## NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Single Technology Appraisal (STA)

### Alteplase for the treatment of acute ischaemic stroke (review of TA 122)

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name: Dr Gavin Young**

**Name of your organisation**
**Royal College of Physicians Intercollegiate Stroke Working Party (RCP ICSWP) & South Tees Hospital NHS Foundation Trust**

**Are you (tick all that apply):**

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **YES - member RCP ICSWP**
- other? (please specify)

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**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

**Response:**

Alteplase is used to treat a proportion of individuals who have experienced an acute ischaemic stroke. Ideally, patients with ischaemic stroke should be managed using a number of complimentary approaches, including:

- care within a specialised environment ("stroke unit")
- intravenous thrombolysis (with alteplase) for appropriate cases
- timely commencement of appropriate treatments to prevent further stroke
- identification and management of stroke complications
- appropriate rehabilitative interventions to aid/enhance recovery

Regarding intravenous thrombolysis for ischaemic stroke, treatment is restricted to patients with the following characteristics:

- acute stroke (currently within 3 to 4.5 hours from stroke onset)
- age 18-80 (though many centres routinely treat patients >80 yrs)
- certain stroke severity (neither too mild nor too severe)
- none of the specified exclusion criteria listed in the alteplase summary of product characteristics (SPC)

Treatment tends to be provided from within specialised units, staffed by doctors and nurses with experience and expertise in diagnosing and managing acute stroke and stroke mimics. With a relatively small number of medical stroke specialists and a requirement to have several specialists working together to provide 24/7 cover,

expertise tends to be concentrated in larger units. Therefore, not all hospitals provide thrombolysis treatment for acute stroke. For a condition in which outcome is so clearly related to the time from onset to initiation of treatment, geographical factors will play some part in determining outcome. All else being equal, patients living closer to an acute stroke unit will have their treatment commenced sooner. Various strategies to minimise this inequality have been developed, such as tele-medicine (delivery of treatment at a distance from the specialist by means of technology links) and mobile units designed to take treatment to the patient (not something routinely provided in the UK).

There are clearly differences, both between units and across regions, in how effectively acute stroke care is delivered, as identified in the Stroke Improvement National Audit Programme (SINAP 2012). Whilst it is relatively easy to identify variability in process and to an extent outcome between units, it is harder to understand exactly why this variability occurs. It is likely due to a number of factors, including patient pathways (length of journey to treating centre, use of hospital pre-alerting, direct versus indirect admission to stroke unit, weekday versus week-end/daytime versus night-time etc.) and the acute stroke service itself (quality and quantity of staff, familiarity with treatment pathways (centres with high numbers versus low numbers), efficiency of laboratory and radiological support etc.). There is also likely to be some variability in how effectively and completely the data for national audit is collected.

Whilst some have questioned the evidence underpinning thrombolysis therapy (e.g. Hoffman 2009), as the evidence-base has strengthened, a consensus does appear to have emerged that this is an effective treatment which should be made available to patients (and iterated in a number of national stroke guidelines). Amongst stroke specialists, any disagreement is now more likely to concern the appropriateness or otherwise of widening the criteria for treating patients. Specifically, there is debate concerning the appropriateness of an upper (and to a lesser extent lower) age cut-off for treatment and regarding the appropriateness of some contraindications listed in the alteplase SPC (e.g. patients taking warfarin, those with previous stroke within 3 months, those with severe strokes etc.).

Intravenous thrombolysis (and specifically intravenous alteplase) is generally complementary to, rather than competetive with, other acute treatments for ischaemic stroke. The other drug treatment that has been shown to benefit patients, (aspirin given within 48 hours of stroke onset), is also available to patients treated with intravenous alteplase.

Some studies assessing intravenous thrombolysis for acute stroke have used different thrombolytic agents (e.g. urokinase, streptokinase and desmoteplase). No convincing differences have been identified between these different drugs (Cochrane 2009), but the evidence-base for comparison is poor. Since the main trials contributing evidence have involved treatment with alteplase, it seems appropriate to suggest that there is currently no reasonable alternative thrombolytic and certainly no licensed alternative.

