006). "Evolution of a model for the thrombolysis of acute stroke patients." *British Journal of Nursing* 15(8): 453-7. The National Audit Office (NAO, 2005) has reported that the priority afforded to stroke care should be increased, given its impact on health and cost to the NHS. It recommends improvements in preventing, treating and managing stroke patients in line with recent evidence. Thrombolysis for acute ischaemic stroke is a proven treatment that produces good results in significant numbers of patients (Mar et al, 2005). However, owing to various barriers, many hospitals in the UK have failed to implement effective systems to facilitate the delivery of this treatment to acute stroke patients. These barriers include a lack of skill, nursing knowledge, and 'fast-track' organization relating to thrombolysis as a treatment for acute stroke. Fears of intracranial bleeding and lack of appropriate stroke unit beds and issues of consent have also been identified as further problems (Innes and International Stroke Trial (IST-3), 2003). Taking these concerns into consideration, Scarborough District General Hospital has developed a multidisciplinary model with the Coronary Care Unit (CCU), integral to the delivery of treatment. Between 2003 and 2005, 24 stroke patients have received

thrombolysis treatment and have been cared for in CCU. Outcome results have been positive, with 51% of patients demonstrating a significant benefit at 7 days post-stroke. This model has broken traditional professional and speciality boundaries to allow patients to receive treatments they otherwise would not have received. Moreover, it provides the potential for further exploration into the wider implementation of thrombolysis for acute stroke patients in the UK.

(6) Kendall, J. (2008). "Thrombolysis for acute ischaemic stroke: a new challenge for emergency medicine." *Emergency Medicine Journal* 25(8): 471-5.

**INTRODUCTION:** Acute ischaemic stroke (AIS) is a leading cause of death and disability within the United Kingdom. Despite evidence of the benefit of thrombolysis for appropriately selected patients with AIS, this intervention remains markedly underutilised in this country when compared with other developed countries. The delivery of thrombolysis for AIS has become a political, as well as a clinical, priority in the United Kingdom. **DISCUSSION:** Research has shown that, although thrombolysis for AIS is associated with increased short-term mortality, this is offset by a significant benefit in terms of reduced long-term death and disability. Recent observational data have shown that it can be safely and effectively delivered in the "normal" clinical setting (ie, a non-research environment). Furthermore, thrombolysis for AIS is supported by the Royal College of Physicians and the National Institute for Health and Clinical Excellence. Emergency physicians are trained to receive and assess patients with possible stroke. The emergency department (ED) is an ideal location in which to perform these clinical duties and to communicate and coordinate the necessary tasks required for the delivery of thrombolysis. All of the skills and resources are already available within the ED, with the exception of a single training requirement: certification in the National Institute for Health Stroke Scale scoring system, which can be acquired following limited Internet-based training. **RESULTS:** Emergency physicians should be integrally involved in the development of protocols for the delivery of thrombolysis to patients with AIS. This will require communication and collaboration locally with stroke physicians and radiologists, a process that should be facilitated by the newly emerging Stroke Networks.

(7) Lees, K. R., G. A. Ford, et al. (2008). "Thrombolytic therapy for acute stroke in the United Kingdom: experience from the safe implementation of thrombolysis in stroke (SITS) register." *Qjm* 101(11): 863-9.

**AIM:** To describe the United Kingdom (UK) experience with thrombolytic therapy with intravenous alteplase (rt-PA) for stroke, as captured by the Implementation of Thrombolysis in Stroke (SITS) project. **METHODS:** The multinational Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) was an observational study to assess the safety and efficacy of thrombolytic therapy, when administered within the first 3 h after onset of ischaemic stroke. SITS-MOST was embedded within the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR), an internet-based, international monitoring registry for auditing the safety and efficacy of routine

therapeutic use of thrombolysis in acute ischaemic stroke. We performed an analysis of data contributed to SITS-MOST and SITS-ISTR from UK centres. RESULTS: A total of 614 patients received thrombolysis for stroke between December 2002 and April 2006, 327 were registered to SITS-MOST and 287 to SITS-ISTR. Thirty-one centres treated patients in the UK, of which 23 registered patients in both SITS-MOST and SITS-ISTR and eight solely to SITS-ISTR. The median age from the UK SITS-MOST was identical to the non-UK SITS-MOST register: 68 years (IQR 59-75). The majority (96.1%) of patients from the UK were treated between 8.00 a.m. and 9.00 p.m., and only 18.4% were treated on weekend days, reflecting the difficulties of maintaining provision of a thrombolytic service out of hours. Median onset-to-treatment-time was 155 min (IQR 130-170 min) for the UK, compared to 140 min (IQR 114-165 min) for the non-UK SITS-MOST group ( $P < 0.001$ ). UK SITS-MOST patients at baseline had more severe stroke in comparison with non-UK patients [median NIHSS 14.5 (IQR 9-19) vs. 12 (IQR 8-17) ( $P < 0.001$ )]. Forty-eight percent of UK patients achieved mRS of 0-2 (independence), compared to 55% of the non-UK SITS-MOST register. There was no significant difference in symptomatic intracerebral haemorrhage rate in the UK compared with the non-UK SITS-MOST patients [2.5% (95% CI 1.3-4.8) vs. 1.7% (95% CI 1.4-2.0)  $P = 0.28$ ]. In the multivariate analysis, there was no statistically significant difference in any outcome between UK and non-UK SITS-MOST patients. CONCLUSION: Thrombolytic therapy for stroke has been implemented successfully at a small number of UK stroke centres, with patchy provision throughout the country. The low frequency of treatment out with office hours suggests deficient infrastructure to support delivery. UK patients tended to be more severely affected at baseline and to be treated later. Outcomes are comparable to those seen at the non-UK SITS centres.

(8) McCormick, M. T., I. Reeves, et al. (2008). "Implementation of a stroke thrombolysis service within a tertiary neurosciences centre in the United Kingdom." *Qjm* 101(4): 291-8.

BACKGROUND: Intravenous alteplase is licensed for treatment of ischaemic stroke within 3 h of onset. Up to one-third of patients in the UK present to hospital within this time window but few are treated. AIMS: To examine the effect of a stroke thrombolysis protocol on service provision for an acute stroke service in the UK, jointly run by Neurology and Medicine for the Elderly providing a comprehensive stroke service to a local population of 370,000. DESIGN: Prospective observational study. METHODS: Data collected prospectively for all thrombolysis referrals over a 12-month period beginning July 2004. RESULTS: One hundred and eighty-eight patients were referred for potential thrombolysis, 129 transferred, 102 had an ischaemic stroke and 49 received intravenous thrombolysis. Referral rates from primary care and accident and emergency increased after guideline dissemination. Forty-three percent of the 49 patients treated with intravenous rt-PA achieved independence (modified Rankin Scale score 0-2) at 3months. CONCLUSION: A high proportion of ischaemic stroke patients can be treated with alteplase within 3 h of onset with organized hospital

services and dissemination of a simple referral protocol to local primary and secondary care services.

(9) Agnew, T. (2009). "Taking stroke care to a new level." *Nursing Older People* 21(4): 18-21.

A new report from the Stroke Association shows how nurses, doctors, paramedics and other members of the multidisciplinary team have worked together at a local level to transform the care provided to people affected by stroke. No other information available.