There is interest in whether more effective revascularisation therapies can be identified and at the present time one candidate is intra-arterial interventional therapy (thrombolysis and/or thrombectomy). Whilst there is some evidence demonstrating benefit of intra-arterial therapy compared to placebo, there is currently no compelling evidence to suggest intra-arterial therapy is superior to intravenous thrombolysis. It

is therefore reasonable to say that there are currently no proven alternatives to the technology under consideration.

There is great interest in identifying patient and/or imaging characteristics which identify a differential response to treatment with alteplase. For example, there have been concerns that certain patient groups such as the very elderly, those with large strokes and those with a prior history of stroke and diabetes may derive less benefit. Likewise for brain imaging, patients with early infarct changes, proximal artery (internal carotid /proximal middle cerebral) occlusion or with no perfusion-diffusion mismatch (i.e. no ischaemic penumbra) may derive less benefit from therapy. The evidence-base upon which sub-group analysis can be performed is relatively small and what evidence there is would suggest the very elderly, those with large strokes and those with pre-existing stroke and diabetes all benefit from intervention (IST 3 2012, SITS-ISTR 2011). The results from the IST-3 study provide support for extending treatment to patients >80 years of age, provided treatment is given within 3 hours of stroke onset. Results from IST-3 also help confirm that patients with early infarct changes on imaging also benefit from intravenous thrombolysis. Large vessel thrombosis may in future identify a sub-group of patients who benefit from intra-arterial interventional treatments, but as discussed above, this will require evidence and is not relevant to the current debate.
There is very limited evidence concerning the benefits and risks of intravenous thrombolysis treatment in patients with acute stroke and significant prior disability (e.g. Oxford Handicap Score ≥3). It would be difficult to give any guidance in these circumstances other than to suggest caution and an individualised discussion /decision process.
Clinical scoring systems have been developed to identify patients at particularly high risk of haemorrhage following treatment with intravenous alteplase. One example is the Haemorrhage After Thrombolysis (HAT) score which includes variables of hypodensity on CT scan, serum glucose/history of diabetes and stroke severity as measured by the NIH Stroke Scale (Lou 2008). Whilst such scales have been shown to predict increased haemorrhage risk they have not reliably identified patients whose risk is sufficiently high as to preclude benefit from treatment.

The current model for delivering intravenous thrombolysis in the UK is through specialist secondary care services. Treatment is either delivered within acute centres directly by specialists or in some cases by non-specialists supported by experts from a distance using video and audio tele-medicine links. Patients may require transport to large centres specifically setup to deliver stroke thgrombolysis, by-passing closer hospitals in the process.
There have been studies looking at delivery of treatment in the community, e.g. involving specialist teams using portable scanners ("scanbulance") to the patient, but this approach is not widely available and as far as I am aware has not undergone cost-benefit analysis.
An important issue is determining which professional groups should deliver thrombolysis therapy. Restricting treatment to specialist centres, under the supervision of a limited number of specialist stroke physicians encourages the safest delivery of treatment. Stroke is overdiagnosed by non-specialists and even with specialist assessment about 1-3% of patients who undergo thrombolysis will ultimately be determined to have a stroke mimic diagnosis such as epilepsy, migraine or psychological weakness. There is some evidence that treating patients with stroke mimics is not associated with a risk of symptomatic intracranial haemorrhage, but the

numbers included in these analyses are small and there is clearly a possibility of publication bias.
The downside to restricting treatment to a limited number of specialist centres is that patients may take longer to get to the point of treatment, especially if there is also a delay in the treating physician attending, as might happen out-of-hours and at week-ends if non-resident consultants are delivering the therapy. If the risks of treating stroke mimics is small and if there is little evidence to restrict treatment to certain patient groups (other than as determined by time from stroke onset), then a valid question is whether we should be less restrictive in who delivers the treatment. Whilst this is a reasonable hypothesis to test, I am not aware of any supporting evidence for adopting this approach now. The integration of other aspects of acute stroke (and TIA) care means that specialised units are likely to remain the appropriate model for the future. Nonetheless, greater involvement and education of non-specilaist acute medical staff with treatment supported (rather than delivered) by senior stroke specialists (medical and nursing) may allow more patients to be treated more quickly.

After a slow start, the delivery of intravenous thrombolysis for acute stroke has increased within the UK, as demonstrated by the National Sentinel Stroke Audit and SINAP (1% of all stroke patients received this treatment in 2008, 8% in 2012).
Use of intravenous thrombolysis "off-license" occurs frequently, most notably in those over 80 years of age (in the most recent SINAP report, 22% of patients thrombolysed were >80 years of age). There is reasonable support for this approach from the available evidence, further enhanced by the recent IST-3 results. Treatment is also frequently given to patients on treatment with warfarin, usually with a requirement for the INR blood test to be <1.7. Many centres will be flexible concerning other exclusion criteria such as stroke or major surgery within the last 3 months. I am aware of some cases where treatment has been given to patients in whom the stroke onset-time was unknown, including cases of "wake-up" stroke (i.e. a patients who waken with symptoms of stroke).

As well as the NICE technology appraisal (TA 122), the other obvious source of guidance within the UK is the NICE Clinical Guideline 68 for Stroke and the also the National Clinical Guideline for Stroke (3rd Edition 2008) prepared by the Intercollegiate Stroke Working Party.

**The advantages and disadvantages of the technology**

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements

for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

**Response:**
The technology is already available. As a single treatment, there would be no stopping rules. Starting rules would equate to indications for treatment. Practice has already largely anticipated the move to extending the time window from 3 to 4.5 hours. There will be interest amongst clinicians as to whether treatment might be extended to other groups currently outside the licensed indication for treatment e.g. those >80 years of age, and those presenting between 4.5 to 6 hours from stroke onset. I believe these questions are beyond the remit of the current technology review. The recently published IST-3 trial and the ongoing SITS registry provide support for extending treatment to the >80 years group, at least in the 0 to 3 hour time-window and I suspect many centres in the UK will now extend treatment to this group, if they are not already doing so. I believe further evidence is required in order to determine the usefulness of treatment in the 4.5 to 6 hour time-window.

I believe the clinical trial evidence does compare favourably and is of relevance to the conditions of use within the UK. There is further support for this stance from the SITS registry database which has identified similar risks and benefits for treatment in UK versus other European patients (despite patients entered into the registry from the UK having slightly more severe strokes)(Lees 2008). There is general agreement regarding the appropriateness of the outcome measures used in these trials and their relevance to the patient population, these same outcomes forming the basis of previous NICE assessments.

**Any additional sources of evidence**

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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**Response**:
I believe the GDG will be familiar with the other relevant data sources. Most notable is the Safe Implementation of Treatments in Stroke (SITS) registry which now contains data from over 70,000 patients. This data is not however likely to be required for the specific remit of the appraisal review given good quality data from randomised controlled trials. The recently published IST-3 trial has provided useful data largely relating to treatment of patients outside the recognised licensed indications. I believe it has been determined that this data will not be included in the NICE review.

**Implementation issues**

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

**Response**:
This review focuses primarily on the issue of whether to extend the time-window for treatment from 3 hours to 4.5 hours. I believe the majority of centres in the UK will have already considered making the move to provide treatment within this time-frame, following publication of the ECASS III trial results. Assuming this review supports the extension of the time-window, I would not therefore anticipate any significant impact on current practice, nor any major funding implications. Those centres who have confined treatment protocols to the strict licensed indications will be faced with the prospect of extending treatment to a wider population, with some resource implications. However, even in these cases, pathways and protocols should already be in place for treatment to the 3 hour window and extending this to the 4.5 hour window is unlikely to require major modifications to services.
If the review does not support extension of the time-window then it may be that fewer patients would be treated, but I suspect many centres would continue with current

arrangements unchanged. Either way, the staffing and service infrastructure is likely, for the most part, to be in place already.

Any guidance to implement an extension to the time-window for treatment should also assert the importance of aiming for the earliest treatment possible. The benefits of treatment at 4.5 hours, whilst worthwhile, are modest and we should be aiming for much earlier treatment whenever possible. Aggressive targets for the time from presentation to treatment would help ensure that extending the time-window does not result in patients simply waiting a little longer for their treatment to be given.

Extra resources would certainly be welcome, not just for acute thrombolysis treatment but for the stroke (and TIA) care pathway in its entirety. The chances of this happening, even with the welcome support of NICE, seem remote to this observer.

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